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MINOR TAXOIDS FROM *TAXUS WALLICHIANA*[1]

LUCIANO BARBONI, PIERLUIGI GARIBOLDI, ELISABETTA TORREGIANI,

Dipartimento di Scienze Chimiche, via S. Agostino 1, 62032 Camerino (MC),

GIOVANNI APPENDINO,* MARCELLA VARESE,

Dipartimento di Scienza e Tecnologia del Farmaco, via Giuria 9, 10125 Torino,

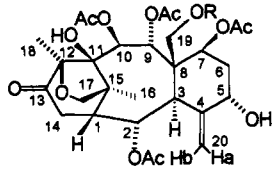
BRUNO GABETTA, and EZIO BOMBARDELLI

Indena S.p.A., via Ripamonti 99, 20141 Milano, Italy

ABSTRACT.—The needles of *Taxus wallichiana* afforded a new analogue of taxinine M [**1a**] and two derivatives of brevifoliol [**2a**,**3a**]. The conformation of **3a** was investigated by nmr spectroscopy with the aid of variable-temperature experiments and *in situ* reactions.

The needles of the Himalayan yew (*Taxus wallichiana* Zucc., Taxaceae) are a valuable and renewable source of paclitaxel (=Taxol®) and paclitaxel analogues (2). Several other taxoids have been isolated, including one of a novel structural type (3) and a more oxygenated derivative of 10-deacetylbaccatin III (4) from which a new class of antitumor taxoids was synthesized (5,6). *T. wallichiana* is the only yew with a significant history of medicinal use (7). Indeed, the basic alkaloids responsible for the poisonous properties of the European yew have not been reported from this plant. A further peculiarity of the Himalayan yew is the presence of substantial amounts of apocarotenoids (8), a class of compounds that is only present in traces in other yews. We now report the isolation of three new taxoids from the needles of *T. wallichiana*.

Compound **1a** was obtained as an amorphous gum. Cims established the molecular formula of $C_{30}H_{40}O_{14}$. The ^{1}H- and ^{13}C-nmr spectra of **1a** were similar to those of taxinine M [**1b**] (9), with the only differences being the absence of the benzoate resonances and the presence of an extra acetyl group in **1a** (Tables 1 and 2). A detailed analysis of the nmr spectra



R
1a Ac
1b Bz

with the aid of 2D techniques (COSY, ROESY, HETCOR) showed that **1a** is 19-debenzoyl-19-acetyltaxinine M. Compound **1a** belongs to the taxagifine class of taxanes (hydroxyl at C-11, oxygen bridge between C-12 and C-17). These compounds show some peculiar ^{1}H-nmr features, certain of which can be rationalized in the light of the solid-state conformation of the two compounds of this type investigated to date [taxagifine (10) and taxacin (11)]. Thus, the small value (ca. 3 Hz) of $J_{9,10}$ is due to an eclipsed conformation around the C-9,C-10 bond (ϕ ca. 120°), that places H-9 and H-10 in an anticlinal fashion (Figure 1, **A**). In the other structural types of taxoids, the conformation around the C-9,C-10 bond is instead staggered, and H-9 and H-10 are either antiperiplanar (**B**, $J_{9,10}$ ca. 10 Hz) or synclinal (**C**, $J_{9,10}$ ca. 4 Hz) (12). The peculiar conformation of ring B in taxagifine-type taxoids is required by the presence of the C-12,C-17 oxygen bridge, and also serves to reduce the severe nonbonded interaction between H-3 and the

[1]Part 19 in the series "The Chemistry and Occurrence of Taxane Derivatives." For Part 18, see Appendino *et al.* (1).

TABLE 1. ^{1}H-Nmr Data (300 MHz, $CDCl_3$, TMS as Reference, J in Hz) for Compounds **1a**, **2a**, and **3c**.

