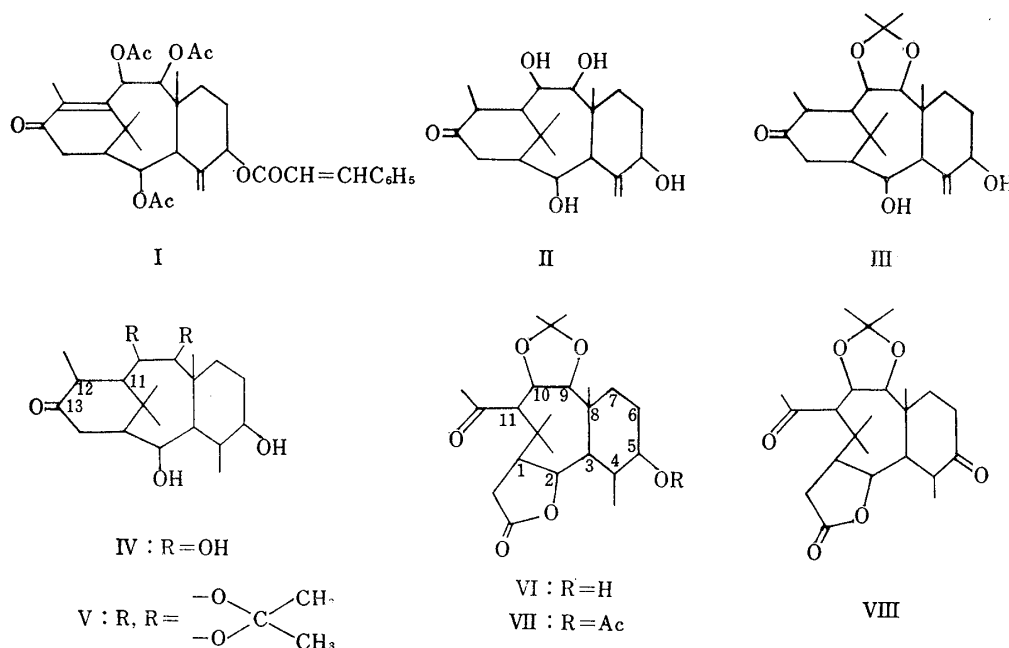


70. Shojiro Uyeo,*¹ Yoshifumi Maki,*² and Yoshitomo Yamamoto*¹ :
Taxine. XIV.*³ The Structure of Isopropylidenedihydrotaxi-
nolactone, an Autooxidation Product of
Isopropylidenedihydrotaxinol.

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As reported in the previous papers,¹⁾ taxinine (I), a constituent of the leaves of *Taxus cuspidata* SIEB. et ZUCC., yielded on treatment with lithium aluminum hydride taxinol (II) which could be converted into its isopropylidene derivative (III), indicating that it contained an α -glycol grouping in the molecule. Likewise dihydrotaxinol (IV) could also be converted into its isopropylidene derivative (V), m.p. 236~238°, which was best obtained in almost quantitative yield on heating it in acetone in the presence of toluenesulfonic acid for 3 hr. When, however the duration of heating was prolonged up to 20 hr., a sparingly soluble substance, m.p. 325~326° was obtained as a by-product along with the desired isopropylidene dihydrotaxinol (V).

This new substance, which we have named isopropylidenedihydrotaxinolactone, was found later to be obtainable more easily and in a better yield (30~40%) on refluxing dihydrotaxinol in acetone with a very small amount of concentrated hydrochloric acid.



Isopropylidenedihydrotaxinolactone (VI) is colorless, neutral and optically active, $[\alpha]_D + 2.4^\circ$ (EtOH). It was assigned the formula $C_{23}H_{36}O_6$ on the basis of combustion analyses and the mass spectrum of its acetate (VII), m.p. 248~250°, which exhibited the parent peak at m/e 450 corresponding to the formula $C_{23}H_{35}O_6 \cdot COCH_3$.

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1) S. Uyeo, K. Ueda, Y. Yamamoto, Y. Maki : *Yakugaku Zasshi*, **84**, 762 (1964); *Ibid.*, **85**, 404 (1965).

