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The Constituent of the Heartwood of *Taxus cuspidata* Sieb. et Zucc.

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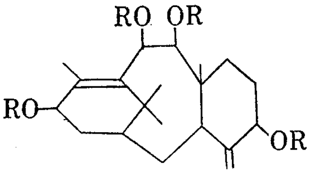
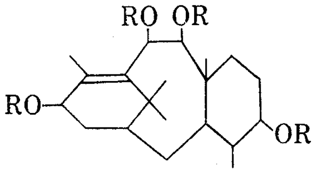
The leaves of *T. cuspidata* Sieb. et Zucc. (Japanese name, Ichii) contain taxinine and many other taxane derivatives.[2] One of the authors isolated a new diterpene from the heartwood of the plant and designated the compound as taxusin (Ia).[3] Taxusin contains four acetyl groups: sodium hydroxide converted to the tetraol (Ib), mp 196—198°, $[\alpha]_D$ $+140°$, treatment of which with acetic anhydride afforded the tetraacetate, *i.e.*, taxusin (Ia).

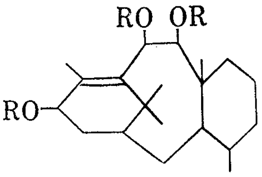
Taxusin contains two double bonds consisting of terminal methylene and tetra substituted olefin. Catalytic reduction of Ia afforded dihydro-derivative (IIa) and desacetoxyl dihydro-derivative (IIIa). Hydrolysis of IIa and IIIa gave the corresponding tetraol (IIb) and triol (IIIb) and these hydrolysed compounds were acetylated to original acetyl compounds (IIa and IIIa) respectively.



Ia : R=Ac
Ib : R=H

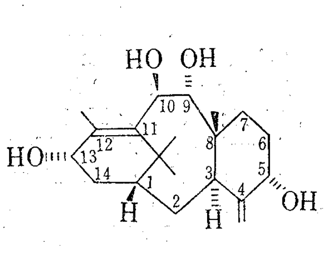


IIa : R=Ac
IIb : R=H

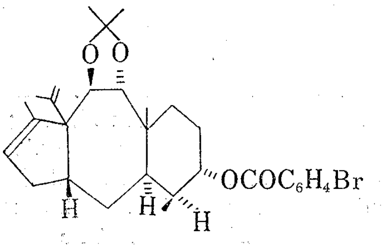


IIIa : R=Ac
IIIb : R=H

Recently, English workers[4] isolated a new diterpene tetraol, $C_{20}H_{32}O_4$, mp 195—198°, $[\alpha]_D$ $+134°$, from the heartwood of yew (*T. baccata* L.) and determined the structure as IV on the basis of X-ray analysis of its dihydro-anhydro-*p*-bromobenzoyl acetonide (V).



IV



V

Our tetraol (Ib) was shown to have the same structure as the English workers' tetraol (IV). We thank Dr. Halsall for identification of these compounds.

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1) Location: *a) Meguro-ku, Tokyo. b) Hiromachi, Shinagawa-ku, Tokyo.*
2) M.C. Woods, K. Sho, Y. Nakahira, and K. Nakanishi, 20th Annual meeting of Japan Chemical Society (1967, Tokyo).
3) M. Miyazaki, K. Schimizu, T. Takahashi, M. Yasue, H. Iamura, and O. Honda, 14th Annual meeting of Japan Wood Research Society (1964, Tokyo).
4) W.R. Chan, T.G. Halsall, G.M. Hornby, A.W. Oxford, W. Sabel, K. Bjåmer, G. Ferguson, and J.M. Robertson, *Chem. Comm.*, 923 (1966).

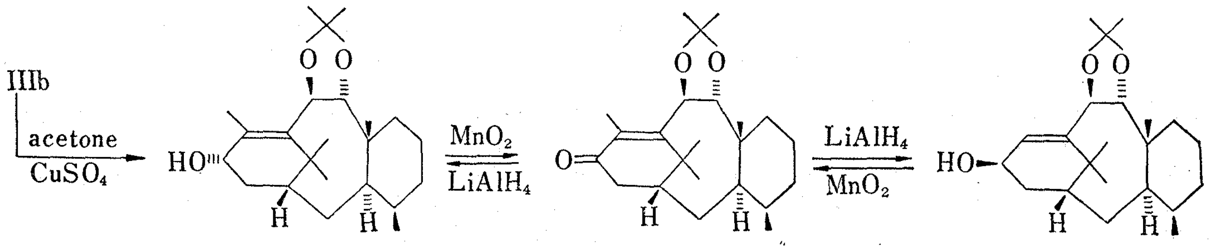
The English workers formulated the configuration of the hydroxyl group at C–13 as α–orientation, but the reason has not been described.

