[Chem. Pharm. Bull. 15(8)1145~1152(1967)]

UDC 547.597.02.04 : 543.422.25 : 541.63

143. Akira Tahara and Ken-ichi Hirao[*1]: Conformational Studies. I. Nuclear Magnetic Resonance Analysis on Conformation of 10β- and 10α-Oxy-*enantio*-deoxypodocarpic Acid Type Isomer.[*2]

(*Rikagaku Kenkyusho, The Institute of Physical and Chemical Research*)

The configuration and conformation of 10β- and 10α-*enantio*-deoxypodocarpic acid type isomer and the corresponding lactone were discussed by their NMR spectrum analysis. The analysis was performed especially on the ABX type proton system as observed between 9-methylene protons and 10-proton.

(Received July 7, 1966)

In the course of our investigation on the chemical transformation to diterpene alkaloid from abietic acid, an interesting, but quite unexpected isomerisation had been occurred under the condition of acidic lactonization.1) Namely, 10β-oxy-*enantio*-deoxypodocarpic acid (I) derived from abietic acid, was quantitatively converted to a lactone (Ⅱ) having 10α-oxy configuration, which was readily hydrolyzed to the isomeric 10α-oxy acid (Ⅲ).

In the same papers,1) syntheses of 10β-oxy and 10α-oxy isomer; the ester (Ⅳ) and (Ⅴ), and the alcohol (Ⅶ) and (Ⅷ), from the corresponding isomeric 10-oxy acid (I) and (Ⅲ), were also reported. Furthermore, 10β-15 and 10α-17 epoxy isomer; the acid (Ⅺ) and (Ⅻ), the alcohol (XⅢ) and (XIV), the amide (XV) and (XVI), and the nitrile (XⅦ) and (XⅧ), were respectively synthesized from the epoxy ester (Ⅸ) and (X) obtained by lead tetracetate oxidation of the corresponding isomeric 10-oxy ester (Ⅳ) and (Ⅴ). In addition to the chemical evidences, proof on the structure, especially on the configuration of C_{10}-O bond of the isomeric 10β- and 10α-oxy series, was undeniably afforded by the analysis on the chemical shifts of the methyl groups of these compounds.2)

For the purpose of an assumption of the conformation of the 10-oxy isomeric series, more accurate NMR examination on protons excepting methyl group is necessary and hence will be discussed herein.

In the many protons attached to these 10β- and 10α-oxy isomers, the protons at C_9 and C_{10} especially attacked our attention. In general, the ABX type proton system as observed on 9-methylene protons and 10-proton attached to the same carbon as hydroxy function, appeared often in many natural products, *e.g.* in steroid and terpenoid field, and also papers dealing with application of NMR analysis on this system were published by many chemists. However, in usual case of typical ABX system, the resonances due to AB protons lie within the bound of the methylene envelope and hence cannot be recoginized readily. Therefore, it is difficult to determine whether sum or good approximate value of these coupling constants (J_{AX} and J_{BX}) is stated from the observed resonances corresponding to X poroton. In

---

[*1] Shimo-niikura, Yamato-machi, Saitama-ken (田原 昭, 平尾健一).

[*2] All NMR spectra were measured at 60Mc by Varian Associates A-60 and Japan Electron Optics Lab. C-60 NMR spectrometer or at 100Mc by Varian Associates HR-100 NMR spectrometer. The compounds were examined in 5~10% $CDCl_3$ solution using Me_4Si as internal reference (Authors thank Dr. K. Takeda, Shionogi and Co., Ltd., Osaka, Prof. T. Okamoto, Univ. of Tokyo, Tokyo, and Dr. T. Hino, National Institute of Radiological Sciences, Chiba, for the NMR measurement.).

1) A. Tahara, K. Hirao: This Bulletin, **12**, 984 (1964); A. Tahara, K. Hirao, Y. Hamazaki: Tetrahedron, **21**, 2133 (1965).

2) A. Tahara, K. Hirao: This Bulletin, **12**, 1458 (1964).

contrast, AB type methylene protons at C_9 of our case resonate in distictly lower field than the usual methylene envelope by the influence of the benzene ring. For this reason, all splitted resonance pattern between 9-H_2 and 10-H (ABX type protons) of our compounds[*3] are completely observed and they could be readily analized. In addition to the analysis of the above ABX protons, the spin-spin interaction between 10(X-proton)- and 11-proton will be discussed for detailed elucidation of their conformation.

