

CARBON-13 AND HYDROGEN-1 NMR STUDIES OF CONFORMATIONS OF LIGULAROL AND
6-EPIGULAROL, NATURALLY OCCURRING *cis*-DECALIN DERIVATIVES

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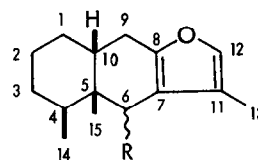
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cis-Decalin derivatives can adopt two alternative chair-chair conformations, commonly termed "steroid-like" (B) and "non-steroid-like" (A) conformations. In a previous paper,¹ we presented evidence for the presence of an equilibrium between the two conformations in naturally occurring *cis*-decalins, ligularone² and ligularol acetate.² As a further extension of this study, we examined variable-temperature ¹³C as well as ¹H NMR spectra of ligularol (1)² and 6-epiligularol (2),² and found that they also exist as two conformational isomers in solution and that their conformational ratios are significantly affected, even reversed in the former (1), by the concentration and the solvent employed. The latter interesting phenomena are reported here; we attempt to explain them by the difference in the hydrogen-bonding mode.

Low-temperature ¹³C NMR (FIG. 2a) as well as ¹H NMR spectra (FIG. 1d) in acetone-d₆ showed two sets of signals in a ratio of 2.3:1 (see the TABLE). These suggested that two conformers of 1 coexist in solution. Conformations of the isomers were assigned by the low-temperature ¹H NMR spectra in acetone-d₆ to which small amounts of D₂O had been added; at 35°, the broad H-6α signal appeared at δ_H 4.71 (FIG. 1a), but at -90°, it turned into a pair of signals, a broad singlet at δ_H 4.95 (W_{1/2} = ca. 6 Hz: axial proton)¹ and a relatively sharp singlet at 4.36 (W_{1/2} = ca. 2 Hz: equatorial proton)¹ in a ratio of 2.3:1 (FIG. 1c). Therefore, the former H-6α should result from the "non-steroid-like" conformer and the latter from the "steroid-like" one, as in the case of ligularol acetate.¹ Consequently, the more abundant conformer in acetone was classified as "non-steroid-like" (A).

In a similar manner, low-temperature ¹³C and ¹H NMR spectra of 2 in acetone-d₆ (FIG. 1h) showed two sets of signals in a ratio of 3.2:1 (see the TABLE). In the ¹H NMR spectrum of 2 in acetone-d₆-D₂O at -70°, the H-6β signals at δ_H 4.50 (W_{1/2} = ca. 6 Hz) and 4.20 (W_{1/2} = ca. 3 Hz) in a ratio of about 1:3 indicated that the "non-steroid-like" conformer was the major one. The