This note reports the application of Mills' rule[5] to determine the absolute configuration of this group.

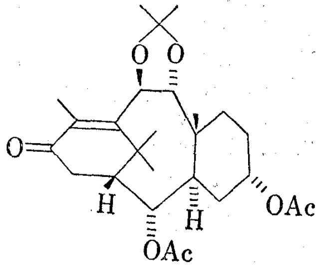
Although the hydrolyzed derivatives (Ib, IIb, and IIIb) are labile to acids, when treated with acetone and a small amount of cupric sulfate at room temperature, the triol (IIIb) afforded an acetonide (VI), which was oxidized to an α,β–unsaturated ketone (VII) with manganese dioxide. Reduction of VII with lithium aluminium hydride resulted into a pair of epimeric alcohols (VI and VIII), one being identified with VI, the other (VIII) was oxidized to VII by manganese dioxide.

The UV maxima of these derivatives (VI, VII, and VIII) are some 25 mμ higher than the value expected for the same olefin and enone types. The unusual light–absorptions are characteristic to taxan derivatives.[4,6]

The optical rotation of VI, $[\alpha]_D$ +189.4° (c=1, EtOH), is more laevorotatory than that of VIII, $[\alpha]_D$ +235.7° (c=1, EtOH). According to Mills' empirical rule[5] for allylic cyclohexenols, the absolute configurations at C–13 of the epimeric alcohols are as shown (VI and VIII). As the ORD curves[7] of VII and taxinine acetonide (IX) are almost superimposed, the stereochemistry at C–1 of taxusin should possess the same configuration as taxinine,[8] the stereostructure of which was determined by X–ray analysis. These observation coincides with the depiction of the English workers.



VI VII VIII



IX

Experimental

Isolation of Taxusin (Ia)——The finely ground heartwood (10 kg) was extracted three times with MeOH at room temperature. The resulting MeOH solution was concentrated and diluted with H_2O. The aqueous solution was extracted with benzene–hexane (2:1). Evaporation of the solvent gave a brownish oil, which

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[5] J.A. Mills, *J. Chem. Soc.*, **1952**, 4976.

[6] J.W. Harrison and B. Lythgoe, *J. Chem. Soc.*, **1966**, 1932.

[7] C. Djerassi, "Optical Rotatory Dispersion, Applications to Organic Chemistry," McGraw–Hill Book Co., New York, N.Y., 1960.

[8] M. Shiro, T. Sato, H. Koyama, Y. Niki, K. Nakanishi, and S. Uyeo, *Chem. Comm.*, 97 (1966).

[9] S. Uyeo, K. Ueda, Y. Yamamoto, and Y. Maki, *Yakugaku Zasshi*, **84**, 762 (1964).

was chromatographed on silica-gel (×30) with ether–hexane (1:1). The eluted terpenoid fraction was crystallized by trituration with ether. Taxusin, recrystallized from ether, melted at 131—132° after drying. Yield was 40 g. *Anal.* Calcd. for $C_{28}H_{40}O_8$: C, 66.64; H, 7.99. Found: C, 66.69; H, 8.18. UV λ_{max}^{EtOH} mμ (ε): 217 (6600).

Hydrogenation of Taxusin (Ia)——A solution of taxusin (10 g) in EtOH (100 ml) was shaken with hydrogen in the presence of 5% Pd–C (4 g). After filtration and evaporation, the residue was introduced on to a column of silica gel (200 g) in ether–hexane (1:1). Elution with ether–hexane (1:1) separated dihydrotaxusin (IIa) in 40% yield, mp 162—163°, and desacetoxyldihydrotaxusin (IIIa), mp 167—168°, in 50% yield. Both products were recrystallized from ether–hexane from analytical purpose. *Anal.* Calcd. for $C_{28}H_{42}O_8$ (IIa): C, 66.38; H, 8.36. Found: C, 66.51; H, 8.42. Calcd. for $C_{26}H_{40}O_6$ (IIIa): C, 69.61; H, 8.99. Found: C, 69.61; H, 9.02.

