Tetrahedron Letters No.24, pp. 1917-1926, 1965. Pergamon Press Ltd.
Printed in Great Britain.

THE STEREOCHEMISTRY OF TAXININE

Masayasu Kurono,[a] Yoshifumi Maki,[b] Koji Nakanishi,[a]* Motoaki Ohashi,[a] Kanichi Ueda,[c] Shojiro Uyeo,[d]* M. C. Woods,[a] Yoshitomo Yamamoto.[d]

a) Department of Chemistry, Tohoku University, Sendai.
b) Gifu College of Pharmacy, Gifu.
c) Basic Research Laboratories, Toyo Rayon Co. Ltd., Kamakura.
d) Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto.

(Received 12 April 1965)

The planar structure 1a (without stereochemistry) has been recently assigned[1, 2, 3] to taxinine, a diterpenoid from the Japanese yew tree. At about the same time, Lythgoe and his co-workers published[4] structures 1a and 1b (both without stereochemistry) for the triacetates of the closely related diterpenoids, O-cinnamoyltaxicin-II and -I; the triacetate of the former has been shown to be identical with taxinine by a direct comparison of the two compounds.[5] From the evidence summarized in this communication, we propose the stereochemistry depicted in 1a** (cf. 8) for taxinine.

Configuration at $C_{(1)}$

The nature of the A/B ring junction in taxinine requires the $C_{(1)}$-H to be equatorial and, as can be seen from Dreiding models (cf. stereostructure 8), causes the C=C-C=O grouping to adopt a definite chirality, the sense of which is governed only by the absolute configuration at $C_{(1)}$.

---

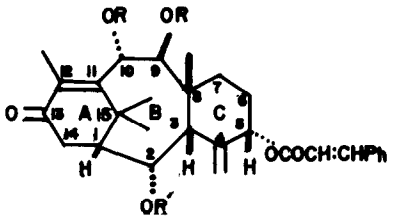
* To whom requests for reprints should be made.

** A proposed numbering system for this type of structure has been published[6] and the name "Taxane" suggested for the saturated nucleus.

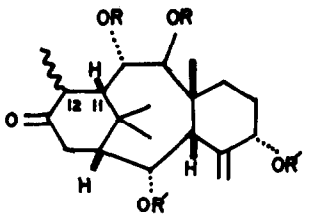
Accordingly, the sign of the Cotton effect in the K-band can be used [7] to determine the absolute configuration at $C_{(1)}$, and on this basis a β-configuration is assigned to the $C_{(1)}$-hydrogen since taxinine and certain of its derivatives, e. g. 1c, 1d, and the hydrogenolysis product [1, 2] (1a with a $C_{(4)}$-Me and $C_{(5)}$-H_2), exhibit large-amplitude positive K-band Cotton effects (superimposed on a negative R-band Cotton effect of small amplitude). Taxinine, for example, in dioxan shows $[M]_{600}$ +650°, $[M]_{380}$ -6070° (trough), $[M]_{369}$ 0°, $[M]_{330}$ +46400° (inflection), $[M]_{284}$ +93400° (peak), $[M]_{280}$ +75000°.

Configurations at $C_{(3)}$, $C_{(5)}$, and $C_{(8)}$.

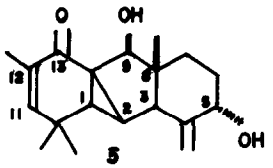
In the NMR spectra of taxinine and derivatives having an intact B-ring, e. g. taxinol tetraacetate (2a), [2] the $C_{(5)}$-proton signal appears as a poorly resolved triplet (half-band width 4 cps), indicating that this proton is only weakly coupled to the two protons at $C_{(6)}$. Such weak couplings can only be explained if the $C_{(5)}$-H bond is equatorial and bisects the angle between the methylene protons at $C_{(6)}$. In the spectrum of secotaxinol diacetate (3), [2] however, the $C_{(5)}$-proton signal is a broad multiplet (half-band width 22 cps), clearly indicating that the 5-hydrogen is axial in this derivative and that inversion of ring C has occurred. From consideration of the substitution pattern in ring C, it is apparent that the very bulky $C_{(3)}$-substituent would adopt the equatorial configuration with ring C in the chair form. Hence the $C_{(3)}$-hydrogen must be axial and therefore on the same side of ring C as the $C_{(5)}$-hydrogen, i. e., $C_{(3)}$-H and $C_{(5)}$-H are cis. Steric interactions in ring B of taxinine and taxinol tetraacetate prevent inversion of ring C before cleavage of the $C_{(9)}$-$C_{(10)}$ bond (cf. steric-structure 8).