- 1: R = β-OH
2: R = α-OH
3: R = H

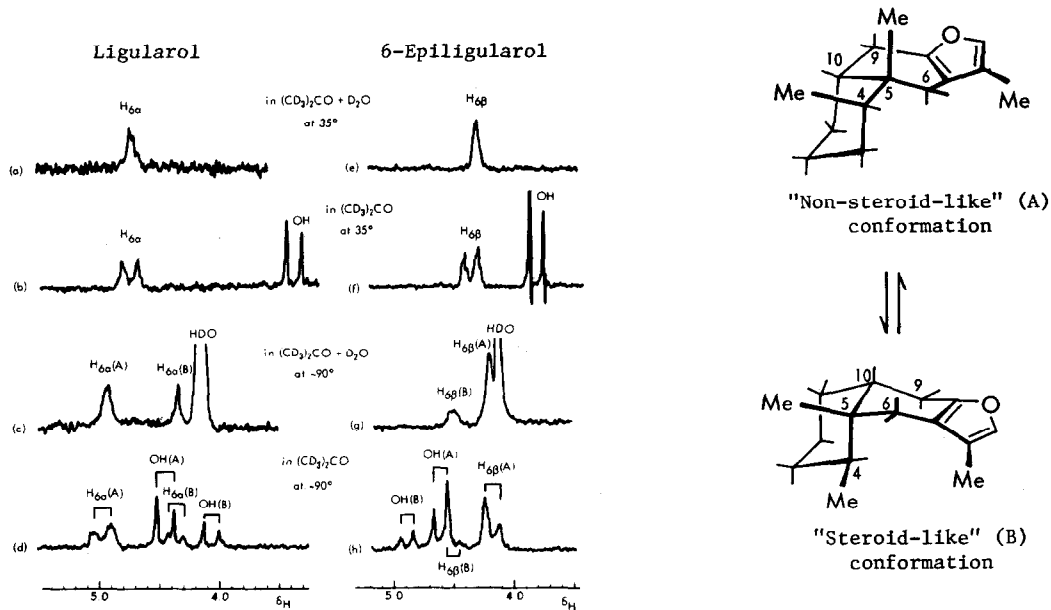


FIG. 1. Variable-temperature ^1H NMR spectra of **1** and **2** at 60 MHz (shown in part).

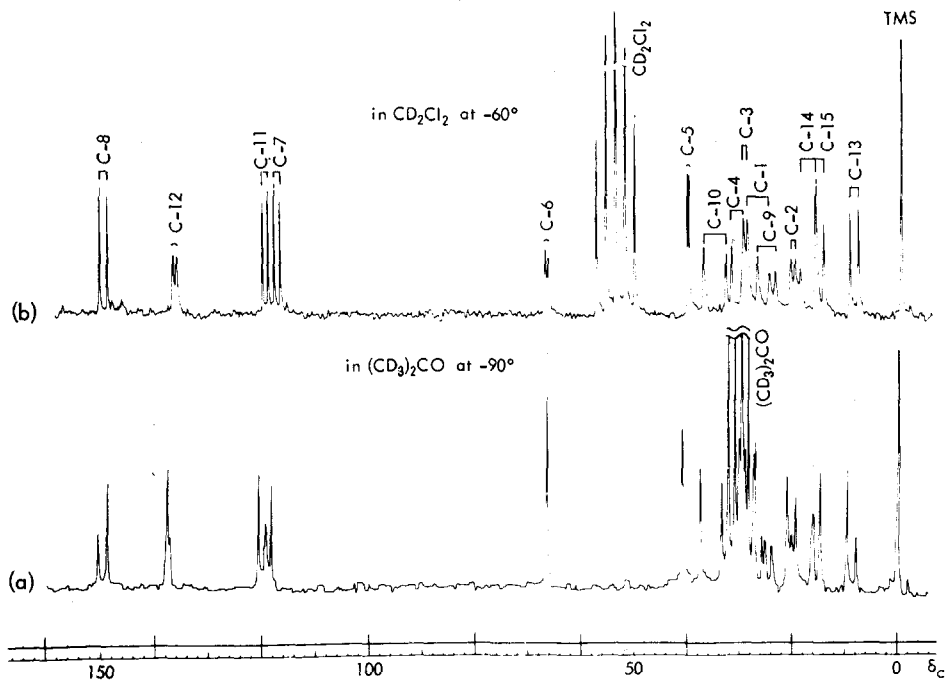


FIG. 2. Low-temperature ^{13}C FT NMR spectra of ligularol (**1**) at 15.087 MHz.

TABLE. Carbon-13 Chemical Shifts, δ_C , of Compounds Examined^a

Carbon No.	Ligularol (1)		6-Epilgularol (2)		Furaoeremophilane (3)			
	CDCl ₃ 30°	CD ₂ Cl ₂ 34° -60° ^b	(CD ₃) ₂ CO 34° -97° ^c	CDCl ₃ 30° ^d	CD ₂ Cl ₂ 30° -80° ^e	CDCl ₃ 30°	CD ₂ Cl ₂ 30° ^g	(CD ₃) ₂ CO 30° ^g
1	27.2 ^h	29.3 ^h (25.1)	28.1 ^h	29.5 ^h [16]	29.7 ^h	29.7	30.0	30.2
2	20.4	20.3	21.2	21.3	21.6	20.9	21.3	21.5
3	29.7 ^h	29.9 ^h (21.0)	30.2 ^h	31.7 ^h [11]	32.0 ^h	29.7	30.0	30.2
4	31.1	32.3 (29.3)	31.9	34.2 [18]	34.5	36.2	36.4	36.8
5	40.7	40.4 (29.9)	41.5	40.5 [23]	40.8	35.9	36.2	36.4
6	68.0	67.2 (40.6)	67.4	75.2 [31]	73.6	28.9	29.3	29.5
7	118.6	118.9 (67.7)	119.8	118.7 [65]	119.3	115.4	115.8	116.0
8	150.9	151.6 (117.8)	150.6	149.8 [32]	150.3	148.8	149.1	149.1
9	25.7	27.3 (150.2)	26.5	26.9 [19]	27.1	26.9	27.2	27.3
10	35.5	33.3 (23.9)	36.4	37.0 [15]	37.3	36.6	36.9	37.2
11	119.9	120.1 (37.7)	121.0	119.7 [18]	120.4	119.9	120.3	120.3
12	137.9	137.3 (121.1)	138.3	137.8 [18]	138.2	137.0	137.3	137.8
13	8.4	8.1 (138.0)	8.7	8.5 [9]	8.6	8.1	8.2	8.1
14	15.3	16.2 (8.0)	15.5	17.7 [8]	17.7	15.2	15.3	15.4
15	17.4	16.2 (14.8)	18.0	23.0 [13]	23.2	23.9	24.1	24.2
		19.7 (16.6) ^f		23.0 [17]	25.4			