Consequently, the present study proceeded with an intention that the obtained result would assist in the structural elucidation of these type compounds. In the present paper, at the start, NMR analysis of these isomeric series will be exemplified by methyl 10β- (Ⅳ) and 10α-oxy-*enantio*-deoxypodocarpate (Ⅴ) in detail and succesively comparison between NMR pattern of their 10β- and 10α-isomeric derivatives will be described by the analogous analysis.

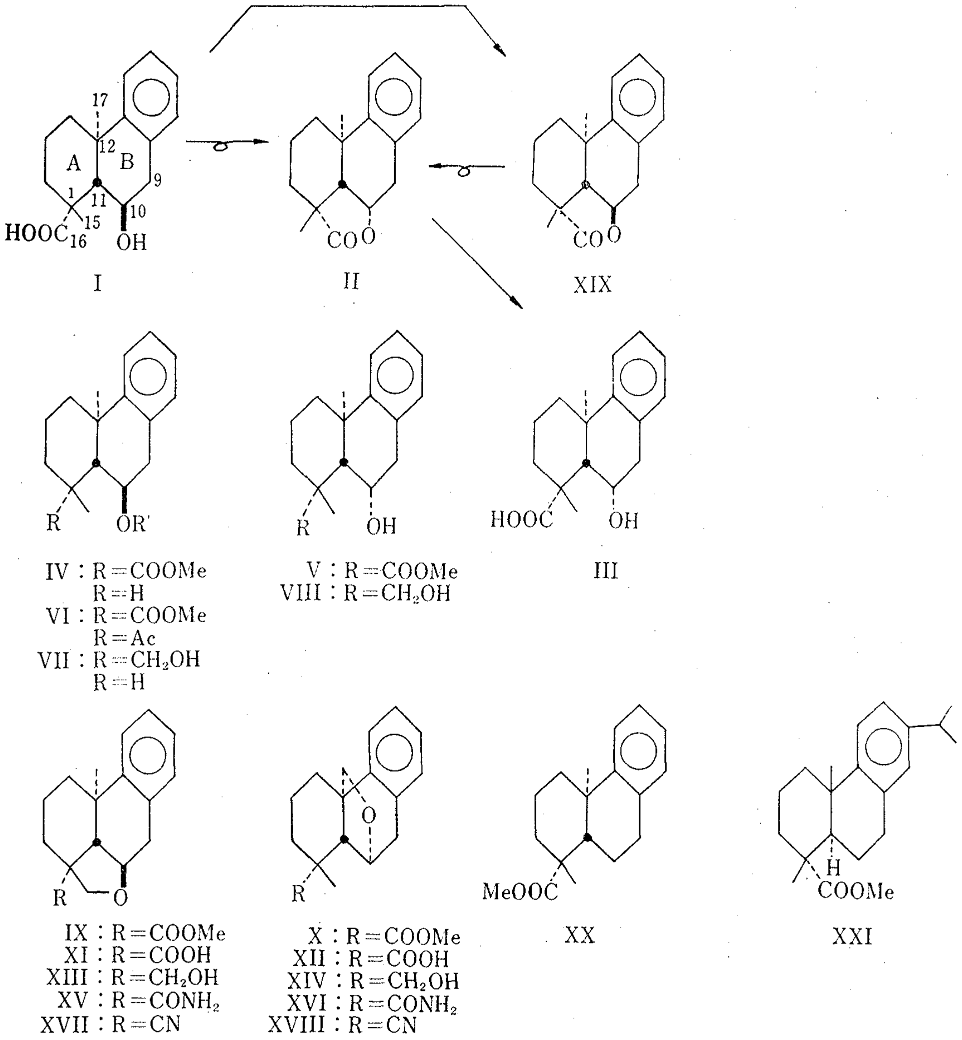

Chart 1.

[*3] Considering difference between chemical shift due to A and B proton, the observed splitting arising from ABX proton interaction of 10β-oxy isomeric series is good approximation to the coupling constant J, while sum of J_{AX} and J_{BX} is only confidently stated from the corresponding observed spplitting in 10α-oxy isomeric series.

