

CONFORMATIONAL ISOMERS OF LIGULAROL ACETATE AND LIGULARONE,
NATURALLY OCCURRING cis-DECALIN DERIVATIVES

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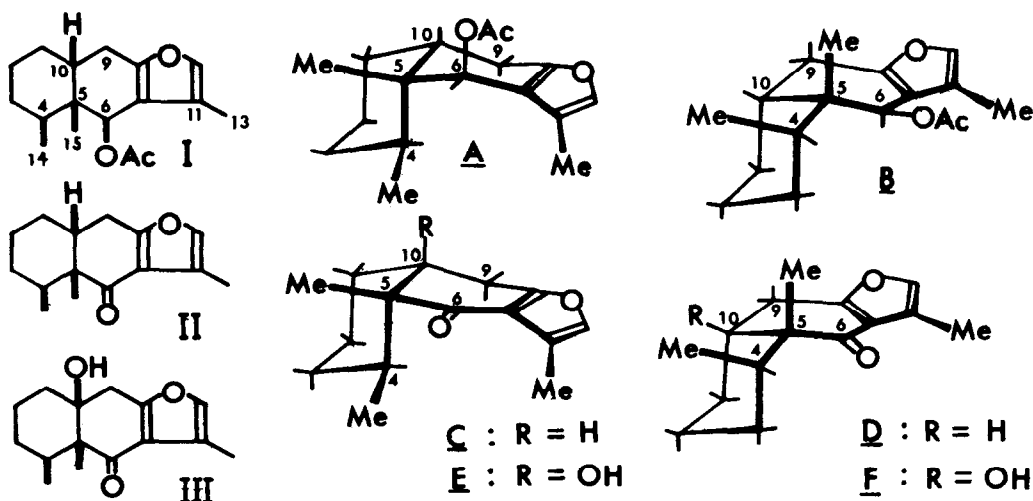
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In the course of the structure investigation of furanoeremophilane derivatives, we have found that the ^1H NMR spectrum of ligularol acetate (I)¹⁾ as well as that of ligularone (II)¹⁾ in CS_2 shows two sets of proton signals each corresponding to one conformational isomer below -50° . Eremophilane is a naturally occurring cis-decalin derivative; cis-decalin can exist in two alternative chair-chair conformations, commonly termed as the "steroid-like" and the "non-steroid-like" conformations. However, naturally occurring cis-decalin derivatives have generally been described so far to adopt a single preferred conformation except for a few cases.²⁾ We report here ^1H NMR and CD spectroscopic evidences that I and II exist in solution equilibrating between the "non-steroid-like" and the "steroid-like" conformations.

The ^1H NMR spectrum of I at room temperature shows one set of relatively sharp signals (Fig. 1a). As the temperature was lowered, the signals broadened (Figs. 1b and 1c); at below -60° , two sets of relatively sharp signals appeared in a ratio of 2 : 1. The signals were assigned by double-resonance experiments at -70° , as shown in Fig. 1d. The signals assigned to $6\alpha\text{-H}_B$ and $6\alpha\text{-H}_A$ were observed at δ 6.21 (broad singlet, $W_{1/2} = 5$ Hz) and δ 5.66 (singlet, $W_{1/2} = 2$ Hz) respectively. On irradiation of the broad singlet at δ 6.21, a broad signal pattern around δ 2.76 ($9\beta\text{-H}_B$) collapsed into a double-doublet ($|J| = 6.5$ and 17.0 Hz); no significant change was observed for a signal pattern around δ 2.08 ($9\alpha\text{-H}_B$). Irradiation at δ 2.76 changed the broad singlet due to $6\alpha\text{-H}_B$ into a sharper singlet ($W_{1/2} = 3$ Hz). The presence of the stronger long-range

coupling in $6\alpha\text{-H}_B$ than in $6\alpha\text{-H}_A$ as well as that of the J-values between $9\beta\text{-H}_B$ and $10\beta\text{-H}_B$ (6.5 Hz) and between $9\alpha\text{-H}_B$ and $10\beta\text{-H}_B$ (<1 Hz) implies that these signals (at δ 6.21 and δ 2.76) are due to $6\alpha(\text{axial})\text{-H}_B$ and $9\beta(\text{axial})\text{-H}_B$, as suggested by a Dreiding model examination.³⁾ Thus, the predominant conformer of I was determined to have the "non-steroid-like" conformation (B). The equilibrium constant (B/A) and the Gibbs' free energy difference at 28° for I were estimated to be 1.6 and 0.3 kcal/mole, respectively, from the chemical shifts of $6\alpha\text{-H}$ at 28° and -70° (for A and B).⁴⁾

