Chem. Pharm. Bull. 18(11)2169—2175(1970)

UDC 547.597.02.03

Diterpenoids. XV. Conformational Studies. III.[1,3] Temperature Dependent Proton Magnetic Resonance Spectra of Ring C Aromatic Tricyclic Diterpene

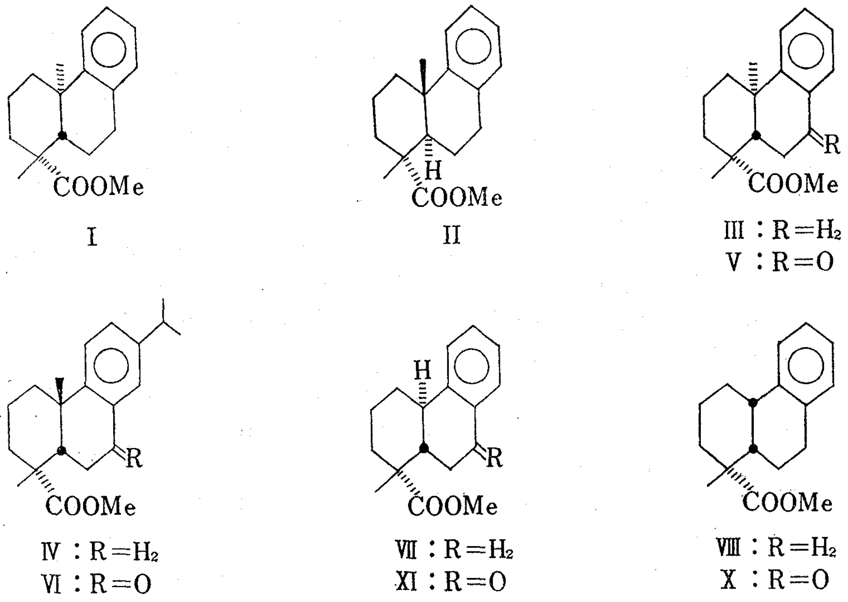
KEN-ICHI HIRAO, SATORU MITSUBAYASHI, JUN UZAWA,
AKIRA TAHARA,[2a] NORIKO MITOMO
and SHOICHI HAYASHI[2b]

The Institute of Physical and Chemical Research[2a] *and*
Japan Electron Optics Laboratory Co., Ltd.[2b]

(Received February 25, 1970)

Temperature dependent proton magnetic resonance studies of four basic ring C aromatic tricyclic diterpenes (I, II, III and IV) are discussed and shown to be able to characterize each stereoisomers. This method is also applied to the analysis of 7-oxo and 20-nor derivatives.

In our previous papers,[1,4] the conformational study of tricyclic C ring aromatic diterpenes has been investigated by the analysis of proton magnetic resonance (PMR) spectra and revealed that the skeleton of this system is not so rigid as expected, but is strongly affected by the nature of 4-, 5-, 6- and 10-substituents and their configuration. On account of this fact, it is expected that the temperature variation reflect the subtle reorientation of the hydrophenanthrene skeleton and the bond rotation of substituents, and that these delicate conformational changes are anticipated to influence the chemical shifts of C_4- and C_{10}- methyl



I

II

III : R=H_2
V : R=O

IV : R=H_2
VI : R=O

VII : R=H_2
XI : R=O

VIII : R=H_2
X : R=O

Chart 1

---

[1] Diterpenoids. XIV. Conformational Studies II: A. Tahara and K. Hirao, *Chem. Pharm. Bull.* (Tokyo), **18**, 1960 (1970).

[2] Location: *a*) *Yamato-machi, Kita-adachi-gun, Saitama*; *b*) *Akishima, Tokyo.*

[3] A preliminary report has appeared: K. Hirao, S. Mitsubayashi, J. Uzawa, A. Tahara, N. Mitomo and S. Hayashi, *Tetrahedron Letters*, **1969**, 29.

[4] *a*) A. Tahara and K. Hirao, *Chem. Pharm Bull.* (Tokyo), **15**, 1145 (1967); *b*) *Idem, Chem. Commun.*, **1967**, 326.

and C_4-carbomethoxy groups. If this is the case, tracing the chemical shifts of these methyl groups with temperature variation should provide their own peculiar patterns having the possibility to characterize their stereochemistry.

