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TEMPERATURE DEPENDENT PROTON MAGNETIC RESONANCE TO CHARACTERIZE STEREOISOMER OF DITERPENE.*

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In stereoisomeric substances having complex structures, subtle differences in ring interconversion and bond rotation of substituents are present. These differences are strongly susceptible to temperature variation and can be expected to give characteristic PMR pattern for each stereoisomer.

Illustration of the above suggestion was provided by the study of the stereoisomers (I)-(VI)(disregarding absolute structure) of tricyclic C_{10}-methyl and C_{10}-nor-methyl diterpenes with aromatic C-ring, the most basic skeleton of diterpenoids. There are two advantages which dictated the choice of these compounds for our purposes. Firstly, study of their conformations and assignment of the chemical shifts of C_4- and C_{10}-methyl groups have been already carried out in our[1] and other laboratories.[2] The second advantage is that a slight conformational drift resulting from temperature variation can be easily detected from the chemical shift changes of C_4-, C_{10}-methyl and C_4-carbomethoxyl groups, which are associated with the changes of anisotropic effects from aromatic C-ring and carbomethoxyl carbonyl group.

The problem of the four basic C_{10}-methyl isomers (I-IV) due to three asymmetric centers at C_4, C_5 and C_{10} was examined firstly. The chemical shift of (I)(eq.COOMe) and (II)(ax.COOMe) having <u>trans</u>-A/B-ring fusion is almost indifferent to temperature

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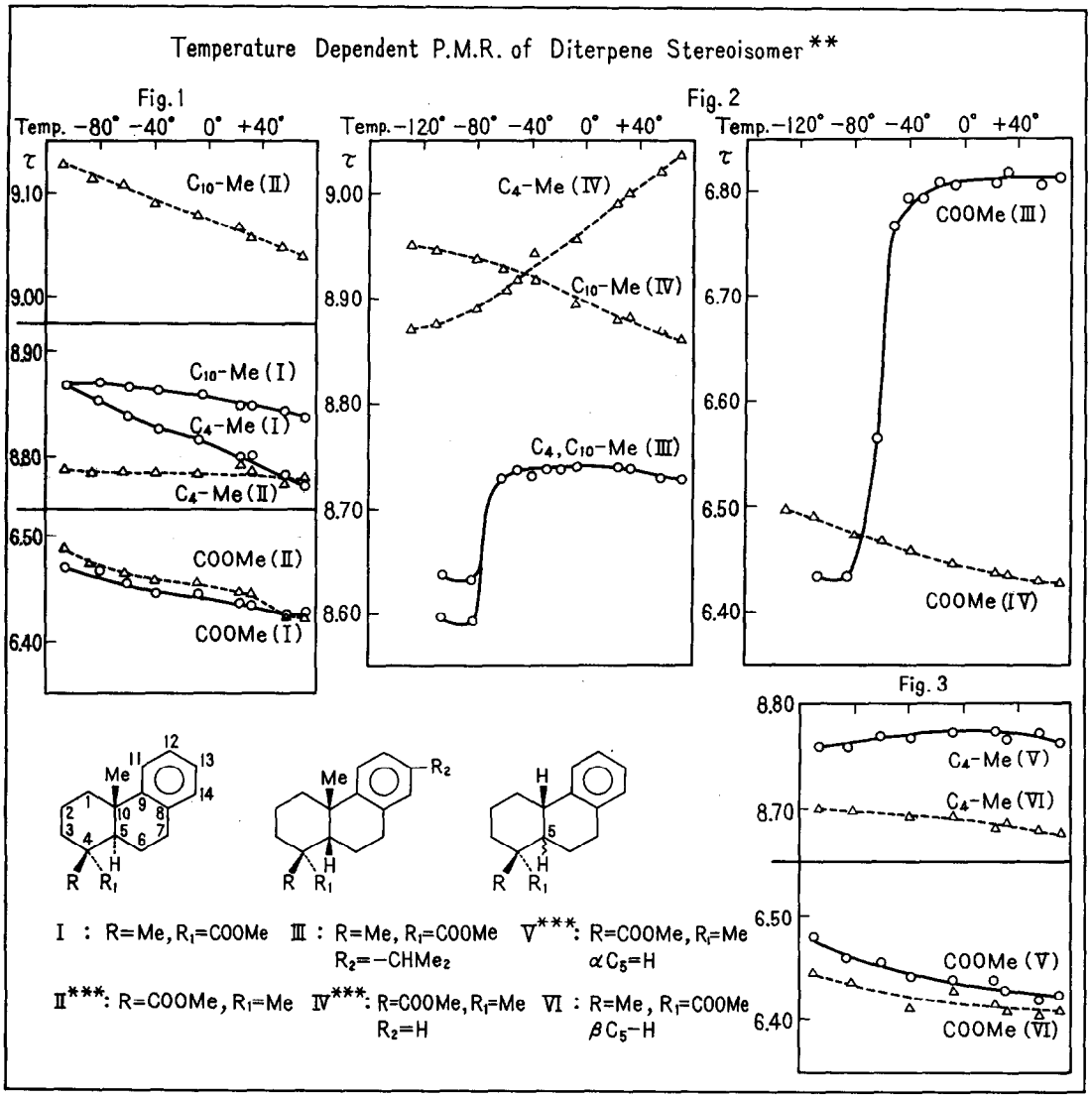

** In the Fig. 1 to 3, these chemical shifts were plotted as a function of temperature. All the spectra were recorded by JEOL's JNM-4H-100 spectrometer equipped with JEOL' JES-VT-3 variable temperature control. Calibrations of temperature disparity between the sample and the variable temperature control were measured by thermocouple in the NMR tube filled with silicone oil. The temperature reproducibility is within ±0.5°C at any sample temperature. The magnetic field was locked with the one sample NMR control. The chemical shifts were directly expressed in Herz from TMS internal reference by mean of an electronic counter and carbon disulfide served as the solvent (6-8%w/v solution except (III)(4.8%w/v)).