Conformation

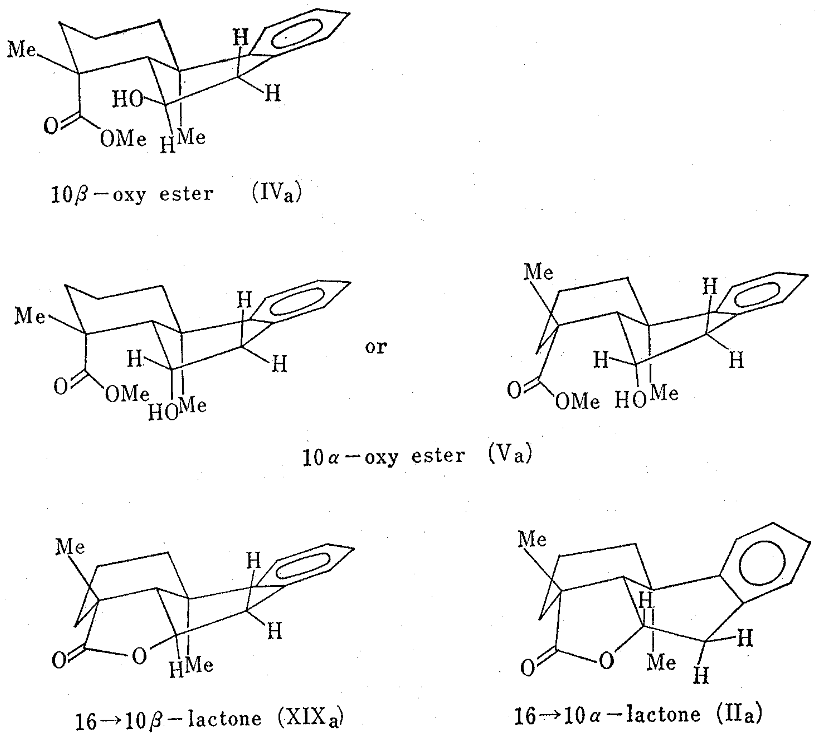

Chart 2.

1. NMR Analysis of 10β- (IV) and 10α-Oxy Ester (V).

Resonance of ABX proton system at C_9 and C_{10} of methyl 10β-oxy- (IV) and 10α-oxy-*enantio*-deoxypodocarpate (V) shows distinctly characteristic pattern as shown in Table I and Fig. 1. The NMR pattern of IV and V shows similar attitude to those of the corresponding 10β-15 (IX) and 10α-17 epoxy ester (X) having a half chair B-ring conformation fixed by the epoxide bridge, therefore it is evident that B-ring of 10-oxy isomers must retain a half chair conformation.

Firstly, NMR spectrum of 9-methylene (AB) protons located on half chair B-ring of 10-oxy isomer (IV) and (V) will be analyzed. The resonance (AB protons) of 10β-oxy isomer (IV) appears as a quartet centered at 6.74τ ($J_{9\alpha,9\beta}=16$ c.p.s., $J_{9\alpha,10\alpha}=5.5$ c.p.s.) and at 7.15τ ($J_{9\alpha,9\beta}=16$ c.p.s., $J_{9\beta,10\alpha}=9$ c.p.s.), while the resonance due to the corresponding protons of 10α-oxy isomer (V) is appeared at same chemical shift centered at 6.95τ and with observed splitting (3 c.p.s.),[*3] so that the system is taken as A_2X type and the both protons are magnetically equivalent.

The chemical shift of these 9-methylene protons can be appreciated to attribute to combination of the following factors. 1) By a long range shielding effect associated with anisotropies of the magnetic susceptibilities of C-C single bonds, it has been established for six-membered ring system that axial ring protons absorb at higher field (their experimental disparity lie in the rang 0.1~0.7 p.p.m.) than do their epimeric equatorial counterparts.3) 2) NMR absorption due to 9-methylene protons is also ascribed to the effect of π-electron ring current associated with the conjugated system (in this case, benzene ring).4) 3) A neighboring substituent (in this case, hydroxy

---

3) L. M. Jackman: Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, 115 (1959). Pergamon Press, London.