The purpose of the present communication is to detail our initial work[3] concerning the temperature dependent chemical shift changes of methyl groups in tricyclic diterpenes for identification of their stereochemistry. Excepting absolute configuration, there are four types of stereoisomers (I—IV) originated from the three asymmetric centers (C_4, C_5 and C_{10}). The two main advantages claimed for this class of compounds have been considered for our present studies. (1) The consideration of their conformation and assignment of the chemical shifts of C_4- and C_{10}-methyl and C_4-carbomethoxy methyl groups have been already done in our[4,5] and other laboratories.[6] (2) A slight conformational drift with temperature variation is expected to cause the chemical shift changes of the attended methyl group. And these changes are associated with the stereochemical alterations from aromatic C ring and carbomethoxy carbonyl group having anisotropic effect.

Experimental

The chemical materials used in the present study have prepared in accordance with the methods already reported in earlier papers. All spectra were recorded by JEOL's JNM-4H-100 spectrometer equipped with JEOL's JES-VT-3 variable temperature controller. Calibrations of temperature disparity between the sample and the variable temperature controller were measured by the thermocouple in the PMR tube filled with silicone oil. The reproducibility of temperature is within ±0.5° at any temperature. The magnetic field was locked with one sample PMR control. The chemical shifts were directly expressed in Herz from TMS internal reference by means of an electronic counter and carbon disulfide served as the solvent (6—8% W/V solution except (IV) (4.8% W/V)).

Result and Discussion

The problem of the four basic C_{10}-methyl isomers (I—IV) will be examined firstly. The chemical shift of attended methyl groups of I (axial (ax.) COOMe) and II (equatorial(eq.) COOMe) having *trans*-A/B ring juncture is virtually indifferent to temperature with the exception of notable motion of C_{10}-methyl group in I (8.7 Hz higer in 71→—106.5°) and of C_4-methyl group in II (9.4 Hz higher in 71→—106.5°) (Table I and Fig. 1).

Considering the preferred rotational conformer of carbomethoxy group,[7] the observation can be understood as follows. As the ax. COOMe group in I is restricted considerably by the steric interaction from angular methyl, C_2- and C_6-protons, anisotropic effect of carbomethoxy carbonyl to C_4-methyl group is essentially immutable with temperature variation. However, the chemical shift of the other C_{10}-methyl group should be strongly affected to be into high field, though a drift of carbomethoxy carbonyl to the plane passing through C_2, C_{10} and angular carbone occurs very slightly regardless of temperature variation.

On the other hand, since the relatively unrestricted eq. COOMe in II is expected to change its spatial orientation more than the ax. COOMe in I, temperature change sufficiently affects to the rotation of ester group and consequently to C_4-methyl chemical shift. Therefore, at lower temperature the population of the most stable conformer, in which carbomethoxy carbonyl nearly eclipses the C_4-axial bond and keep the C_4-methyl group in positive region of carbonyl group,[8] increases. This consideration ensures the respective assignment of C_4-

---

5) A. Tahara and K. Hirao, *Chem. Pharm. Bull.* (Tokyo), **12**, 1121 (1964); A. Tahara, K. Hirao and Y. Hamazaki, *Tetrahedron*, **21**, 2133 (1965).

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

7) *cf.* C.R. Narayanan and N.R. Bhadane, *Tetrahedron Letters*, **1968**, 1565.

8) G.R. Karabatsos, G.C. Sonnichien, N. Hsi and D.J. Fenoglio, *J. Am. Chem. Soc.*, **89**, 5067 (1967).