Isopropylidenedihydrotaxinolactone exhibited in the infrared spectrum bands at 3600 (OH), 1755 (γ -lactone) and 1710 cm^{-1} (ketone) while the acetate showed at 1765 (γ -lactone), 1715 (acetate) and 1705 cm^{-1} (ketone) but no hydroxyl absorption in the 3600 cm^{-1} region, showing clearly that the parent compound has one acetylatable hydroxyl group. Chromic acid oxidation of isopropylidenedihydrotaxinolactone in acetic acid gave the diketone (VIII), $\text{C}_{23}\text{H}_{34}\text{O}_6$, m.p. 258~260°, which exhibited infrared absorptions at 1780 (γ -lactone), and 1710 cm^{-1} (diketone), demonstrating that the hydroxyl group in isopropylidenedihydrotaxinolactone was secondary and attached to a carbon atom of a six-membered ring.

Isopropylidenedihydrotaxinolactone exhibited in the nuclear magnetic resonance spectrum in $\text{CDCl}_3\text{-C}_6\text{D}_6\text{N}_6$ (1 : 1) five singlets (3H each at 0.96, 1.15, 1.21, 1.31, and 1.39 p.p.m.) for tertiary methyls, one doublet (3H) centered at 1.01 p.p.m. ($J=7.0$ c.p.s.) for a secondary methyl and a sharp singlet (3H) at 2.21 p.p.m. for a methyl adjacent to a carbonyl group. The presence of a methyl ketone moiety in the molecule was confirmed by its positive iodoform test and corresponded to the band at 1710 cm^{-1} in the infrared spectrum. The five tertiary methyls in the region of 0.96~1.39 p.p.m. suggested the presence of an isopropylidene function which was also supported by the molecular weight of this compound (see above).

The nuclear magnetic resonance spectrum of the acetate (VII) (Fig. 1 a) showed two singlets (3H each), one at 2.26 and the other at 2.06 p.p.m., the later peak being attributed to the acetyl group, and a diffuse doublet (1H) ($J=2.0$ c.p.s.) at 4.91 p.p.m. which was identified with the proton geminal to the acetoxy group. In accord with this view the signal at 4.91 p.p.m. disappeared in the spectrum of the diketone (VIII) (Fig. 1b), confirming our view that the hydroxyl group in isopropylidenedihydrotaxinolactone is secondary.

Treatment of isopropylidenedihydrotaxinolactone with 0.1*N* ethanolic potassium hydroxide under reflux afforded after acidification an unsaturated compound (IX) $\text{C}_{20}\text{H}_{30}\text{O}_5 \cdot \text{H}_2\text{O}$, m.p. 124~125°, which exhibited an α , β -unsaturated carbonyl band at 232 $\text{m}\mu$ (ϵ 5720) in the ultraviolet absorption spectrum. In accord with this finding the carbonyl band in the infrared spectrum of this compound was at a low frequency (1660 cm^{-1}) and a vinylic proton appeared at 5.79 p.p.m (1H, doublet, $J=7.5$ c.p.s.) in the nuclear magnetic resonance spectrum. The ready elimination of the elements of acetone would suggest that one of the isopropylidene hydroxyl groups in isopropylidenedihydrotaxinolactone is on a carbon β to a carbonyl group.