4) L. M. Jackman: *Ibid.*, 125 (1959).

group) affects the chemical shift of the axial and equatorial protons attached to the adjacent carbon atom.[5]

The conformational view of 10β-oxy ester (Ⅳ) having half chair B-ring shows that the plane of benzene ring and hydroxy C-O bond approximately bisects the angle between the 9-methylene AB protons, so the difference between chemical shifts of these protons, 0.41 p.p.m., is presumably caused by the first factor and hence the quasi-axial 9β-H and quasi-equatorial 9α-H resonate at higher and lower magnetic field respectively. Alternatively, in 10α-oxy isomer (V) having also half chair B-ring, the first (C-C single bond anisotropy) and the second factor (benzene ring anisotropy) are affected in the same way as the respective factors in the case of Ⅳ, however only the axial hydroxy (the third factor) give different effect to 9-AB protons from that of Ⅳ.

Namely, the effect of a hydroxy substituent upon AB protons is important to analyze the difference between their spectra due to AB protons of Ⅳ and V. On the effect of hydroxy group, it is known that shift of an axial and equatorial proton due to vicinal axial hydroxy group indicates oposite direction each other; an upfield shift (+0.24~0.36 p.p.m. from 4 examples) for an equatorial proton and downfield shift (−0.26 and −0.29 p.p.m. from 2 examples) for an axial proton in cyclohexane chair conformation.[5] Accordingly, magnetically equivalent 9-methylene protons of 10α-oxy isomer (Ⅳ) can be explained by the empirical shift trend due to vicinal axial hydroxy group that upfield shift of an equatorial α-proton resonance appeared in lower field (6.74τ in Ⅳ) and downfield shift of axial β-proton resonance absorbed in higher field (7.15τ in Ⅳ) would be offset to give the same chemical shift (6.95τ in V).

The geminal H-H coupling is, in general, dependent on the number of adjacent π-bond and also varies with the angle between the methylene group and the adjacent π-bond.[6] Thus the fact that the methylene protons coupling (16 c.p.s.) of 10β-oxy isomer (Ⅳ) is larger than the standard (12.4 c.p.s.) of methane, can be sufficently convinced by considering of the dihedral angle concerned.[6]

Next, NMR pattern (chemical shift and coupling constant with 9-H_2 and 11-H) of 10-proton of isomeric 10-oxy ester (Ⅳ) and (V) will be discussed. The proton of Ⅳ attached to the same carbon atom as hydroxy function is deshielded and its resonance appears as six splitting line centered at 5.36τ ($J_{9\beta,10\alpha}=9$ c.p.s., $J_{9\alpha,10\alpha}=5.5$ c.p.s., $J_{10\alpha,11\beta}=9$ c.p.s., half band width =24 c.p.s.). In contrast, the 10-proton of V resonates as triplet centered at 5.22τ (observed $\text{value}_{9\alpha(9\beta),10\beta}=3$ c.p.s., $J_{10\beta,11\beta}=0\sim1$ c.p.s., half band width =7 c.p.s).[*3] It is reasonable that axial 10-proton (5.36τ) of Ⅳ resonates in higher field than the corresponding equatorial proton (5.22τ) of V.

From many observations on the coupling pattern between the protons attached to the carbon substituted by hydroxy (or acetoxy) group and the vicinal methylene protons at resonance due to X proton of steroid series, it is evident that the observed splitting arising from axial-axial and axial-equatorial proton interaction is *ca.* 10~11 and 5.5±1 c.p.s. respectively when hydroxy group is equatorial in a cyclohexane chair ring. Alternatively, when the hydroxy function is axial in a chair ring, the observed splitting as triplet arising from equatorial-axial and diequatorial proton interaction is roughly equal in the range of 2.5~3.2 c.p.s. (the observed splitting due to vicinal axial-equatorial proton is generally larger when hydroxy function is equatorial than it is axial).[7]

---

5) N. S. Bhacca, D. H. Williams: Applications of NMR Spectroscopy in Organic Chemistry, 183 (1964). Holden-Day, Inc., San Francisco.

6) M. Barfield, D. M. Grant: J. Am. Chem. Soc., **85**, 1899 (1963).

7) D. H. Williams, N. S. Bhacca: *Ibid.*, **86**, 2742 (1964).