Table I. Temperature Dependent PMR (τ) of I and II

Comp.	Me °C	71	32	−38.5	−84.5	−106.5
I	C_4-Me	8.780	8.788	8.785	8.784	8.786
	C_{10}-Me	9.040	9.057	9.088	9.114	9.127
	COOMe	6.425	6.445	6.458	6.473	6.485
II	C_4-Me	8.773	8.802	8.826	8.854	8.867
	C_{10}-Me	8.838	8.849	8.862	8.870	8.867
	COOMe	6.426	6.437	6.446	6.468	6.472

Table II. Temperature Dependent PMR (τ) of III and IV

	Me °C	71	32	−38.5	−51	−61.5	−81	−106.5
III	C_4-Me	9.030	9.000	8.934	8.916	8.906	8.889	8.874
	C_{10}-Me	8.860	8.879	8.916	8.916	8.925	8.936	8.943
	COOMe	6.428	6.436	6.458	6.450	6.468	6.473	6.490
	Me °C	71	32	−38.5	−51	−62.5	−84.5	−106.5
IV	C_4, C_{10}-Me	8.726	8.737	8.730	8.736	(8.729)	8.592 —	8.598 —
	COOMe	6.812	6.816	6.794	6.767	(6.565)	6.434	6.435 7.355

Table III. Temperature Dependent PMR (τ) of V and VI

Comp.	Me °C	76	38	−11	−44	−70	−85
V	C_4-Me	9.377	9.406	9.446	9.486	9.539	9.538
	C_{10}-Me	8.710	8.706	8.706	8.705	8.686	8.700
	COOMe	6.404	6.408	6.416	6.420	6.418	6.437
VI	C_4, C_{10}-Me	8.736	8.744	8.745	8.748	8.750	8.752
	COOMe	7.176	7.203	7.226	7.250	7.268	7.283

Table IV. Temperature Dependent PMR (τ) of VII and VIII

Comp.	Me °C	71	32	−38.5	−84.5	−106.5
VII	C_4-Me	8.765	8.769	8.768	8.757	8.760
	COOMe	6.422	6.428	6.440	6.459	6.479
VIII	C_4-Me	8.676	8.686	8.693	8.699	8.700
	COOMe	6.409	6.407	6.410	6.435	6.445

Table V. Temperature Dependent PMR (τ) of IX and X

Comp.	Me °C	76	38	−44	−70	−85
IX	C_4-Me	8.749	8.754	8.760	8.769	8.779
	COOMe	6.374	6.383	6.395	6.414	6.428
X	C_4-Me	8.634	8.644	8.652	8.653	8.659
	COOMe	6.372	6.380	6.403	6.410	6.427