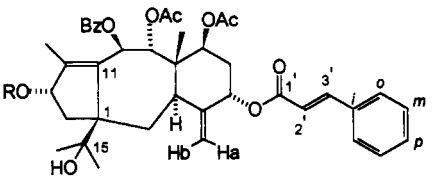
Proton	Compound		
	1a	**2a**[a]	**3c**[b]
1	2.42 br d (11.5)	—	—
2α	—	1.47 br d (14.3)	—
2β	6.16 dd (10.2, 2.0)	2.40 dd (14.3, 9.1)	5.97 d (9.4)
3	3.63 d (10.2)	2.86 d (9.1)	3.18 d (9.4)
5	4.38 br t (2.5)	5.52 dd (3.9, 2.1)	5.26 br t (2.5)
6α	2.16 m	2.04 m	1.98 m
6β	1.62 m	1.94 m	1.80 m
7	5.44 dd (10.5, 6.1)	5.66 dd (11.3, 5.6)	5.37 dd (10.8, 5.0)
9	5.48 d (3.1)	6.04 br d (10.6)	5.74 br d (10.8)
10	5.28 d (3.1)	6.67 d (10.6)	6.31 d (10.8)
13	—	4.49 br t (7.2)	5.60 br t (7.7)
14α	2.70 d (19.2)	1.21 dd (13.9, 7.1)	1.93 dd (14.9, 8.0)
14β	3.00 dd (19.2, 11.5)	2.37 dd (13.9, 7.5)	2.46 dd (14.9, 7.0)
16	1.59 s	1.31 s	1.70 s
17	4.19 d (8.0) 3.69 d (8.0	1.00 s	1.55 s
18	1.17 s	2.15 s	2.01 s
19	4.40 d (12.3) 4.28 d (12.3)	0.92 s	0.99 s
20A	5.31 s	5.31 s	4.61 s
20B	4.44 s	4.92 s	5.28 s
Ac	2.18 s, 2.11 s, 2.10 s 1.99 s, 1.96 s	2.06 s, 1.75 s	2.12 s, 2.07 s, 2.06 s, 2.05 s, 2.01 s, 1.86 s

[a]Signal of OH-15: δ 2.85 (1H, br s). Signals of the cinnamoyl moiety: δ 6.49 (1H, d, J=16.2 Hz, H-2′), 7.65 (1H, d, J=16.2 Hz, H-3′), 7.60–7.32 (5H, aromatic protons). Signals of the benzoyl moiety: δ 7.90 (2H, d, J=7.7 Hz, H-ortho), 7.60 (1H, t, J=7.7 Hz, H-para), 7.45 (2H, t, J=7.7 Hz, H-meta).

[b]Signal of the imide proton: δ 8.40 (1H, br s).

18-methyl caused by pyramidalization at C-11 and C-12. Other important nmr features of taxagifine-type taxoids are the large value of $J_{2,3}$ (10–11 Hz) and the fact that H-2 is the most deshielded acyloxymethine of ring B (Table 1). In the corresponding taxicines (C-11, C-12 double bond), H-2 is the most shielded oxymethine of ring B, and $J_{2,3}$ is ca. 7 Hz (13), although, at least in the solid state, the C-1,C-2 and the C-2,C-3 torsion angles are similar (14).

Compound **2a** ($C_{40}H_{46}O_{10}$, cims) was obtained as an oil. Its ^{1}H-nmr spectrum was similar to that of the 11(15→1)*abeo*-taxane taxuspine A (=5-cinnamoyl-13-acetylbrevifoliol, **2b**) (15,16), but one acetyl was missing and H-13 was moved upfield (Δδ −0.91). This suggested the presence of a free hydroxyl at C-13, as confirmed by a detailed analysis of the



R
2a H
2b Ac

^{1}H- and ^{13}C-nmr spectra (COSY, ROESY, FLOCK) that also confirmed the location of the ester groups (cinnamate at O-5, benzoate at O-10, acetates at O-7 and O-9) via inspection of the long-range correlations between the oxymethine protons and the corresponding ester groups. Thus, **2a** is 13-deacetyltaxuspine A (=5-cinnamoylbrevifoliol). Taxuspine A [**2b**] was also obtained from the fractions containing **2a**. The nmr spectra of **2a** and

TABLE 2. ^{13}C-Nmr Data (75.43 MHz, $CDCl_3$, TMS as Reference) for Compounds **1a**, **2a**, and **3c**.

Carbon	Compound		
	1a	**2a**[a]	**3c**[b]
C-1	48.7 d	63.1 s	68.4 s
C-2	70.4 d	29.2 t	66.7 d
C-3	38.4 d	39.1 d	43.2 d
C-4	144.6 s	145.6 s	139.6 s
C-5	72.7 d	74.2 d	75.7 d
C-6	39.2 t	33.9 t	34.7 t
C-7	68.7 d	69.7 d	68.7 t
C-8	49.7 s[c]	44.8 s	44.7 s
C-9	69.5 d	77.1 d	76.0 d
C-10	64.1 d	70.7 d	67.3 d
C-11	80.3 s	134.1 s	134.4 s
C-12	91.4 s	151.2 s	149.6 s
C-13	204.5 s	76.9 d	78.4 d
C-14	33.9 t	47.4 t	37.9 t
C-15	49.1 s[c]	75.5 s	77.0 s
C-16	15.1 q	24.8 q	22.6 q
C-17	82.2 t	27.0 q	22.1 q
C-18	12.1 q	11.9 q	12.1 q
C-19	61.6 t	12.9 q	13.6 q
C-20	113.0 t	114.1 t	115.5 t
Ac	172.1 s, 170.5 s, 169.8 s, 168.5 s, 168.1 s	169.9 s, 169.9 s	171.4 s, 171.2 s, 170.4 s, 169.6 s 169.3 s, 168.8 s
	21.4 q, 21.3 q, 20.8 q, 20.7 q, 20.7 q	21.4 q, 20.7 q	21.8 q, 21.2 q, 21.1 q, 21.0 q, 20.8 q, 20.6 q