The two kinds of the observed splitting of the steroid as stated above, are very similar to those of our 10β-oxy (IV) and 10α-oxy compound (V) respectively (Table I), even though the observed pattern of 10α-oxy ester (V) only shows an accurate value as sum of J_{AX} and J_{BX}. From this point of view, it can be stated that IV have equatorial 10-hydroxy function and so V have axial 10-hydroxy group either in half chair conformation of B-ring. Slight variation in our case from the observation of steroid examples is understandable under consideration of half chair B-ring. Conclusively, the conformation of IV and V are represented as IVa and Va respectively on basis of NMR analysis discussed above.[*4]

Besides, NMR absorption due to hydroxy proton of IV and V appears at 6.98τ and 5.25τ in 100Mc spectrum respectively and they are disappeared when D_2O is added to the solution. According to assertion that resonance of hydroxy proton having stronger hydrogen bond appears in lower magnetic field, the hydroxy proton of V (5.25τ) forms stronger hydrogen bond than that of IV (6.98τ). The discussion is not contradictory to the conformational model concluded as above and also certainly supported by infrared spectrum analysis of the esters (IV, $\nu_{\mathrm{max}}^{\mathrm{CCl_4}}$ 3618 (free OH), 3548 (hydrogen bonding OH) cm^{-1} and V, $\nu_{\mathrm{max}}^{\mathrm{CCl_4}}$ 3485 (hydrogen bonding OH) cm^{-1})1) and by comparison of $\mathrm{pK}^{*}_{\mathrm{MCS}}$ value of the corresponding acid (I), $\mathrm{pK}^{*}_{\mathrm{MCS}}$ 7.13 and (III), $\mathrm{pK}^{*}_{\mathrm{MCS}}$ 6.37. *cf.* deoxy-*enantio*-podocarpic acid, $\mathrm{pK}^{*}_{\mathrm{MCS}}$ 8.45,[*5] which have same conformational structure as the corresponding ester as described later.

2. NMR Analysis of the Other 10β- and 10α-Oxy Series.

In NMR spectrum of 10β-acetoxy compound (VI), the pattern due to 9-methylene (AB) protons and 10α(X) proton attached to the same carbon atom as acetoxy function, is similar to that of 10β-oxy ester (IV), however the chemical shift of 10-proton places to lower field centered at 3.88τ than that of IV at 5.36τ.

Furthermore, exactly analogous argument on 9-, 10- and 11-protons of 10β-oxy (IV) and 10α-oxy ester (V) can be applied to the corresponding derivatives obtained from IV and V respectively as shown in Table I and Fig. 1.

3. NMR Analysis of Lactone (II) and (XIX).1,2)

At last, conformation of 16→10α-lactone (II) and 16→10β-lactone (XIX) will be mentioned. The lactone (II) haxe α-configuration in C-O bond, nevertheless its NMR pattern is not similar to that of 10α-oxy isomer, but to that of 10β-oxy isomer. Dihedral angle calculated by the Williamson and Johnson's modified equation10) using observed coupling constants ($J_{9\alpha,10\beta}$ =8.5 c.p.s., $J_{9\beta,10\beta}$ = $J_{10\beta,11\beta}$ =6.0 c.p.s.) of II,

---

[*4] The A-ring conformation of 10β-oxy ester (IV) can be reliably considered to be chair form as in IVa, because chemical shift (8.51 τ) of 1-methyl appears in lower field than that (8.73 τ) of the standard (XX) by effect of the nearly located 10β-hydroxy function in half chair B-ring and chemical shift (8.98 τ) of 12-methyl affected by 1-carbomethoxy group is about same as that (8.97 τ) of the standard (XX) having chair A-ring conformation.1,2) While, it is undefinite to determine A-ring conformation of 10α-oxy ester (V) on the basis of discussion on whether or not 1-carbomethoxy group exert an influence upon chemical shift of 12-methyl group, for the effect of its α-hydroxy group also overlaps to 12-methyl group.

[*5] OH streching vibration in infrared spectrum absorbs in lower frequency region according as hydrogen bond strength.8) pK Value ($\mathrm{pM}^{*}_{\mathrm{MCS}}$ in this case) of acid decreases in proportion as hydrogen bond intensifies with hydroxy group of same molecular.9) The $\mathrm{pK}^{*}_{\mathrm{MCS}}$ values were measured by Dr. R. McGrindle, Glasgow, and Dr. W. Simon, Zurich, to whom the authors greatly indebted. More detailed report on correlation of acidity and intramolecular hydrogen bond of these isomers by $\mathrm{pK}^{*}_{\mathrm{MCS}}$ and IR, will be published in cooperation with Glasgow and Zurich group.