^a ¹³C NMR spectra were recorded on a Varian NV-14 FT NMR spectrometer at 15.087 MHz using TMS as an internal reference (δ_C 0). FT measurement conditions were: spectral width, 3923 Hz; pulse flipping angle, ca. 16°; acquisition time, 0.6 sec; number of data points, 4820. ^b Values in parentheses are for the minor conformer A (ratio, 1.3:1). ^c Values in parentheses are for the minor conformer B (ratio, 2.3:1). ^d Values in square brackets are for LIS (in ppm) obtained from the shift curves. ^e The minor conformer was not detected. ^f Values in parentheses are for the minor conformer B (ratio, 3.2:1). ^g Slow inversion was not observed down to -100°. ^{h-j} Assignments may be reversed. ^k Not assignable.

concentration did not affect the isomer ratios both in 1 and 2.

Variable-temperature NMR spectra of both compounds were further examined in less polar solvents (see the TABLE). The ^{13}C NMR spectrum of 1 in CD_2Cl_2 at -70° surprisingly showed that "steroid-like" conformer B is the major one in a ratio of 1.3:1 at a high concentration (200 mg/cm^3) (FIG. 2b). However, the ratio of the "non-steroid-like" conformer was increased by diluting the solution (100 mg/cm^3). In ^1H NMR in $\text{CS}_2\text{-CDCl}_3$ (2:1) (30 mg/cm^3), the "non-steroid-like" conformer was also more abundant in a ratio of 1.3:1. On the other hand, 2 was found to predominantly adopt the "non-steroid-like" conformation in these solvents, because signals corresponding to the minor conformer were not observed below -60° (see the TABLE).

These observations suggest that in both 1 and 2, intermolecular hydrogen bonding between solute molecules plays a significant role in determining the equilibrium ratios between the two conformers. The preferred conformer B of 1 having a quasi-axial-OH in CD_2Cl_2 as well as $\text{CS}_2\text{-CDCl}_3$ could be intermolecularly hydrogen-bonded with other solute molecules in the same conformations more easily than the minor conformer A having a quasi-equatorial-OH.³ However, in acetone- d_6 , 1 should be preferably hydrogen-bonded with a smaller acetone molecule in conformation A. On the other hand, the predominant conformer A of 2 in CD_2Cl_2 or $\text{CS}_2\text{-CDCl}_3$ may be very stable and not influenced by the concentration. However, in acetone, only a small population of the "steroid-like" conformer having a quasi-equatorial-OH was found, probably due to its strong hydrogen bonding to the solvent molecules. An attempt to find which conformer is preferred for furanoeremophilane (3) using variable-temperature ^{13}C NMR down to -100° was not successful, because the ΔG^\ddagger value is much smaller for 3 (see the TABLE).

The ^{13}C signals were assigned in CDCl_3 using known chemical shift rules, several ^1H decoupling techniques,⁴ and chemical-shift comparisons from compound to compound. Lanthanoid-induced shifts (LIS) for 2 obtained from shift curves using $\text{Yb}(\text{fod})_3$ were particularly useful for this purpose (see the TABLE). The chemical shifts assessed for the conformers at low temperatures agree with their stereochemical relationships.

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