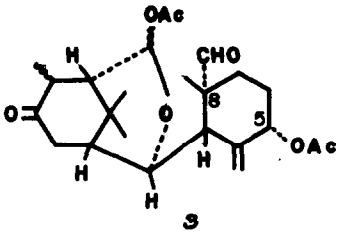
1a: R=R′=Ac
1b: R=R′=Ac; 1β-OH
1c: R, R=>CMe$_2$; R′=H; 5α-OH
1d: R, R=>CMe$_2$; R′=Ac
1e: R=H, R′=Ac
1f: R, R=>CMe$_2$; 2-oxo; 5α-OH



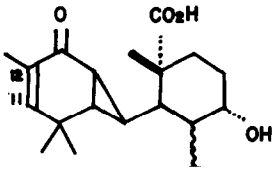
2a: R=R′=Ac
2b: R=R′=H
2c: R, R=>CMe$_2$; R′=Ac



5

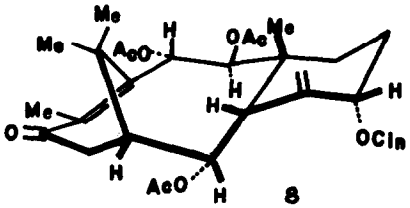


3

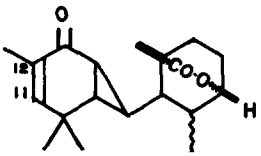


6

6a: satd. at C_{11}, C_{12}

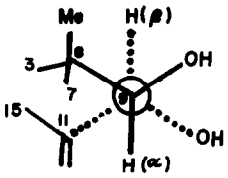


8

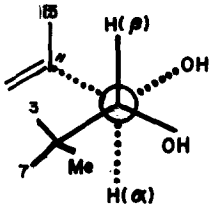


7

7a: satd. at C_{11}, C_{12}



B



C

The dihydroxy dienone (5), prepared[8] from anhydrotaxininol (4),[8,9] has been converted into a hydroxy acid (6), m. p. 195-197°, by selective hydrogenation (Pt/H_2 in ethanol) of the exocyclic double bond and acetylation of the 5-hydroxyl followed by mild oxidation of the 9-hydroxyl and alkaline cleavage of the 9,14-bond in the resulting diketone. Reduction of both double bonds (Pt/H_2 followed by $Pd\text{-}C/H_2$ in ethanol) in 5, followed by the same series of reactions afforded the saturated hydroxy acid (6a), m. p. 189-190°. Both these acids form lactones (7 and 7a), m. p. 234-235° and 196-197°, respectively, on treatment with acetic anhydride. This requires the 5-hydrogen and 8-methyl to be on the same side of ring C in these acids and also in taxinine since it is unlikely that any alteration of the configurations at $C_{(3)}$, $C_{(5)}$, and $C_{(8)}$ would have occurred during the transformation of taxinine into these lactones.

The foregoing evidence provides the relative configurations of $C_{(3)}$, $C_{(5)}$, and $C_{(8)}$. their absolute configurations were determined by application of the recently devised method of Horeau[10] to the compounds listed in Table 1. In each case, the α-phenylbutyric acid isolated was levorotatory indicating the presence of a 5α-hydroxyl group, in the above compounds.