8) L.W. Reeves, E.A. Allan, K.O. Strφmme: Canad. J. Chem., **38**, 1249 (1960).

9) W. Baker: Nature, **137**, 236 (1936). *cf.* P.F. Sommer, C. Pascual, V.P. Arya, W. Simon: Helv. Chim. Acta, **46**, 1734 (1963).

10) K.L. Williamson, W.S. Johnson: J. Am. Chem. Soc., **83**, 4623 (1961).

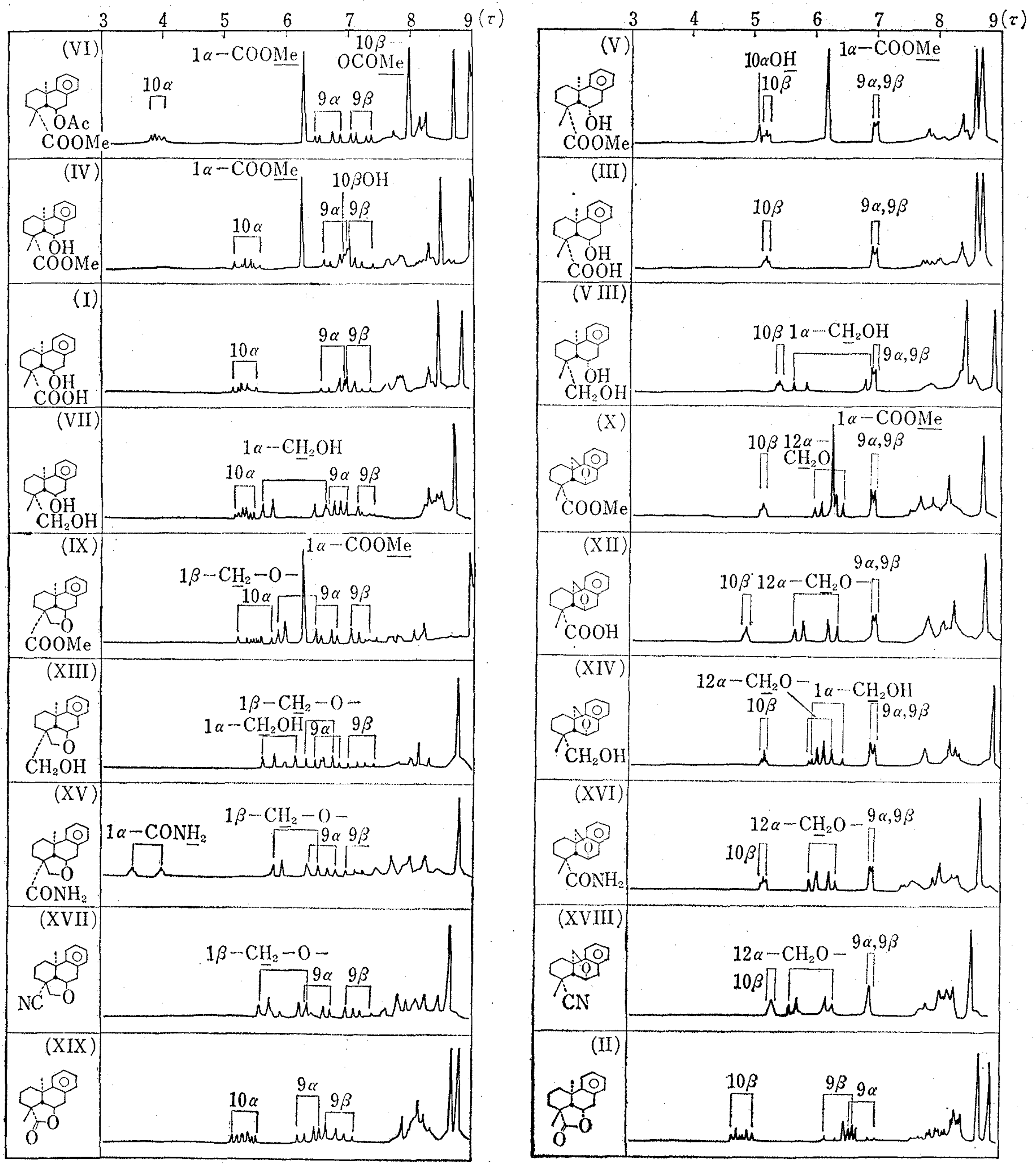

Fig. 1.