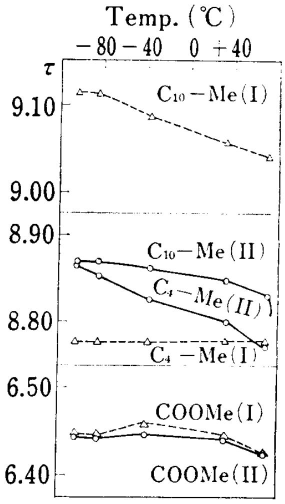


Fig.1

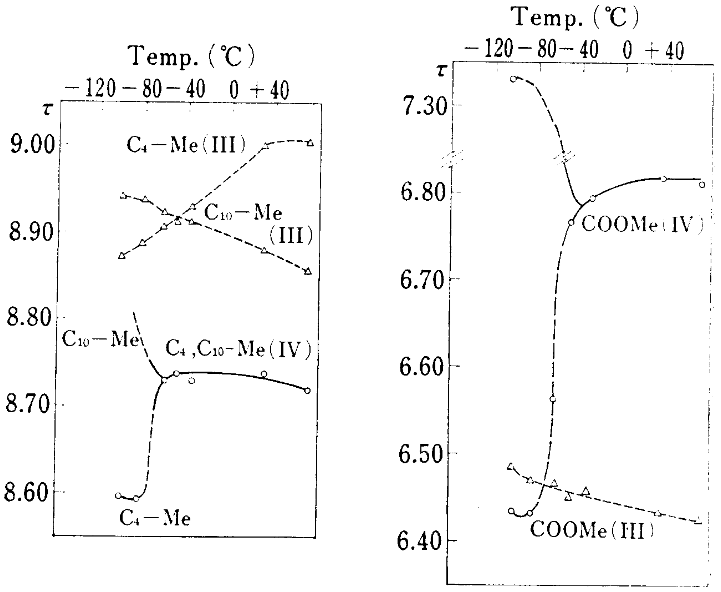


Fig.2

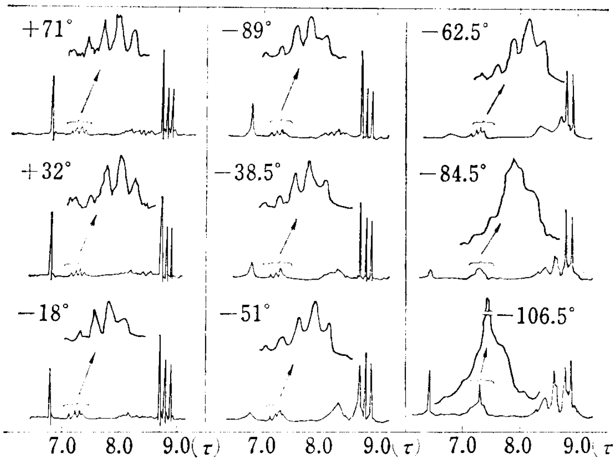


Fig. 4. Temperature Dependent PMR Spectra of Compound (IV)

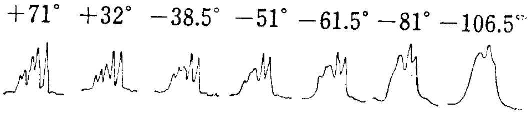


Fig. 3. Temperature Dependent C_2-Methylene Proton in Compound (III)

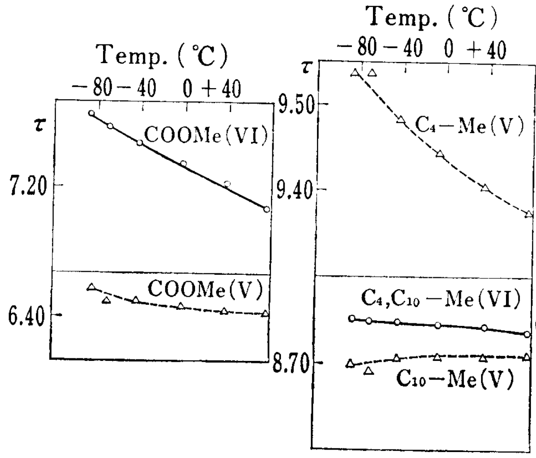


Fig. 5

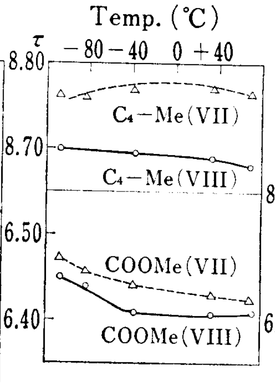


Fig. 6

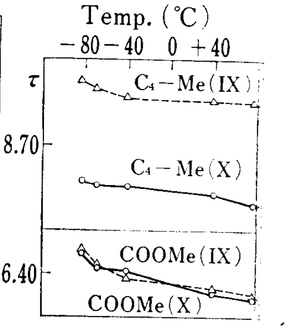


Fig. 7

and C_{10}-methyl signals in methyl dehydroabietate.[9]

Contrary to the A/B-*trans* system, the chemical shift change of methyl groups of A/B-*cis* compounds is more remarkable (Table II and Fig. 2). Before the discussions, it should be recalled that the preferred conformation of III and IV is steroid type and consequently C_4-methyl in III and carbomethoxy group in IV are situated under the concave of the molecule.[1,3,4b,6b] In the case of III, the noticeable variations of C_4-methyl (15.6 Hz lower in 71→−106.5°) and C_{10}-methyl group (8.3 Hz higher in 71→−106.5°) are observed. These variation can be only explained by the alteration of the anisotropic effect from benzene ring which is reflected by a conformational changes of B ring. If this is indeed the case, downfield shift of C_4-methyl and highfield shift of C_{10}-methyl group are reasonable. According to the previous consideration,[3,4b,6b] the half boat conformation of B ring predominates over the half chair conformation at ordinal temperature and C_4-methyl group is highly shielded. The ratio of half chair conformation slightly increases at lower temperature, so that C_4-methyl group in this conformation gets free from the strong shielding zone of the benzene ring. However, the degree of paramagnetic shift is not considered to be enough as expected, thus it can be assumed that the chemical shift of C_4-methyl group in fact should be conversely affected by eq. COOMe just as discussed in the case of II, in which C_4-methyl group shifts to highfield at lower temperature. Diamagnetic shift of C_{10}-methyl group at lower temperature is also understood by the perturbation of benzene ring along with the reorientation of B ring. The described assumption of the conformational change of B ring in III is consistent with the fact that the pattern of C_7-methylene protons in III is only varied with temperature variation among the examined four stereoisomers I, II, III and IV. Fig. 3 shows the shape of C_7-methylene in III at various temperature.