[a]Signals of the cinnamoyl moiety: δ 165.8 (s, C-1′), 118.3 (d, C-2′), 165.8 (d, C-3′), 134.4 (s, ipso), 128.1 (d, ortho), 128.8 (d, meta), 130.2 (d, para). Signals of the benzoyl moiety: δ 164.1 (s), 129.2 (s, ipso), 129.4 (d, ortho), 128.7 (d, meta), 133.2 (d, para).

[b]Signals of the trichloroacetyl carbamoyl group: δ 90.5 (s, -CCl_3), 159.2, 148.8 (s, -CO-).

[c]Interchangeable assignments.

2b were sharp, and only the rotamer with ring B in the twist-boat conformation ($J_{9,10}$=10.6 Hz, see **B** in Figure 1) and ring C in the chair conformation ($J_{5,6\alpha}$=2.1 Hz, $J_{5,6\beta}$=3.9 Hz) (12) could be detected. In the alternative rotamer, ring B has a twist-chair conformation ($J_{9,10}$=ca. 4 Hz, see **C** in Figure 1) and ring C a boat conformation ($J_{5,6\alpha=5,6\beta}$=ca. 5 Hz) (12,17). Many brevifoliol derivatives exist instead as a mixture of rotamers (12, 17–19), and their slow interconversions give rise to broad nmr spectra (see below).

The structure elucidation of **3a** ($C_{26}H_{38}O_{10}$, cims) turned out to be a rather challenging undertaking. At room temperature only broad humps could be observed in the ^{1}H-nmr spectrum $CDCl_3$, and most resonances in the ^{13}C-nmr spectrum were too broad to be detected. At low temperature (−20°, MeOH-d_4) three sets of sharp lines were present, but assignment was difficult because of overlapping. Most resonances of the ^{1}H-nmr spectrum could be assigned at 160° (DMSO-d_6, sealed tube), where **3a** was stable for ca. 1 h. The results showed that **3a** is 10-debenzoyl-2α-acetoxybrevifoliol. An alternative structure with the acetate at O-10 was ruled out by chemical shift considerations. Indeed, the acyloxymethine proton of the H-9,H-10 AB system resonated at relatively high

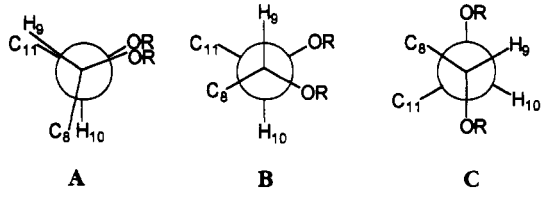
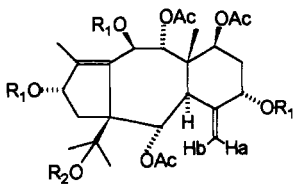


FIGURE 1. Newman projections along C-9, C-10 in the three major conformational types of taxoids.

field (δ 4.89), a value typical of H-9 in 11(15→1)*abeo*-taxane esters having ring B in the twist-chair conformation (see below). In compounds of this type, an H-10 acyloxymethine would resonate instead at δ >6 (12,17).[2] The value of $J_{9,10}$ (4.7 Hz) showed that at 160° the conformational equilibrium of **3a** is shifted toward the rotamer having ring B in the twist-chair conformation. The splitting pattern of H-5 was instead unusual (d, $J_{5,6a}$=8.8 Hz, $J_{5,6b}$ ca. 0 Hz), and raised doubts on the stereochemistry at this center. Indeed, the same splitting pattern is observed in oxetane-type taxoids, where H-5 is α. To solve this matter, **3a** was acetylated. The resulting triacetyl derivative [**3b**] still showed broad nmr