Table I. (Chemical shift (τ), J (c.p.s.))*³
10β-Oxy Type Compound

	1α-Substituent	1β-CH₂-O-	9α-H	9β-H	10α-H	10β-Substituent
VI	COOMe 6.31		6.63 $J_{9\beta}$ 16.2 $J_{10\alpha}$ 5.5	7.22 $J_{9\alpha}$ 16.2 $J_{10\alpha}$ 4.5	3.88 $J_{9\alpha}$ 5.5 $J_{9\beta}$ 4.5 $J_{11\beta}$ 7.0	OAc 8.03
IV	COOMe 6.25		6.74 $J_{9\beta}$ 16.0 $J_{10\alpha}$ 5.5	7.15 $J_{9\alpha}$ 16.0 $J_{10\alpha}$ 9.0	5.36 $J_{9\alpha}$ 5.5 $J_{9\beta}$ 9.0 $J_{11\beta}$ 9.0	OH (100 Mc) 6.98

I			6.71 $J_{9\beta}$ 16.0 $J_{10\alpha}$ 5.5	7.13 $J_{9\alpha}$ 16.0 $J_{10\alpha}$ 8.5	5.28 $J_{9\alpha}$ 5.5 $J_{9\beta}$ 8.5 $J_{11\beta}$ 8.5
VII	CH_2OH 5.72 6.51 J 10.5		6.73 $J_{9\beta}$ 14.0 $J_{10\alpha}$ 5.5	7.16 $J_{9\alpha}$ 14.0 $J_{10\alpha}$ 9.5	obscurity
IX	COOMe 6.28	5.88 6.36 J 8.5	6.59 $J_{9\beta}$ 15.5 $J_{10\alpha}$ 6.0	7.21 $J_{9\alpha}$ 15.5 $J_{10\alpha}$ 9.5	5.44 $J_{9\alpha}$ 6.0 $J_{9\beta}$ 9.5 $J_{11\beta}$ 11.5
XIII	CH_2OH 5.98 6.33 J 10.5	5.67 6.15 J 7.5	6.61 $J_{9\beta}$ 15.5 $J_{10\alpha}$ 6.0	7.22 $J_{9\alpha}$ 15.5 $J_{10\alpha}$ 9.0	obscurity
XV	$CONH_2$ 3.51 3.95 broad	5.84 6.44 J 8.4	6.59 $J_{9\beta}$ 15.0 $J_{10\alpha}$ 5.3	7.15 $J_{9\alpha}$ 15.0 $J_{10\alpha}$ 9.0	*ca.* 5.62 multiplet
XVII		5.61 6.31 J 8.5	6.56 $J_{9\beta}$ 16.5 $J_{10\alpha}$ 6.0	7.18 $J_{9\alpha}$ 16.5 $J_{10\alpha}$ 9.0	*ca.* 5.72 multiplet

10α-Oxy Type Compound (Ob=Observed value)

