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Taxinine Derivatives. The Stereochemistry of Isopropylidenedihydrotaxinolactone, a Novel Autooxidation Product of Isopropylidenedihydrotaxinol[1]

YOSHIFUMI MAKI and KAZUYUKI YAMANE

Gifu College of Pharmacy[2]

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The stereochemistry of isopropylidenedihydrotaxinolactone, a novel autooxidation product of dihydrotaxinol derivatives (*e.g.* III and IV), was proposed as represented by (V) (*cf.* IX). Furthermore, some additional findings relating to the stereochemistry of taxinine derivatives were described.

In a previous paper,[1] we demonstrated that dihydrotaxinol (III) and isopropylidenedihydrotaxinol (IV) undergo a novel autooxidative cleavage of the C_{12}–C_{13} bond in their ring A. The planar structure (without stereochemistry) of a crystalline product, isopropylidenedihydrotaxinolactone (V)[3], was elucidated.

The absolute configuration of taxinine, a parent diterpenoid from the Japanese yew tree, has been shown to be represented by formula (I) on the basis of chemical and physicochemical studies[4] and an X-ray crystallographic study[5] of bromotetraacetyltaxinol (II). At about the same time, Lythgoe and his co-workers[6] also reached the same conclusion regarding the stereochemistry of taxinine (under the name O-cinnamoyltaxicin II triacetate).

The transformations of III and IV into V were carried out successfully in an acidic medium: *e.g.* V was obtained directly by refluxing III in acetone containing a trace of acid.[1]

The role of acid and the effects of steric features[7] of ring A in the autooxidation are uncertain, but we tentatively suggest the mechanism outlined in Chart 1.

The configurations at positions 1, 2, 3, 5, 8, 9 and 10 of the lactone V were derived from those of the molecules I, II, III and IV. Accordingly, determination of the configurations at position 4 and 11 can lead to a complete stereostructure for V.

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[1] Previous paper: S. Uyeo, Y. Maki and Y. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **14**, 502 (1966).

[2] Location: *Mitahora, Sakanoshita, Gifu.*

[3] In this paper, numbering of isopropylidenedihydrotaxinolactone derivatives (*cf.* V) was based upon that of taxinine (I). For nomenclature and numbering of taxane derivatives see: B. Lythgoe, K. Nakanishi and S. Uyeo, *Proc. Chem. Soc.* (London), **1964**, 301.

[4] M. Kurono, Y. Maki, K. Nakanishi, K. Ueda, M. Woods, Y. Yamamoto and S. Uyeo, *Tetrahedron Letters*, **1965**, 1917.

[5] M. Shiro, T. Sato, H. Koyama, Y. Maki, K. Nakanishi and S. Uyeo, *Chem. Comm.*, **1966**, 97.

[6] M. Duked, D.H. Eyre, J.W. Harrison and B. Lythgoe, *Tetrahedron Letters*, **1965**, 4765; D.H. Eyre, J.W. Harrison and B. Lythgoe, *J. Chem. Soc.*, **1967**, 452.

[7] Ring A of taxinol derivatives (*e.g.* III, IV and tetraacetyltaxinol) beside II would also adopt a boat conformation for the following reasons: X-ray crystallographic data clearly showed that ring A of II exists in a boat form and a bromine atom in ring A is equatorial in the solid state. Optical rotatory dispersions of II and tetraacetyltaxinol (in dioxane) exhibited positive Cotton effect courves ($a=+118$ and $a=+29$) respectively, which are explicable by applying the octant rule to their ring A modelled on a boat form. Contributions of an eq. bromine atom in II to its ORD ($a=+89$), to its infrated spectrum ($+20\ \text{cm}^{-1}$) and to its ultraviolet spectrum ($-5\ \text{m}\mu$) are compatible with the introduction of an eq. bromine to ring A of tetraacetyltaxinol, which would originally adopt a boat form rather than a chair form.