TABLE 1

Compound	Esterification Yield	Optical Yield	Rotation
Methyl ester of 6	79%	53%	-0.17°
Anhydrotaxininol (4) (Scheme 1)	46%	67%	-0.37°
The ketol 1f	15%	82%	-0.13°

Although anhydrotaxininol has two hydroxyl groups only the 5-hydroxyl is acylated under these conditions; this was confirmed by isolation of the

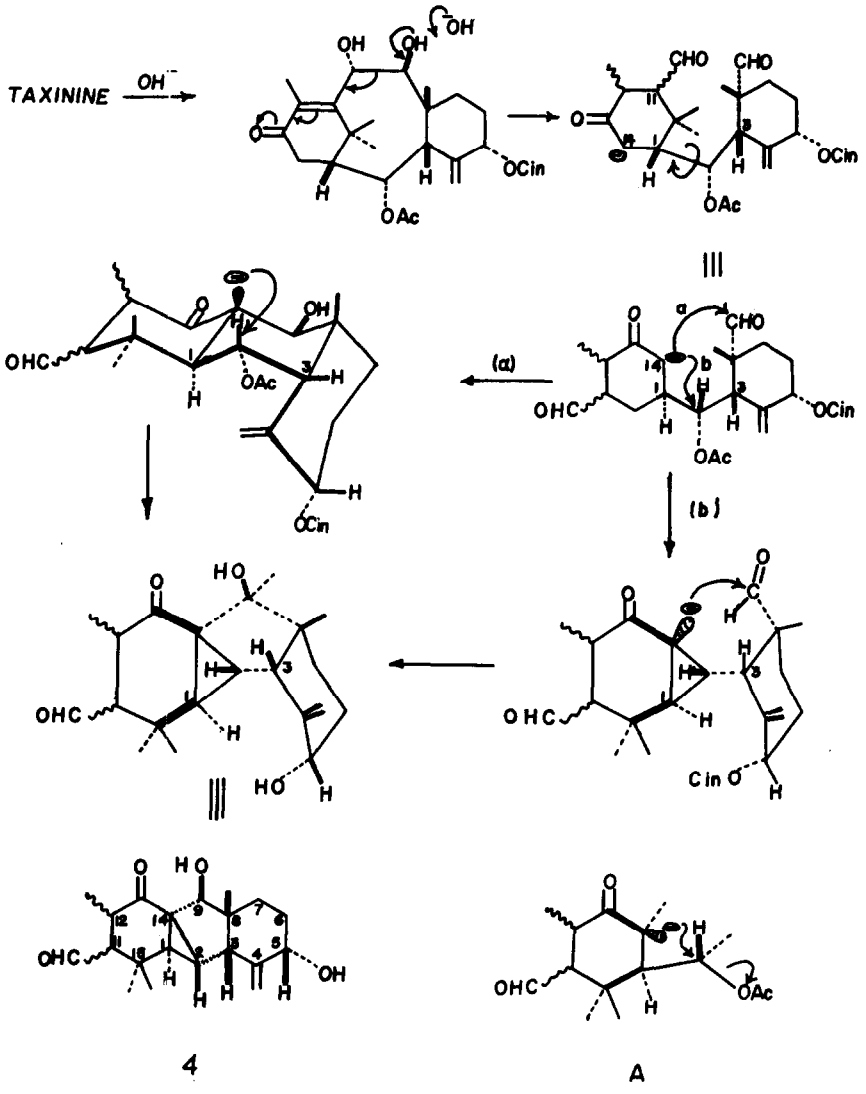
crude product which showed the presence of only starting material and the 5-acyl derivative (by IR, NMR, and thin layer chromatography). The methyl ester of 6 could not be obtained crystalline but appeared to be homogeneous.