Behavior of the methyl group in IV is more complicated. From Table II and Fig. 4 notable change of carbomethoxy methyl and tertiary methyl signals is observed below −38.5°. The explanation for these demeanor can not be due to only the reorientation of B ring as in the case of III, since the shape of C_7-methylene in IV is almost indifferent to temperature variation, though the spectra around C_7-methylene are not clear due to the overlap of newly appeared carbomethoxy methyl signal below −84.5° (Fig. 4).

At first carbomethoxy methyl showing remarkable temperature variation in IV will be described. The intensity of the methyl signal gradually begins to decrease at −29→−38.5° and the signal is disappeared. Subsequently, the new two peaks due to carbomethoxy methyl separately appears in lower (6.565 τ) and higher field (7.355 τ) than its original region. The latter signal clearly comes out from the piled cloud of the C_7-methylene signal at −106.5°. These remarkable variation at lower temperature can be understood by the consideration of bond rotation between C_4 and carbonyl cabon. Considering the preferred steroid type conformation for IV,[3,4b] carbomethoxy group is put between A and C ring. Therefore, two following main conformations could be mentioned for carbomethoxy group (*viz.*) (a) carbomethoxy carbonyl double bond is nearly parallel to the plane of benzene nucleus being the carbonyl oxygen turned away from C_{10} and (b) carbonyl double bond is nearly parallel to the C_2–C_3 bond, in which carbonyl oxygen directs towards C_{10}. In the case of conformation (a), the absorption due to carbomethoxy methyl is expected to be at higher field than its customary position (6.3 τ) being situated in the diamagnetic field of benzene ring. On the other hand, methyl group is free from shielding zone of aromatic ring in the conformation (b). Thus, at higher temperature very rapid equilibrium between conformers (a) and (b) exists, and with lowering the temperature the life time to be kept in each conformation is prolonged

---

[9] Previous assignments of C_4- and C_{10}-methyl chemical shifts of compounds (II, XIX and XXI) (shown in ref. 4a) should be changed to those of C_{10}- and C_4-methyl respectively, though the conformational conclusion is not influenced.

and the signal turns obscure. Lastly the interconversion of one isomer into the other becomes slow enough to allow two separate signals corresponding to (a) and (b) to be obtained. According to the qualitative assumption comparing the relative height of two signals and the difference of chemical shifts from the peak of equilibrated methyl to each signal of methyl group in conformation (a) and (b), the conformer (b) is more densely populated than the conformer (a) at −106.5°. This fact is in good accordance to the anticipation from molecular models. Namely, the barrier hindering of internal rotation of C_4-ester bond originates in the interferance from C_7-methylene group to the carbomethoxy group.

Subsequently, C_4- and C_{10}-methyl in IV will be considered. As in the case of carbomethoxy methyl, these methyl signals also start to decrease at −38.5°, and substantially disappear at −62.5° and then are gradually observed in the low field. The conformational isomer (a) and (b) due to the rotation of ester group given in the above discussion can be essentially applicable for the explanation of C_4– and C_{10}-methyl variation. Accordingly, in the most preferred conformation (b) estimated above, both C_4- and C_{10}-methyl groups are located in the paramagnetic zone of carbomethoxy carbonyl[8] and strongly deshielded. On the other hand, another conformation (b) in which C_{10}-methyl peak is expected to shift into higher field by the anisotropy of ester group to the region of isopropyl protons. However, the spectrum is dimed by the absorption of isopropyl and methylenes, so that the more minutes consideration on this point should be deferred to further study.

As have been discussed on the temperature dependent PMR spectral characteristics of four basic C ring aromatic tricyclic diterpene I, II, III, and IV, it is revealed that methyl groups in these compounds are strongly susceptible to temperature and each stereoisomer has their own peculiar pattern of variation.