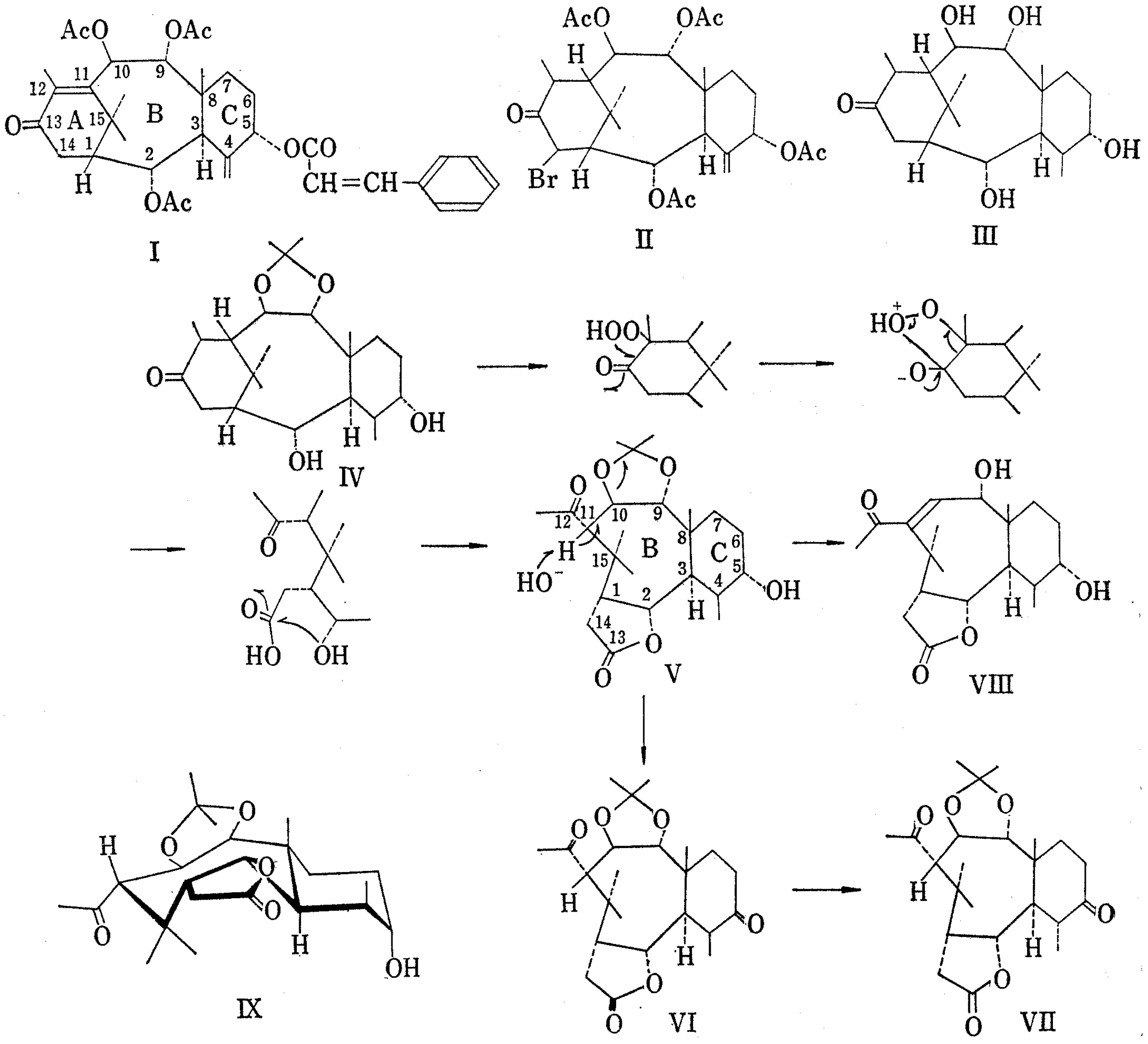

Chart 1

In this paper, we propose the stereochemistry depicted in V or the perspective (IX) for the lactone and wish to report some additional findings relating to the stereochemistry of Taxinine derivatives.

Configuration at C_4

Chromic acid oxidation[1] of V in acetic acid gave the diketone (VI), mp 258—260°. On heating in acetone containing a small amount of hydrochloric acid for several hr, VI was converted in almost quantitative yield to its epimer (VII), mp 235°.

While the optical rotatory dispersion (ORD) curve of VI exhibits a positive Cotton effect ($a=+30$), its epimer VII shows a negative one ($a=-29$). To estimate the contribution of the C_5-ketone in their ORD, the small amplitude positive Cotton effect of V ($a=+13$) was subtracted from those of VI and VII to give $a=+17$ for VI and $a=-42$ for VII respectively. These data are in good agreement with the signs and amplitudes predicted from octant projections of six-membered rings modelled of the chair form in VI and VII.

In view of the above findings, it is reasonable to be concluded that the C_4-methyl groups of both V and VI adopt the less stable β-configuration (axial).

This assignment can be applied directly to the C_4-methyl groups of dihydrotaxinol derivatives[8] (*e.g.* III and IV).

Configuration at C_5

Application of the Horeu method to taxinine derivatives[4] indicated that the 5-hydroxy function had the α-configuration.