The spectra of II in CS_2 and $10\beta\text{-hydroxyligularone}$ (III)⁵⁾ in a mixture of CS_2 and CDCl_3 (3 : 1)⁶⁾ were then examined at various temperatures. At room temperature, the spectra of both compounds showed one set of signals, but as the temperature was lowered, a set of signals for II broadened, and at -63° the signals were clearly separated into two sets of signals in a ratio of about 1 : 4 (Fig. 1f), while the signals of III showed no significant changes down to -60° .⁷⁾ As shown in Fig. 1, the signals due to $9\alpha\text{-H}$ and $9\beta\text{-H}$ of the major conformer of II appear as an AB-type quartet further split into doublets at δ 2.45 ($|J| = 17.5$ and < 1 Hz) and δ 3.10 ($|J| = 17.5$ and 6.0 Hz), respectively, whereas those due to $9\alpha\text{-H}$ and $9\beta\text{-H}$ of the minor conformer appear as more broadened signals. These J-values indicate that the major and minor conformations may be assigned to D and C, as suggested by a molecular-model examination. The CD spectra of II in



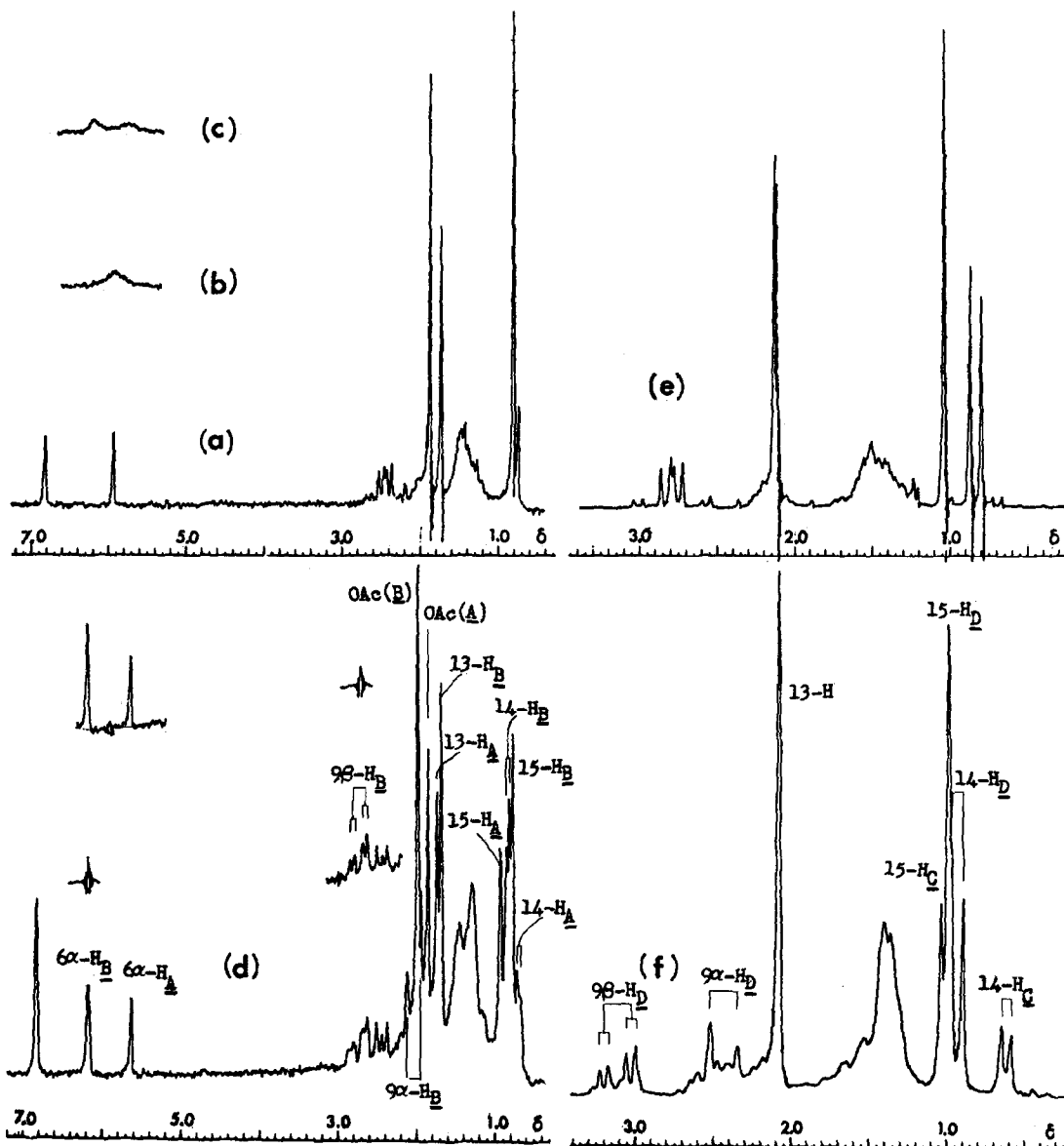


Fig. 1. Variable-temperature ^1H n.m.r. spectra of ligularol acetate (I) and ligularone (II) in CS_2 at 100 MHz. Ligularol acetate : (a) 28° , (b) -40° (only for $6\alpha\text{-H}$), (c) -50° (only for $6\alpha\text{-H}$), (d) -70° ; ligularone : (e) 28° , (f) -63° .

E.P.A. showed a positive $n \rightarrow \pi^*$ Cotton effect curve whose $[\theta]_{\max}$ value increased as the temperature was lowered,⁸⁾ indicating the predominance of the conformer II_B at lower temperature. Thus, the predominant conformer of II can be concluded to adopt the "non-steroid-like" conformation (D).⁹⁾ The equilibrium constant ($\underline{D}/\underline{C}$) and the Gibbs' free energy difference at 28° for II were estimated to be 2.2 and 0.5 kcal/mole, respectively, from the chemical shifts of 4 β -Me at 28° (δ 0.84) and at -63° [δ 0.62 (C) and 0.94 (D)].⁴⁾