Configuration at $C_{(2)}$

Taxinine is converted into anhydrotaxininol by a mechanism, depicted in Scheme 1, which involves partial hydrolysis of the acyl groups, a retroaldol cleavage of the 9, 10-diol grouping, and, after rotation of ring A through 180° about the $C_{(1)}$-$C_{(2)}$ bond (causing the 1β-hydrogen in taxinine, (cf. 8), to become a 1α-hydrogen in anhydrotaxininol (4)), either an aldol condensation followed by a rear-attack at $C_{(2)}$ by the $C_{(14)}$-carbanion leading to expulsion of the $C_{(2)}$-acetoxyl as OAc (route a), or the carbanion attack first, to form the three-membered ring, and then an aldol condensation (route b). Since neither the five- nor the six-membered rings in anhydrotaxininol can be trans-fused to the cyclopropane ring, it follows that the $C_{(1)}$-hydrogen, which is α as shown above, must be trans to the $C_{(2)}$-hydrogen which is therefore β. A cyclopropane ring having this arrangement of substituents can only be formed from an intramolecular S_N2 attack by the $C_{(14)}$-carbanion on a $C_{(2)}$ having the substituents arranged as depicted in A, irrespective of whether route (a) or route (b) is followed. With a 2β-hydroxyl the cyclopropane ring could not have been formed.

That anhydrotaxininol has the stereochemistry depicted in 4 follows from the above mechanism and from the existence of strong intramolecular hydrogen-bonding between the 9-hydroxyl and the ketone, as evidenced by its infrared absorption[8] and NMR spectrum (9-OH proton signal is a sharp

SCHEME 1



doublet at 6.08 ppm).

Configurations at $C_{(9)}$ and $C_{(10)}$.

Although a firm assignment of the configurations at $C_{(9)}$ and $C_{(10)}$ in taxinine cannot be given, the following evidence suggests that the configurations depicted in structure 8 are probably correct. The ease with which dideacetyltaxinine (1e) and taxinol (2b) form acetonides,[1,2] suggests that the dihedral angle (ϕ) between the hydroxyls is small. Confirmation of this is provided by the following; (i) dilute solutions of the diol 1e in CCl_4 (0.0015 and 0.0030 M) show a band at 3620 cm^{-1} (free OH) and a concentration independent band at 3590 cm^{-1} indicating the presence of intramolecular hydrogen-bonding between the 9- and 10-hydroxyls, and (ii) the coupling constant between the $C_{(9)}$- and $C_{(10)}$-protons is large (9-11 cps) in taxinine (1a), taxinol tetraacetate (2a), dideacetyltaxinine (1e) and its acetonide (1d), and taxinol acetonide diacetate (2c). The large $J_{9,10}$ is more in accord with a trans-9,10-diol than a cis-diol, since the latter would need to have the 9- and 10-hydroxyls practically eclipsed, which is most unlikely to be stable in a flexible eight-membered ring. Moreover, from an examination of Dreiding models, it does not seem to be possible for taxinol to form an acetonide without introducing a considerable amount of strain into the molecule, if the 9,10-diol is cis-oriented.

In the NMR spectra of taxinine, dideacetyltaxinine (1e), and its acetonide (1d), the 9- and 10-protons appear as an AB-type quartet in which the high-field doublet (due to the 9-proton) is invariably somewhat shorter and broader than the low-field doublet. This indicates that the 9-proton must be subject to an additional small coupling. The only proton(s) likely to be engaged in this long-range coupling are the $C_{(8)}$-methyl

protons, and these will be coupled to the 9-proton only when the 9-hydrogen and 8-methyl are in an anti-trans relationship ($\phi = 180^{\circ}$)[11, 12] which is the case with a 9α-proton (as in B) but not with a 9β-proton (as in C). Preliminary attempts at decoupling the 9-proton from the 8-methyl protons (by double resonance) tend to substantiate the above.

Furthermore, in taxinol tetraacetate* (2a) and taxinol acetonide diacetate* (2c), the coupling between the 10- and 11-protons is very small (about 1 cps). Dreiding models indicate that only in the case of a structure with a 9β, 10α-orientation of the oxygen functions, can such a small coupling constant be easily explained (dihedral angle between the 10- and 11-hydrogens is about 90°).

