Structures of Some Taxane Diterpenoids, Baccatins-III, -IV, -VI, and -VII and 1-Dehydroxybaccatin-IV, Possessing an Oxetan Ring

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Summary Baccatin-III (**3**), -IV (**5**), -VI (**7**), and -VII (**8**) and the 1-dehydroxy derivative of baccatin-IV are taxane derivatives with an oxetan ring.

RECENTLY taxol (**1**),[1] a natural product with potent antileukemic and tumour inhibiting properties, was shown to be a taxane derivative with an oxetan ring. This ring system in natural products is rare. One other taxane derivative containing it is baccatin-V (**2**).[2,3]

The structures of further oxetan-containing taxanes have now been determined. They are baccatin-IV[4] (**5**), $C_{32}H_{44}O_{14}$, m.p. 254—255° (decomp.), $[\alpha]_D + 19°$, λ_{max} 219 nm, ϵ 5000; 1-dehydroxybaccatin-IV (**6**), $C_{32}H_{44}O_{13}$, m.p. 286° (decomp.), $[\alpha]_D + 5°$, λ_{max} 218 nm, ϵ 7000; baccatin-IV (**7**), $C_{37}H_{46}O_{14}$, m.p. 244—245° (decomp.), $[\alpha]_D - 5°$, λ_{max} 225, 274, and 282 nm, ϵ 17,600, 860, and 640; and baccatin-VII (**8**), $C_{36}H_{52}O_{14}$, m.p. 270° (decomp.), $[\alpha]_D + 9°$, λ_{max} 218 nm, ϵ 2500.

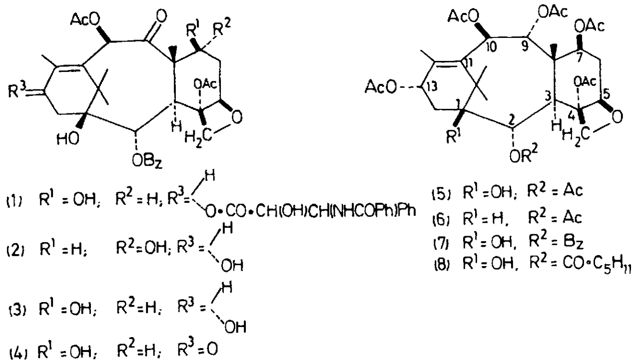
TABLE

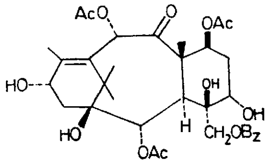
N.m.r. data (τ units) (J values given in Hz)

	H on carbon carrying oxygens							C*H*$_3$ groups on				
Compound	C-2	C-5	C-7	C-9	C-10	C-13	C-20	C-15β	C-12	C-15α	C-8	C-3-*H*
(**5**)	4·38d *J* 6	5·00d *J* 10	4·48q *J* 7; 10	4·05d *J* 11	3·78d *J* 11	3·80m	5·45d, 5·86d *J* 8	8·79	8·00	8·30	8·45	6·94d *J* 6
(**6**)	4·40	5·00d *J* 10	4·42 *J* 5; 9	4·08d *J* 11	3·82d *J* 11	4·10m	5·45d, 5·78d *J* 8	8·88	8·00	8·21	8·47	7·10d *J* 6
(**7**)	4·10d *J* 6	5·02d *J* 10	4·43bt *J* 8	3·95d *J* 10	3·78d *J* 10	3·80m	5·65,d 5·87d *J* 8	8·78	7·88	8·22	8·46	6·81d *J* 6
(**8**)	4·37d *J* 6	5·02d *J* 10	4·50bt *J* 8	4·06d *J* 11	3·81d *J* 11	3·85m	5·50d, 5·83d *J* 8	8·80	8·00	8·29	8·45	6·95d *J* 6
(**4**)[a]	4·29 *J* 6	5·04q[c] *J* 4·9	5·52		3·52s		5·65d, 5·85d *J* 8	8·80	7·72	8·75	8·33	6·08 *J* 6
(**4**)[b]	4·29 *J* 6	5·04bd *J* 10	[d]		3·54s		5·64d, 5·84d *J* 6	8·80	7·72	8·74	8·34	6·04 *J* 6
(**3**)	4·38 *J* 7	5·01q *J* 10; 4	5·54q *J* 10·5;6		3·70s	5·15m	5·70d, 5·83d *J* 8	8·91	7·75	8·91	8·35	6·14 *J* 7

[a] Prepared from baccatin-III (ref. 6). [b] Prepared from taxol (ref. 1). [c] This signal is a poorly resolved quartet. [d] Not reported.