For further confirmation of the above assumption on A/B-*cis* system and for the study of the influence of C_7-carbonyl group to the chemical shift of C_4-methyl in III and to that of carbomethoxy methyl in IV, compounds (V and VI) were also examined (Table III and Fig. 5). At first the chemical shift change of C_4- and C_{10}-methyl group in V will be discussed. In contrast with the variation in III, the peak of C_4-methyl group in V shifts to higher at lower temperature (+16.1 Hz higher in 76→−85°) and C_{10}-methyl group is almost indifferent to temperature variation. It is reason for the above observation that the interaction between C_7-methylene and C_4-methyl in III is diminished by the introduction of carbonyl group to C_7 position, so that the equilibrium between B ring half boat and half chair conformation tends to drift to the latter conformation. In fact, when temperature lowers, the ratio of the latter conformation increases slightly and C_4-methyl should be arranged into diamagnetic field of C_7-carbonyl group. Furthermore, as stated above in the discussion of II and III, equatorial carbomethoxy carbonyl affects the signal due to C_4-methyl to drift into higher field. Since the drift of B ring is very small to temperature variation, the chemical shift of C_{10}-methyl remains to be unchanged. Then the consideration will be made about VI. As shown in Table III C_4- and C_{10}-methyl groups are indifferent to temperature change. On the other hand carbomethoxy methyl group is shielded at lower temperature (−10.7 Hz higher in 76→−85°). For the deficiency of C_7-proton in VI, the internal rotation of C_4-carbonyl carbon bond is less hindered than that of IV. So that rapid interconversion between (a) and (b) conformation (see the discussion of IV) occurs and the disappearance of methyl signals cannot be observed in the spectrum in the course of cooling. From molecular models it can be assumed that the conformers (a) and (b) essentially have the same stability but the population of (a) conformation having interaction between C_2-α hydrogen and ester group, barely decreases at lower temperature. In such a conformation of (b), carbomethoxy methyl is strongly shielded by C_7-carbonyl group. Thus, the explanation of the variation of methyl chemical shift in V and VI can be made analogoulsy to that of corresponding III and IV, even though their observed behaviors are different each other.

Finally, the spectrum of 20-nor diterpene derivatives VII, VIII, IX and X will be described. The chemical shift of C_4- and carbomethoxy methyl of these compounds does not change practically with temperature variation as shown in Table IV and V. These observations are attributed to the following effects. In the podocarpic acid-type system (A/B-*trans*, ax.-COOMe) of VII and IX, carbomethoxy group is heavily hindered by three 1,3-diaxial interactions from C_2-β, C_6-β and C_{10}-hydrogens (*cf.* discussion of I), so that C_4-methyl group in these compounds is insensitive to temperature change.

Considering the discussions concerning to compound III, IV, V and VI, it can be assumed that both VIII and X also show a remarkable change in their temperature dependent PMR spectra. However, as we have reported previously[1,4b)] that non-steroid type conformation of VIII and X prefers to steroid type conformation, the circumstances around C_4-methyl group in VIII and X molecule are closely analogous to those of II (Table IV and V). In the case of II, chemical shift of C_4-methyl shows high field shift at lower temperature but not in the case of VIII and X. This fact is consistent to the assumption from molecular models. Namely, it could be assumed that carbomethoxy carbonyl nearly eclipses the C_3–C_4 bond to be the most stable rotational conformation of VIII and X. The observed spectra of VIII and X which are practically indifferent to temperature denote the assigned conformation[1,4b)] to be correct.

Conclusively, the temperature dependent PMR spectra of stereoisomeric compounds examined in this paper revealed that inherent characteristics related to the nature of their own stereochemistry was observed and this method could be applicable for the characterization of stereoisomers having more complex structures.

Acknowledgement The authors are indebted to Dr. K. Kuriyama, Shionogi and Co., Ltd., Osaka, for his valuable discussion. Financial support from the Ministry of Education (Grant-in-Aid for Scientific Research, No. 75020 (1967) and 8745 (1968)) and Hōan-sha, are gratefully acknowledged.