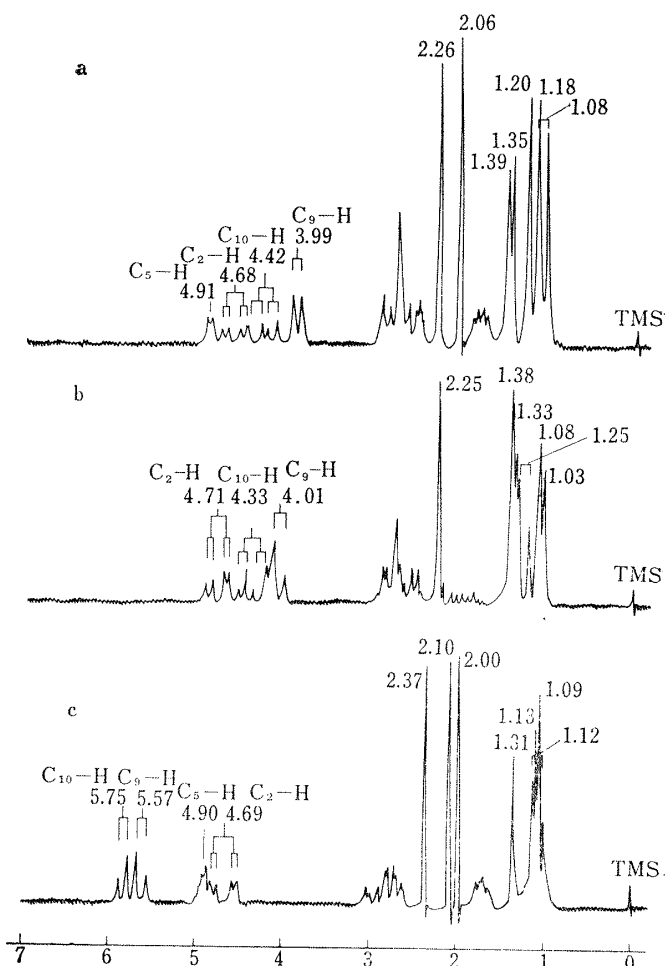


Fig. 1. Nuclear Magnetic Resonance Spectra in Deuteriochloroform

a) Isopropylidenedihydrotaxinolactone acetate (VII)
b) Diketone (VIII) c) Enonediacetate (X)

The α , β -unsaturated carbonyl compound still contained a lactone grouping as shown by its infrared absorption band at 1760 cm^{-1} and by the fact that it was soluble in hot aqueous sodium hydroxide and was recovered unchanged on acidification of the solution. That the α , β -unsaturated carbonyl compound contained two secondary hydroxyl groups, one as in the parent compound and the other as a result of elimination of the elements of acetone from the isopropylidene α -glycol was demonstrated clearly by the nuclear magnetic resonance spectrum (Fig. 1 c) of its diacetate (X), $\text{C}_{24}\text{H}_{34}\text{O}_7$, m.p. $228\sim 229^\circ$, which showed three singlets (3H each) at 2.37, 2.10 and 2.00 p.p.m. Of these signals, one was assigned to methyl protons of the methyl ketone while the remaining two peaks were attributed to the acetyl groups. Moreover, it showed the presence of only three tertiary methyls at 1.09, 1.13 and 1.31 p.p.m. and one secondary methyl centered at 1.12 p.p.m. ($J=7.0$ c.p.s.); no signals consistent with the retention of the original isopropylidene moiety were observed. In agreement with this inference the infrared spectrum exhibited absorption bands at 1765 (γ -lactone), 1720 and 1725 (acetyl groups), and 1670 cm^{-1} (conjugated CO) but no hydroxyl absorption in the region of 3600 cm^{-1} . On the basis of the evidence thus accumulated, it seemed plausible to assign formula (VI) to isopropylidenedihydrotaxinolactone and IX to its transformation product, the α , β -unsaturated carbonyl compound (Chart 1).