The CD spectra of III in E.P.A. showed a negative $n \rightarrow \pi^*$ Cotton effect curve with increase of its $|[\theta]_{\max}|$ value when the temperature was lowered.¹⁰⁾ The preferred conformation of III is considered to be a "steroid-like" conformation⁷⁾ when compared with the CD spectral data of 2-acetoxy-5 β -spirost-2-en-1-one¹¹⁾ showing a negative $n \rightarrow \pi^*$ Cotton effect curve.¹²⁾

In conclusion, we have firstly found the equilibrium between "steroid-like" and "non-steroid-like" conformations in eremophilane derivatives, naturally occurring cis-decalins, on ¹H NMR time scale at room temperature.

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3. Cf. S. Sternhell, *Pure Appl. Chem.*, 14, 15 (1964).
4. These results could hardly be explained by a simple conformational analysis. Further studies will be discussed later.
5. M. Tada, Y. Tanahashi, Y. Moriyama and T. Takahashi, *Tetrahedron Lett.*, 1972, 5255.
6. Crystals precipitated from CS₂ solution of III at low temperature.
7. A simple conformational analysis (based on the Gibbs' free energy difference for II) suggested that the equilibrium constant ($\underline{E}/\underline{F}$) for III at 28° in CS₂ is > 20.
8. $[\theta]_{327.5} +610$ at +24.5° ; $[\theta]_{327} +2650$ at -190°.
9. Solvents used for ¹H NMR and CD spectral measurements are different. This may cause some or drastic change for a preferred conformation. However, the latter was not the case for II as is seen in the present text.
10. $[\theta]_{327.5} -910$, $[\theta]_{314.5} -940$ at +24.5° ; $[\theta]_{326} -2960$, $[\theta]_{313.5} -2890$ at -190°.
11. Private communication from Dr. K. Kuriyama.
12. A full detail of CD experiments will be discussed elsewhere.