*** These compounds were actually used an antipode of the absolute structural formular as shown.

with the exception of notable motion in C_4-methyl group of (I)(9.4Hz higher in 71° ⟶ -106.5°) and in C_{10}-methyl group of (II)(8.7Hz higher in 71°⟶-106.5°)(Fig. 1). The observation can be explained by a consideration of preferred rotatory conformation of C_4-carbomethoxyl bond.[3] The bond rotation of C_4-carbomethoxyl group of (II) is already more restricted by its steric hinderance than that of (I) and, consequently, less spatial change depending on temperature in the carbomethoxyl bond rotation of (II) is expected in comparison with that of (I). Therefore, a drift of anisotropic contribution to C_4-methyl group by C_4-carbomethoxyl carbonyl group of (I) is more obvious than that of (II). However, C_{10}-methyl group of (II) is nearly located to the carbonyl plane of C_4-carbomethoxyl group, so that the temperature change sufficiently affected to C_{10}-methyl chemical shift.

Considering a preferred steroid type conformation for cis-A/B-fused ring of the isomeric ester (III)(ax.COOMe) and (IV)(eq.COOMe), both carbomethoxyl methyl group of (III) and C_4-methyl group of (IV) are nearly located on the plane of the benzene ring. The remarkable and abrupt temperature dependent variation (36Hz lower in -40° ⟶ -84.5°)(Fig. 2) of carbomethoxyl methyl group of (III) can be understood from molecular models. Namely, free rotation is abruptly frozen below ca.-40° in the most stable conformation, in which the carbomethoxyl carbonyl double bond is piled in parallel with the plane of benzene ring and is in antiposition to C_4-methyl group. Accordingly, the carbomethoxyl methyl group is out of the benzene plane and, thus, diamagnetic effect of benzene ring on the methyl group is rapidly decreased. Since the preferred conformational model shows that C_4- and C_{10}-methyl groups are situated in paramagnetic field cumulatively affected by both the benzene ring and the carbonyl group, the methyl groups can be considered to be more strongly affected (10.3 and 14.4Hz lower due to C_4- or C_{10}-methyl in -51°⟶-84.5°) at temperature, at which the ester group is contented with the preferred confonformation. On the other hand, chemical shift variations of C_4-methyl (16Hz lower in 71°⟶-128.5°) and C_{10}-methyl group (8.9Hz higher in 71°⟶-128.5°) of (IV) are noticeable (Fig. 2). Preferred conformation (steroid type) of (IV) shows that C_4-methyl group is oriented in front of the benzene ring as the ester group in (III). However, the chemical shift change of C_4- and C_{10}-methyl group can not be explained only by bond rotation, so that the phenomenon arises most likely from perturbation of the benzene ring plane along with conformational change in B-ring (half boat$\overset{1}{\longrightarrow}$half chair conformation). It is

consistent with a consideration that stronger paramagnetic effect to C_4-methyl and diamagnetic effect to C_{10}-methyl group are coincidently affected at lower temperature. Also the above assumption is supported by the fact that the shape of allylic C_7-methylene protons of (IV) is varied with temperature change.

Finally, analytical result of C_{10}-nor-methyl diterpene (V and VI) will be described. C_4-Methyl chemical shift of (V)(trans-A/B-ring fusion, ax.COOMe) is affected from the sterically hindered ester. Thus, its temperature dependent variation can not be practically detected (Fig. 3) as the variation of the corresponding C_{10}-methyl compound (II), even though a hydrogen is substituted at C_{10} in (V) instead of the more bulky methyl group in (II). In our previous work[1], preferred conformation of (VI)(cis-A/B-ring fusion, eq.COOMe) was evidently proved to be not steroid type, but non-steroid type conformation. Consequently, it can be expected that temperature dependent spectrum of (VI) is entirely different (Fig. 3) from that of the C_{10}-methyl compound (III) having steroid type conformation. The carbomethoxyl methyl group of (VI) is located in far from the benzene ring plane, that is because the chemical shift remains unchanged contrary to the dramatic variation of the similar methyl group of (III).

Conclusively, the application of the temperature dependent PMR analysis obviously embosses the differences from the respective isomeric structure.**** For expatiation of the method for the general structural elucidation, the work is now in progress.

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References

1) A.Tahara, K.Hirao, Y.Hamazaki, Tetrahedron 21, 2133(1965); A.Tahara, K.Hirao, Chem. Comm. 1967, 326.

2) J.C.W.Chien, J. Am. Chem. Soc. 82, 4762(1960); E.Wenkert, A.Afonso, P.Beak, R.W.J.Carney, P.W.Jeffs, J.D.McChesney, J. Org. Chem. 30, 713(1965).

3) cf. C.R.Narayanan, N.R.Bhadane, Tetrahedron Letters 1968, 1565.

**** PMR analyses of characterized spectral figures due to 7-oxo derivatives of (III), (IV), (V) and (VI) are also consistently understood, these data will be opened in detail in the near future.