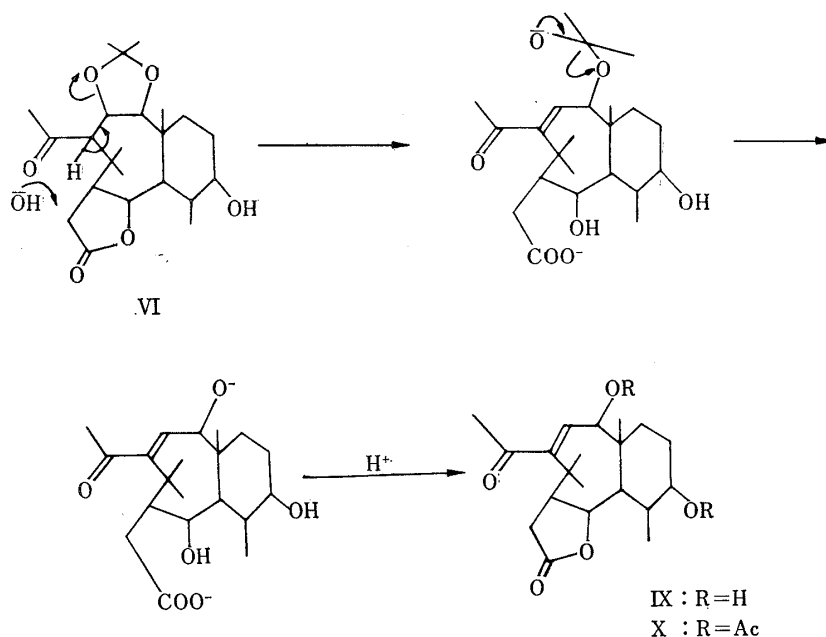


Chart 1.

The cleavage of ring A took place also when dihydrotaxinol (IV) itself was heated in ethanol or in methanol containing a small amount of hydrogen chloride for 20~30 hr. Although the reaction product was not crystalline, it showed the expected infrared absorption bands at 1760 (γ -lactone) and 1710 cm^{-1} (ketone). The oily product was however converted easily into isopropylidenedihydrotaxinolactone (VI) upon treatment with acetone containing a trace of acid.

Taking into consideration all of these experimental results, there seems to be no doubt that the key step is autooxidative cleavage of $\text{C}_{12}\text{-C}_{13}$ bond in dihydrotaxinol (IV).

Experimental

The NMR spectra were determined with a Varian A-60 spectrometer.

1) **Isopropylidenedihydrotaxinolactone (VI) and Its Acetate (VII)**—A mixture of IV (0.12 g.) and *p*-toluenesulfonic acid (0.02 g.) in acetone (20 ml.) was refluxed for 20 hr. The mixture was basified with aqueous

K_2CO_3 and the acetone was removed by evaporation under reduced pressure. The resulting aqueous solution was extracted with $CHCl_3$ and the organic phase was washed with H_2O , dried (Na_2SO_4) and concentrated to dryness to give a crystalline mass (0.11 g.) which was chromatographed in $CHCl_3$ on silica gel. The first $CHCl_3$ eluate gave VI (55 mg.), m.p. $325\sim 326^\circ$ after crystallization from MeOH. $[\alpha]_D + 2.4^\circ$ ($c=0.4$, EtOH). *Anal.* Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.44; H, 8.88. IR ν_{max}^{KBr} cm^{-1} : 3600 (OH), 1755 (γ -lactone), 1710 (methyl ketone). NMR ($CDCl_3$ - C_5D_5N , 1:1) (p.p.m.): 0.96, 1.15, 1.21 ($-C-CH_3$); 1.31, 1.39 (isopropylidene methyl); 1.01 (doublet, $J=7.0$ c.p.s., $CHCH_3$); 2.21 ($COCH_3$); 3.90 (multiplet, C_5-H); 4.10 (doublet, $J=7.0$ c.p.s., C_9-H); 4.66 (quartet, $J=7.0$, 11.5 c.p.s., $C_{10}-H$); 4.85 (quartet, $J=13.0$, 8.0 c.p.s., C_2-H).

Further elution with the same solvent gave isopropylidenedihydrotaxinol (V) (55 mg.), m.p. and mixed m.p. $236\sim 238^\circ$ (from hexane-acetone).

Treatment of VI with Ac_2O -pyridine gave the acetate (VII) as prisms, m.p. $248\sim 250^\circ$ (from MeOH). $[\alpha]_D -13.6^\circ$ ($c=0.8$, EtOH). *Anal.* Calcd. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.82; H, 8.70. IR ν_{max}^{KBr} cm^{-1} : 1765 (γ -lactone CO), 1715 (OAc), 1705 (methyl ketone).