	R_1	R_2
3a	H	H
3b	Ac	H
3c	Ac	$CONHCOCCl_3$

spectra. However, after *in situ* acylation of the tertiary hydroxyl at C-15 with trichloroacetyl isocyanate (TAI) (20), a carbamate [**3c**] showing sharp spectra was obtained. This could be analyzed by 1D and 2D nmr techniques (COSY, NOESY, FLOCK, Tables 1 and 2), and the results showed that the oxygen function at C-5 is α and H-5 β, as observed in all the non-oxetane-type taxoids. The values of $J_{9,10}$ and $J_{5,6\alpha(6\beta)}$ (10.8 and <3 Hz, respectively) indicated that the preferred rotamer of **3c** has ring B in the twist-boat conformation and ring C in the chair conformation (12,17). Inspection of nOe correlations confirmed this (correlations H-9,H-16, H-9,H-2, and H-10,H-3) and also showed that the *pro-E* 20-hydrogen resonated at lower field than the *pro-Z*-hydrogen, in contrast to what is commonly observed in $\Delta^{4(20)}$-taxoids. Monoesters of 9,10-dihydroxylated taxanes are generally unstable toward acyl rearrangement, and equilibrate in solution (13,21). Interestingly, no acyl rearrangement of this type has instead been reported for the corresponding monoesters of 11(15→1)*abeo*-taxanes. For compounds of this type, only the *O*-9-monoesters are known (12,19,22), and **3a** was stable in solution at room temperature.

No clear picture of the conformational preferences of 11(15→1)*abeo*-taxanes of the brevifoliol type (4,20–double bond) is emerging from the scattered information available in the literature. Hydrogen bonding plays an important role, since fully acylated derivatives are generally monorotameric in solution, but a detailed rationalization is still elu-

[2]The upfield chemical shift of H-9 in 11(15→1)*abeo*-taxanes with ring B in the twist-chair conformation is responsible for the large difference in the chemical shifts of H-9 and H-10 in the minor rotamer of 2α-acetoxybrevifoliol [Δδ (H-10, H-9)=1.34] (17) and in the major rotamer of taxchinin D [Δδ (H-10, H-9)=1.31] (12). In the other rotamer of these 9,10-diesters, ring B has the twist-boat conformation, and the corresponding Δδ values are 0.56 and 0.68, respectively (12,17).

sive. Some trends are instead emerging for compounds of the oxetane-type, where the *cis*-junction with a four-membered ring makes ring C rigid and the conformational analysis simpler (23).

Compounds **2a** and **2b** are minor constituents of the needles of Himalayan yew, but represent the first taxoids bearing a cinnamoyl group isolated so far from this source. Because compounds of this type generally co-occur with their corresponding Winterstein acid esters (13), it is also likely that the Himalayan yew contain basic alkaloids, although their concentration might be much lower than in the European or the Japanese yew. Furthermore, basic alkaloids might be degraded during drying and storage more easily than in the needles of other yews, since we have been unable to get compounds of this type from dried plant samples of the Himalayan yew.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were determined on a Büchi SMP 20 apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter. Uv and ir spectra were taken on a Beckman DB-GT and a Perkin-Elmer model 237 spectrophotometer, respectively. ^{1}H- (300 MHz) and ^{13}C-nmr (75 MHz) spectra were recorded on a Varian Unity 300 spectrometer, using TMS as internal reference. Cims were taken on a VG EQ 70/70 apparatus. Cc was carried out on Si gel (Merck, 70–230 mesh). A Waters microPorasil column (0.8×30 cm) and a Waters Delta Pack C_{18} column (0.78×30 cm) were used for hplc, with detection by a Waters 3401 differential refractometer.

PLANT MATERIAL.—*Taxus wallichiana* Zucc. was collected near Simla in the western Himalayas and was identified by Dr. U. Boni (Indena S.p.A.). A voucher specimen (#BE 4343) is kept at the Indena laboratories, Milano, Italy.

EXTRACTION AND ISOLATION.—The dried needles (18 kg) were extracted with MeOH (350 liters). The extract was concentrated and treated with CH_2Cl_2 (5×10 liters). The pooled organic phases were evaporated, and the residue (500 g) was chromatographed on Si gel (3,000 g), eluting sequentially with CH_2Cl_2 (fraction A), CH_2Cl_2-Me_2CO (4:1) (fraction B), and Me_2CO (fraction C). Evaporation of fractions B and C gave 273 g and 120 g of residue, respectively. A portion (6 g) of fraction B was chromatographed on Si gel using $CHCl_3$-MeOH (99:1) as eluent. Fractions containing mainly **2a** and **2b** were obtained (tlc monitoring, hexane-EtOAc, 3:7, as eluent). The final purification was achieved by reversed-phase hplc [eluent: CH_3CN-H_2O-MeOH (35:15:1) for **2a** and CH_3CN-H_2O-MeOH (40:10:1) for **2b**]. The final yield was 58 mg of **2a** and 6 mg of **2b**. A part of fraction C (4 g) was chromatographed on Si gel using $CHCl_3$/MeOH (5⟶10%) as eluent. Fractions containing mainly **1a** and **3a** were obtained (tlc monitoring, hexane-EtOAc, 1:9, as eluent). After purification by hplc (hexane-*i*-PrOH, 4:1, and hexane-EtOAc, 1:9), 30 mg of **3a** and 58 mg of **1a** were obtained, respectively.