Brewster's benzoate rule[9] is widely employed to determine the absolute configuration of cyclic *sec*-alcohols, but is not applicable to certain types of compounds, *e.g.*, those in which the carbinyl carbon is flanked by two methylene groups, and those in which one of the carbons adjacent to the carbinyl carbon is the bulkier and also the more polar.

This limitation of the benzoate rule makes it impossible to apply to taxinine and taxinol derivatives[10] having an exomethylene group at position 4.

Lactone V, however, seems to be adequate for application of the benzoate rule.

The lactone V was treated with pyridine-benzoylchloride to give isopropylidenedihydrotaxinolactone benzoate, mp 150°. The positive shift of molecular optical rotation (+69.53) in going from *V*, $[M]_D+9.97$, to its benzoate, $[M]_D+79.50$, clearly showed that the C_5-assymmetric center adopts the S-configuration (5α-hydroxy) in accord with previous assignment.[4]

Configuration at C_{11}

In the NMR spectra of taxinol and lactone derivatives, we can observe a significant difference between their C_2–H and C_{10}–H signals. For example, the 10-proton of diacetylisopropylidenedihydrotaxinol (Fig. 1b) appears as a doublet ($J_{9,10}=10.5$ cps), indicating a very weak coupling of the 10-proton with the 11-proton, and its 2-proton is observed as a diffuse signal. On the contrary, signals of the 10- and 2-protons of acetylisopropylidenedihydrotaxinolactone (Fig. 1a) appear as distinct quartets ($J_{10,11}=11.5$ cps, $J_{10,9}=7.0$ cps and $J_{1,2}=4.5$ cps, $J_{2,3}=10.5$ cps) respectively.

The eight-membered ring of taxinol derivatives are clearly modelled on a boat-chair conformation in the solid state on the basis of the X-ray crystallographic study of II.[5]

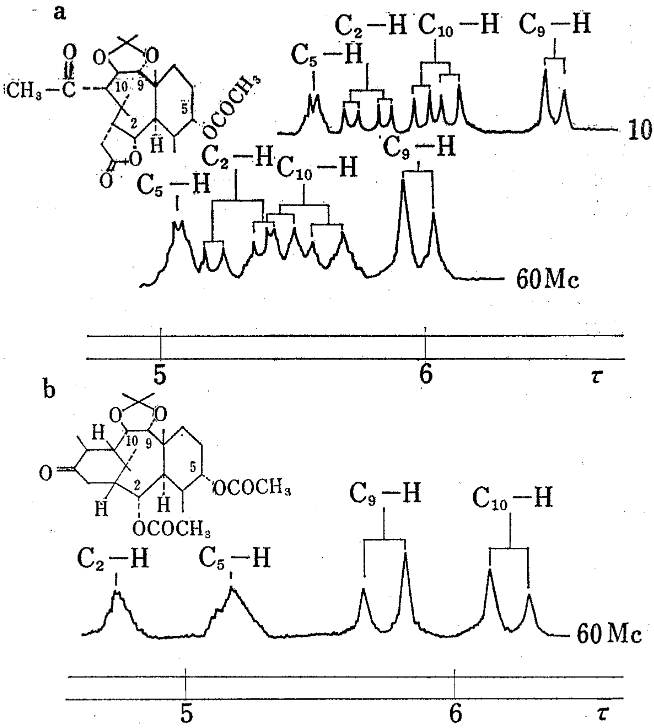

Fig. 1. NMR Spectra of Acetylisopropylidenedihydrotaxinolactone and Diacetylisopropylidenedihydrotaxinol (in $CDCl_3$)

a. acetylisopropylidenedihydrotaxinolactone (100 Mc and 60 Mc)
b. diacetylisopropylidenedihydrotaxinol (60Mc)

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[8] Recently, British workers[6] proposed that the configuration of C_4-methyl group in 4, 16-dihydrotaxicin-II is β. Their result can be extended to dihydrotaxinol derivatives in accordance with our independent conclusions.

[9] J.H. Brewster, *Tetrahedron*, **13**, 106 (1961); *J. Am. Chem. Soc.*, **81**, 5475, 5483, 5493 (1959).

[10] Recent work by K. Nakanishi, *et al.* showed that the strong Cotton effect of benzoate due to π–π^* transition at *ca.* 225 mμ permits one to predict the absolute configuration of cyclic *sec*-hydroxy groups even in those compounds (*cf.* N. Harada, M. Ohashi and K. Nakanishi, Abstracts of Papers, Symposium of the Chemistry of Natural Products, Sendai, Japan, Oct. 1968, p. 50).