2) A solution of dihydrotaxinol (IV) (0.3 g.) in acetone (20 ml.) containing two drops of conc. HCl was refluxed for 24 hr. After adding one more drop of conc. HCl, the reflux was continued for a further 10 hr. The resulting light brown mixture was concentrated under reduced pressure to give a semicrystalline solid, which was collected and washed with H_2O . Recrystallization from MeOH with charcoal treatment gave isopropylidenedihydrotaxinolactone (VI) (0.13 g.) as colorless needles, m.p. and mixed m.p. $325\sim 326^\circ$.

3) A solution of IV (0.2 g.) in EtOH (20 ml.) containing two drops of conc. HCl was refluxed for 20 hr. The resulting light brown solution was concentrated under reduced pressure to give an oil (0.1 g.), which was chromatographed in $CHCl_3$ on silica gel. The first fraction showed a single spot on thin-layer chromatogram and in the infrared spectrum absorptions at 1760 (γ -lactone), and 1710 (ketone) were noted. After refluxing the oil in acetone (10 ml.) containing one drop of HCl for 10 hr., needles (0.05 g.), m.p. and mixed m.p. $325\sim 326^\circ$, were obtained.

Chromic Acid Oxidation of Isopropylidenedihydrotaxinolactone (VI)—To a solution of CrO_3 (0.04 g.) in 80% AcOH (2 ml.) VI (0.13 g.) in AcOH (2 ml.) was added. After allowing to stand the mixture at room temperature for 15 hr., it was poured into a saturated NaCl solution, extracted with $CHCl_3$, and the organic phase was washed with H_2O , dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The residue (0.15 g.) was crystallized from acetone-isopropyl ether to afford the diketone (VIII) as prisms, m.p. $258\sim 260^\circ$. *Anal.* Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.02; H, 8.23. IR ν_{max}^{KBr} cm^{-1} : 1780 (γ -lactone), 1710 (methyl ketone and six-membered ketone).

Treatment of Isopropylidenedihydrotaxinolactone (VI) with 0.1N Ethanolic Sodium Hydroxide—A solution of VI (0.21 g.) in 0.1N ethanolic NaOH (10 ml.) was refluxed on a water bath for 2 hr. The mixture was evaporated to dryness under reduced pressure, the residue taken up in H_2O , washed with $CHCl_3$, acidified with HCl, and extracted with EtOAc. The latter extract was washed with H_2O , dried (Na_2SO_4), and evaporated to leave an oil (0.14 g.) which was chromatographed in $CHCl_3$ on silica gel. Elution with MeOH- $CHCl_3$ (1:100) gave needles (0.12 g.) which were crystallized from hexane-MeOH to afford the α,β -unsaturated ketone (IX), m.p. $124\sim 125^\circ$. *Anal.* Calcd. for $C_{20}H_{30}O_5 \cdot H_2O$: C, 65.19; H, 8.75. Found: C, 65.21; H, 8.75. IR ν_{max}^{KBr} cm^{-1} : 3600, 3400, 3300 (OH), 1760 (γ -lactone), 1660 (α,β -unsaturated ketone). UV λ_{max}^{EtOH} $m\mu$ (ϵ): 232 (5720).

The same compound (IX) was also obtained on treatment of the acetate (VII) with alkali under the same conditions as described above.

Acetylation of compound (IX) with Ac_2O in pyridine gave the diacetate (X) as needles, m.p. $228\sim 229^\circ$ (from MeOH). $[\alpha]_D -54.8^\circ$ ($c=0.9$, EtOAc). *Anal.* Calcd. for $C_{24}H_{34}O_7$: C, 66.34; H, 7.89. Found: C, 66.47; H, 7.84. IR ν_{max}^{KBr} cm^{-1} : 1765 (γ -lactone), 1725, 1720 (OAc), 1670 (α,β -unsaturated ketone). UV λ_{max}^{EtOH} $m\mu$ (ϵ): 228 (4000).

Summary

A new compound, isopropylidenedihydrotaxinolactone, $C_{23}H_{36}O_6$, has been isolated as a by-product on treatment of dihydrotaxinol with acetone in the presence of toluene-sulfonic acid or hydrochloric acid and shown to be represented by formula VI.

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