19-Debenzoyl-19-acetyltaxinine M [**1a**].—Gum, $[\alpha]^{25}D$ +2.8° (*c*=0.35, $CHCl_3$); ir (liquid film) ν max 3500, 1740, 1720, 1410, 1240, 1030, 950 cm^{-1}; cims (NH_3) *m/z* $[M+NH_4]^+$ 642 $[C_{30}H_{40}O_{14}+NH_4]^+$ (100); ^{1}H- and ^{13}C nmr data, see Tables 1 and 2; significant rOe correlations for diastereotopic methylene protons: δ 2.16 (H-6α)/3.63 (H-3); 5.31 (H-20A)/4.38 (H-5); 4.44 (H-20B)/6.16 (H-2); 3.00 (H-14β)/2.42 (H-1).

5-Cinnamoylbrevifoliol (=13-deacetyltaxuspine A) [**2a**].—Oil; $[\alpha]^{25}D$ −41.5° (*c*=0.91, $CHCl_3$); uv (EtOH) λ max 278, 218 nm; ir (nujol) ν max 3500, 1726, 1265, 710 cm^{-1}; cims (NH_3) *m/z* $[M+NH_4]^+$ 704 $[C_{40}H_{46}O_{10}+NH_4]^+$ (100); ^{1}H- and ^{13}C-nmr data, see Tables 1 and 2; significant rOe correlations for diastereotopic methylene protons: δ 1.47 (H-2α)/2.86 (H-3); 5.31 (H-20A)/5.52 (H-5); 2.04 (H-6α)/5.66 (H-7); 1.21 (H-14α)/1.47 (H-2α); 1.94 (H-6β)/0.92 (H-19).

10-Debenzoyl-2α-acetoxybrevifoliol [**3a**].—White powder, mp 180°, $[\alpha]^{25}D$ +32.6° (*c*=2.2, MeOH); ir (nujol) ν max 3420, 1720, 1250, 720 cm^{-1}; cims (NH_3) *m/z* $[M+NH_4]^+$ 528 $[C_{26}H_{38}O_{10}+NH_4]^+$ (100); ^{1}H nmr (DMSO-d_6, 160°, multiplicities after D_2O exchange) δ 5.82 (1H, d, *J*=8.8 Hz, H-2), 5.29 (1H, t, *J*=1.9 Hz, H-20), 4.89 (1H, d, *J*=4.7 Hz, H-9), 4.78 (1H, dd, *J*=9.6 and 7.6 Hz, H-7), 4.69 (1H, br s, H-20′), 4.68 (1H, d, *J*=4.7 Hz, H-10), 4.41 (1H, d, *J*=7.8 Hz, H-5), 4.37 (1H, t, *J*=8.8 Hz, H-13), 3.10 (1H, d, *J*=8.8 Hz, H-2), 1.89, 1.88, 1.87 (Ac), 1.67, 1.40, 1.13, 0.99 (methyls).

ACETYLATION OF **3a**.—To a solution of **3a** (30 mg) in pyridine (0.5 ml), Ac_2O (0.5 ml) was added. After stirring overnight at room temperature, MeOH (ca. 100 μl) and H_2O (5 ml) were added, and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated. Removal of the solvent gave 25 mg of **3b** as an oil, $[\alpha]^{25}D$ −27.9° (*c*=0.81, MeOH); ir (nujol) ν max 3420, 1715, 1260, 720 cm^{-1}; cims (NH_3) *m/z* $[M+NH_4]^+$ 654 $[C_{32}H_{44}O_{13}+NH_4]^+$ (100); ^{1}H- and ^{13}C-nmr (after derivatization with TAI) data, see Tables 1 and 2; significant rOe correlations for diastereotopic

methylene protons: δ 4.61 (H-20A)/5.26 (H-5); 1.98 (H-6α)/5.37 (H-7); 1.80 (H-6β)/0.99 (H-19); 1.93 (H-14α)/3.18 (H-3).

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