In accordance with this, the NMR spectra of taxinol derivatives are easily explainded, *e.g.*, a very small coupling constant ($J_{10,11}$) in the NMR spectrum of diacetylisopropylidenedihydrotaxinol corresponds to a dihedral angle (about 90°) between the 10- and 11-protons observed from its Dreiding models.

An examination of Dreiding models, however, indicates that the eight-membered ring of lactone derivatives adopts a deformed conformation with a satisfactory rigidity, as illustrated by IX. This deformation of the ring accounts well for the change of the NMR patterns of the 2- and 10-protons in going from taxinol derivatives to lactone derivatives.

It can be observed from Dreiding models of the lactone V that dihedral angles between the 10-proton and the 11α- or 11β-protons are about 80° and 170° respectively. A large coupling ($J_{10,11}=11.5$ cps) in the NMR spectra of the lactone derivatives permits us to adopt only the *trans*-orientation of the 11-proton to the 10-proton: an acetyl group on the lactone molecule attaches at position 11 with α-configuration, and therefore no epimerization occurs during the transformation of dihydrotaxinol derivatives into the lactone V in an acidic medium.

In a previous paper, it was demonstrated that V undergoes easily β-elimination with alkali to give the α,β-unsaturated ketone (VIII). The present aspect regarding the stereochemistry of the 11-proton suggests that β-elimination of V proceeds by a *syn*-elimination mechanism.

Experimental[11]

Benzoylation of Isopropylidenedihydrotaxinolactone (V)——To a cooled solution of V (0.2 g) in anhydrous pyridine (3 ml) was added dropwise benzoylchloride (1 ml). The reaction mixture was allowed to stand at room temperature for two days, diluted with ice water (30 ml) and extracted with $CHCl_3$ (50 ml). The extract was washed with 5% Na_2CO_3 and H_2O, dried over anhydrous Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$ again and chromatographed on silicagel. The crystalline compound eluted with $CHCl_3$ was recrystallized from ether to give the benzoate, mp 150°, (0.14 g) as colorless needles. *Anal.* Calcd. for $C_{20}H_{40}O_7$: C, 69.57; H, 8.05. Found: C, 67.70; H, 7.96. $[\alpha]_D^{25}$ +15.88 ($c=1.15$, $l=1$, EtOH). IR ν_{max}^{KBr} cm^{-1}: 1780 (C=O of γ-lactone), 1705 (C=O of benzoyl and methylketone). NMR (in $CDCl_3$) τ: 8.96, 8.91, 8.74, 8.65, 8.60 (each 3H, singlet, CH_3), 8.87 (3H, doublet, $J=6.5$ cps, CH_3), 7.70 (3H, singlet, $COCH_3$), 5.93 (1H, doublet, $J=7.5$ cps, C_9–H), 5.44 (1H, quartet, $J=7.5$ and $J=11.0$ cps, C_{10}–H), 5.27 (1H, quartet, $J=9.5$ and $J=4.5$ cps, C_2–H), 4.78 (1H, multiplet, C_5–H), 2.40 (3H, multiplet, phenyl ring protons), 1.90 (2H, multiplet, phenyl ring protons).

Epimerization of Diketone (VI)——VI (0.4 g), mp 258—260°, was refluxed in acetone (50 ml) containing 35% hydrochloric acid (1 ml) for 7 hr. A thin-layer chromatographic analysis showed absence of VI in the reaction mixture. After removal of acetone, the residue was recrystallized from acetone–isopropyl ether mixture to give VII, mp 235°, (0.31 g) as colorless needles. *Anal.* Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.81; H, 8.62. IR ν_{max}^{Nujol} cm^{-1}: 1760 (C=O of γ-lactone), 1700 (C=O of methyl and six-membered ketones). NMR (in $CDCl_3$) τ: 8.98, 8.83, 8.66 (each 3H, singlet, CH_3), 8.60 (6H, singlet, $2CH_3$), 8.83 (3H, doublet, $J=8.0$ cps, CH_3), 7.74 (3H, singlet, CH_3CO), 5.99 (1H, doublet, $J=7.0$ cps, C_9–H), 5.67 (1H, quartet, $J=7.0$ and 11.0 cps, C_{10}–H), 5.29 (1H, quartet, $J=11.0$ and 4.0 cps, C_2–H).

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[11] All melting points were uncorrected. NMR spectra were measured on a Varian A-60 spectrometer. The chemical shifts were expressed in τ value from TMS.