Six acetate groups and at least one hydroxy-group, indicated by the effect of D_2O exchange on the n.m.r. spectrum, account for thirteen oxygen atoms of baccatin-IV (**5**). It was unaffected by acetylation, by treatment with Jones reagent or Me_2SO–Ac_2O, or by ozone. Any hydroxy-group is therefore tertiary or very hindered and there is no exocyclic methylene group. A signal at τ 8·00 shows the C-12 vinylic methyl group of a tax-11-ene. The 9α,10β-diacetoxy system gives the typical AB system at τ 4·05 and 3·78. The fourteenth oxygen atom affords another AB system at τ 5·45 and 5·86 indicative of a -CH_2-O group of an oxetan. Two coupled doublets at τ 6·94 and 4·38 indicate a proton on C-3 coupled with a proton on C-2 carrying an acetoxy group and the absence of protons at C-1 and C-4. A signal at τ 4·48 (q, *J* 7 and 10 Hz) shows an axial proton on C-7 carrying a β-acetoxy group, the proton being coupled with the C-6 methylene group. A proton on C-13 with an α-acetoxy-group is coupled with the C-14 methylene group, giving a signal at τ 3·80 (m). The hydroxy-group is placed on C-1 in the β-configuration because of its deshielding effects on the C-8 and C-15β methyl signals and its shielding effect on the C-15α methyl signal.† The remaining acetoxy group must be at C-4 and α-orientated since the signal of 8-Me at τ 8·45 shows the typical downfield shift found with the β-orientated oxetan ring.





(**9**)

1-Dehydroxybaccatin-IV (**6**) has one less oxygen atom than baccatin-IV and has a very similar n.m.r. spectrum to it (see Table) except for the signal at τ 4·40 which shows that the proton at C-2 is coupled to protons at both C-1 and C-3 and that there is no hydroxy-group at C-1.

Baccatin-VI (**7**) differs from baccatin-IV (**5**) in having a benzoate instead of an acetate group in the 2α-position. This is indicated by its n.m.r. spectrum (see Table) which is very similar to that of baccatin-IV except that the signal due to the C-2 proton has moved downfield.

The mass spectrum of baccatin-VII (**8**), $C_{38}H_{52}O_{14}$, had a peak at *m/e* 575 (*M* − 115) corresponding to the loss of a molecule of water and of the capro-oxy-group ($C_5H_{11}CO{\cdot}O{\cdot}$). Its n.m.r. spectrum (see Table) is also very similar to that of baccatin-IV and indicates that the structures of baccatins-IV and -VII are identical except for the presence of one caproate group, which is placed at C-2, instead of an acetate group.

In 1970 structure (**9**) was proposed[5] for baccatin-III. The original formula proposed for it was $C_{31}H_{38}O_{11}$[4] but this was revised[5] to $C_{33}H_{42}O_{13}$ (containing the elements of $MeCO_2H$ more than the original formula). The existence of taxane derivatives with an oxetan ring has led to a reconsideration of its structure. It also is an oxetan which gives rise to the AB system at τ 5·70 and 5·83 (*J* 8 Hz) and has the first proposed $C_{31}H_{38}O_{11}$ formula. Its structure is (**3**), being confirmed by the identity of the physical constants of the αβ-unsaturated ketone, m.p. 210—212° (decomp.), obtained on allylic oxidation of baccatin-III with those reported[1] for the αβ-unsaturated ketone (**4**), m.p. 210—212°, obtained by oxidation of taxol (**1**) with activated manganese dioxide under mild basic conditions in acetone. Their respective n.m.r. signals are given in the Table. Baccatin-III (**3**) differs from baccatin-V (**2**) only in the configuration of the hydroxy-group at C-7, that in baccatin-V having the uncommon α configuration.

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† This effect has also been found with other 1β-hydroxy-taxanes and will be discussed in the full paper.

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