	1α-Substituent	12α-CH_2-O-	9α- and 9β-H	10β-H	10α-Substituent
V	COOMe 6.21		6.95 $Ob_{10\beta}$ 3.0	5.21 $Ob_{9\alpha,\beta}$ 3.0 $J_{11\beta}$ 0~1.0	OH (100 Mc) 5.25
III			6.94 $Ob_{10\beta}$ 3.0	5.22 $Ob_{9\alpha,\beta}$ 3.0 $J_{11\beta}$ 0~1.0	
VIII	CH_2OH 5.77 6.82 J 12.0		6.97 $Ob_{10\beta}$ 3.0	5.42 $Ob_{9\alpha,\beta}$ 3.0 $J_{11\beta}$ 0~1.0	
X	COOMe 6.30	6.06 6.40 J 8.0	6.90 $Ob_{10\beta}$ 3.0	5.07 $Ob_{9\alpha,\beta}$ 3.0 $J_{11\beta}$ 0~1.0	
XII		5.75 6.27 J 8.5	6.88 $Ob_{10\beta}$ 3.0	4.78 $Ob_{9\alpha,\beta}$ 3.0 $J_{11\beta}$ 0~1.0	
XIV	CH_2OH 6.06 6.40 J 11.5	5.97 6.22 J 8.0	6.90 $Ob_{10\beta}$ 3.0	5.19 $Ob_{9\alpha,\beta}$ 3.0 $J_{11\beta}$ 0~1.0	
XVI	$CONH_2$ obscurity	5.99 6.32 J 7.5	6.90 $Ob_{10\beta}$ 2.5	5.14 $Ob_{9\alpha,\beta}$ 2.5 $J_{11\beta}$ 0~1.0	
XVIII		5.68 6.27 J 8.0	6.93 $Ob_{10\beta}$ *ca.* 2.5	5.38 $Ob_{9\alpha,\beta}$ *ca.* 2.5 $J_{11\beta}$ obscurity	

16→10β- and 16→10α-lactone

	1-Me and 12α-Me	9α-H	9β-H	10α-H	10β-H
XIX	8.70 (12α-Me) 8.83 (1β-Me)	6.40 $J_{9\beta}$ 15.5 $J_{10\alpha}$ 6.5	6.86 $J_{9\alpha}$ 15.5 $J_{10\alpha}$ 10.5	5.37 $J_{9\alpha}$ 6.5 $J_{9\beta}$ 10.5 $J_{11\beta}$ 11.5	
II	8.71 (12α-Me) 8.87 (1β-Me)	6.81 $J_{9\beta}$ 17.5 $J_{10\beta}$ 8.5	6.46 $J_{9\alpha}$ 17.5 $J_{10\beta}$ 6.0		4.89 $J_{9\alpha}$ 8.5 $J_{9\beta}$ 6.0 $J_{11\beta}$ 6.0

$\phi_{9\alpha,10\beta}$ =*ca.* 135°, $\phi_{9\beta,10\beta}=\phi_{10\beta,11\beta}$ =*ca.*40°,[*6] is close upon dihedral angle as measured in Dreiding model of II having boat B-ring, therefore it can be more reasonably explained that B-ring of II must be half boat conformation rather than half chair as in the case of uaual 10α-oxy series. Accordingly, the formation of the lactone ring between 10α-hydroxy group in half boat B-ring and 1α-carboxy group in A-ring indicates that the conformation of A-ring also must be boat as shown in XIXa.

On the other hand, NMR pattern for 9-, 10- and 11-protons of unstable 16→10β-lactone (XIX) produced with retained 10β-configuration by thermal treatment of 10β-oxy acid (II), belongs to that of 10β-oxy isomeric system having half chair B-ring conformation. The lactone model having 10β C-O bond in half chair B-ring shows that its A-ring conformation should be boat as shown in IIa.

Furthermore, the conformation of the 16→10α- (IIa) and 16→10β-lactone (XIXa) is also supported by consideration of chemical shift of their methyl group. Since 12-methyl group of the both lactone IIa (boat A-ring and half boat B-ring) and XIXa (boat A-ring and half chair B-ring) is almost oriented out positively shielding region and rather undergo paramagnetic shift by carbonyl group of lactone ring, it is evident that τ-values for 12-methyl of II (8.71τ) and XIX (8.70τ) appear in same field as that (8.72τ) of methyl dehydroabietate (XXI) having a similar paramagnetic effect by equatorial 1-carbomethoxy group. Sterical relation between axial 1-methyl and equatorial 1-carboalkoxy group of IIa and XIXa is about same as that of methyl dehydroabietate (XXI), therefore chemical shift of 1-methyl of II (8.87τ) and XIX (8.83τ) are almost similar as compared with that (8.80τ) of the standard XXI.

The authors are greatly indebted to Dr. Y. Kawazoe, National Cancer Center Research Institute for his kind discussions. Financial support from the Ministry of Education (Grant-in-Aid for Scientific Research, No. 750294) and from Hôan-sha, are gratefully acknowledged.

[*6] The ϕ-values are calculated under the condition that axial 9α-H and equatorial 9β-H of (II) having half boat B-ring resonate in higher (6.81 τ) and lower magnetic field (6.46 τ) respectively.