Finally, Reeves[13] has pointed out that in the sugar series, the absolute configuration of a 1, 2-diol appears to be related to the rotational shift in going from the diol to its acetonide; a diol with an arrangement of the hydroxyls as in (B) would give a positive shift whereas that as in (C) would give a negative shift. Since this relationship seems to hold for steroidal 1, 2-diols,[14] it may also be applicable in the case of taxinine derivatives. The positive shift ($+118^{\circ}$) in going from dideacetyltaxinine (1e) ($M_D + 952^{\circ}$) to its acetonide ($M_D + 1070^{\circ}$) is therefore in accord with a 9β, 10α-diol (B) but not a 9α, 10β-diol (C).

---

* Taxinol (2b) is considered to possess an 11β-hydrogen since it is formed from taxinine by a 1, 4-addition of hydrogen[2] to the β-face (i. e. the less hindered side) of the C=C-C=O grouping. Moreover, it does not seem possible to construct a stable Dreiding model of taxinol with a trans-A/B ring junction.

Acknowledgements

The authors are indebted to Dr. Nakadaira who participated in the early stage of the stereochemical studies and to Dr. N. S. Bhacca for measuring some of the 100 Mc NMR spectra.

REFERENCES

1) K. Ueda, S. Uyeo, Y. Yamamoto, and Y. Maki, Tetrahedron Letters, 2167 (1963); Yakugaku Zasshi, 84 762 (1964).

2) M. Kurono, Y. Nakadaira, S. Onuma, K. Sasaki, and K. Nakanishi, Tetrahedron Letters, 2153 (1963).

3) K. Nakanishi, M. Kurono, and N. S. Bhacca, ibid., 2161 (1963).

4) D. H. Eyre, J. W. Harrison, R. M. Scrowston, and B. Lythgoe, Proc. Chem. Soc., 271 (1963).

5) Personal communication from Professor B. Lythgoe.

6) B. Lythgoe, K. Nakanishi, and S. Uyeo, Proc. Chem. Soc., 301 (1964).

7) C. Djerassi, R. Records, E. Bunnenberg, K. Mislow, and A. Moscowitz, J. Am. Chem. Soc., 84 870 (1962).

8) Y. Yamamoto, S. Uyeo, K. Ueda, Chem. Pharm. Bull. (Japan), 12 386 (1964).

9) J. I. Taga, Chem. Pharm. Bull. (Japan), 12 389 (1964); Yakugaku Zasshi, 84 1067 (1964).

10) A. Horeau and H. B. Kagan, Tetrahedron, 20 2431 (1964).

11) C. W. Shoppee, F. P. Johnson, R. Lack, and S. Sternhell, Tetrahedron Letters, 2319 (1964).

12) D. H. Williams and N. S. Bhacca, Applications of NMR Spectroscopy in Organic Chemistry, p. 108. Holden-Day, San Francisco (1964).

13) R. E. Reeves, Advances in Carbohydrate Chemistry, 6 107 (1951).

14) A cursory survey of the literature has produced ten examples of steroidal diols which comply with this rule and no exceptions. See for example: J. Pataki, G. Rosenkranz, and C. Djerassi, J. Am. Chem. Soc., 73 5375 (1951) ($\Delta[M]_D$+158° for 22-isoallospirostan-2α, 3α-diol); M. Fieser, A. Quilico, A. Nickon, W. E. Rosen, E. J. Tarlton, and L. F. Fieser, ibid., 75 4066 (1953) ($\Delta[M]_D$-217° for ergosta-7, 22-diene-3β, 5α, 6α-triol); D. L. Klass, M. Fieser, and L. F. Fieser, ibid., 77 3829 (1955) ($\Delta[M]_D$+35° for 22a, 5α-spirostane-2β, 3β-diol); P. Ziegler, Canad. J. Chem., 34 1528 (1956) ($\Delta[M]_D$+64° for methyl 3α, 6β, 7β-trihydroxy allocholanate).