Hydrolysis of Taxusin——A solution of taxusin (10 g) and NaOH (4 g) in MeOH–H_2O (120 ml, 5:1) was refluxed for 5 hr and the reaction mixture was diluted with H_2O. The resulting precipitates were collected and recrystallized from EtOH. The tetraol (Ib) melted at 196—198°. Yield was quantitative (5.8 g). *Anal.* Calcd. for $C_{20}H_{32}O_4$ (Ib): C, 71.39; H, 9.59. Found: C, 71.29; H, 9.57. UV λ_{max}^{EtOH} mμ (ε): 227 (5000).

Acetylation of the tetraol with Ac_2O and pyridine gave tetraacetate, mp 130—132°, which was identified with taxusin.

Hydrolysis of IIa and IIIa——Dihydrotaxusin (IIa) and its desacetoxyl compound (IIIa) were hydrolyzed with KOH by the same manner as taxusin.

Dihydrotetraol (IIb) recrystallized from EtOH melted at 209—214°. *Anal.* Calcd. for $C_{20}H_{34}O_4$ (IIb): C, 70.97; H, 10.13. Found: C, 70.91; H, 10.32.

Dihydrotriol (IIIb) recrystallized from ether–hexane melted at 180—182° (presoftened at 175°). *Anal.* Calcd. for $C_{20}H_{34}O_3$ (IIIb): C, 74.49; H, 10.63. Found: C, 74.20; H, 10.63.

Acetonide of Dihydrotriol (VI)——The dihydrotriol (IIIb) (1.0 g) and anhydrous $CuSO_4$ (1.0 g) was shaken in dry acetone (50 ml) for 1 hr. The filtrate was made alkaline with saturated aqueous $NaHCO_3$ and concentrated to low volume, and was diluted with H_2O and extracted with ether. The ether solution was washed with H_2O and evaporated. The residue (1.0 g) was recrystallized from hexane as needles, mp 170—172°, $[\alpha]_D$ $+189.4°$ ($c=1$, EtOH). *Anal.* Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.34; H, 10.50. UV λ_{max}^{EtOH} mμ (ε): 224 (6500).

α,β-Unsaturated Ketone (VII)——The alcohol (VI) (2.0 g) and MnO_2 (6.0 g) was shaken in $CHCl_3$–hexane (60 ml, 1:1) for 5 hr. Filtration and evaporation of the reaction mixture gave a crystalline residue (1.8 g), which was recrystallized from ether–hexane (1:1) as needles, mp 154°. *Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.50; H, 9.98. UV λ_{max}^{EtOH} mμ (ε): 275 (6800). ORD in dioxane ($c=0.13$, 500—300 mμ): $[\alpha]_{500}$ $+370°$, $[\alpha]_{425}$ 0°, $[\alpha]_{386}$ -1350, $[\alpha]_{370}$ 0°, $[\alpha]_{340-320}$ $+9730$ (shoulder).

Reduction of the Ketone (VII)——To a stirred slurry of 1.0 g of $LiAlH_4$ in 100 ml of anhydrous ether was added the ketone (VII) (0.5 g) under ice-cooling. After standing overnight, the reaction mixture was treated with AcOEt and H_2O. Evaporation of the filtrate gave an oil (1.0 g), which was chromatographed on alumina (Grade III) with hexane. The major fraction (0.5 g) is consisted of an epimeric alcohol (VIII), mp 155—156°, $[\alpha]_D$ $+235.7°$ ($c=1$, EtOH), which was oxidized to the α,β-unsaturated ketone (VI) with MnO_2 in quantitative yield. The minor fraction (0.2 g) is consisted of an alcohol, mp 170—172°, $[\alpha]_D$ $+189.4°$ ($c=1$, EtOH), which was identified with the alcohol (VI). *Anal.* Calcd. for $C_{23}H_{38}O_3$ (VIII): C, 76.19; H, 10.57. Found: C, 76.01; H, 10.48. UV λ_{max}^{EtOH} mμ (ε): 226 (6900).

Isopropylidenedecinnamoyltrisdeacetyltaxinine Diacetate (IX)——Isopropylidenedecinnamoyltrisdeacetyltaxinine[9] was acetylated with Ac_2O and pyridine as usual. The acetate, mp 160—161°, was recrystallized from hexane. *Anal.* Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.59; H, 8.08. ORD in dioxane ($c=0.12$, 500—300 mμ): $[\alpha]_{500}$ $+80°$, $[\alpha]_{440}$ 0°, $[\alpha]_{384}$ -1560, $[\alpha]_{365}$ 0°, $[\alpha]_{340-310}$ $+7210$ (shoulder).