The Structure of Baccatin-III, a Partially Esterified Octahydroxy-monoketo-taxane Derivative Lacking a Double Bond at C-4

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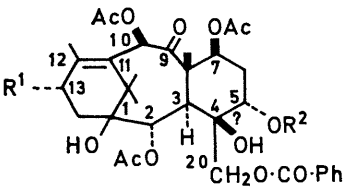
Summary Baccatin-III is the triacetate monobenzoate of 1β, 2α, 4(?β), 5α, 7β, 10β, 13α, 20-octahydroxytax-11-en-9-one.

RECENTLY we described[1] the isolation of a complex ester, baccatin-III, from the heartwood of yew (*Taxus baccata* L.) and provisionally formulated it as $C_{31}H_{38}O_{11}$. It has now been shown to be $C_{33}H_{42}O_{13}$ (containing the elements of one more acetic acid than the original formulation) and to have m.p. 233—234°, $[\alpha]_D$ — 93°, λ_{max} 230, 274, and 280 nm, ϵ 13,900, 1000, and 850. Structure (I) is suggested for the ester. It is thus the first example of a naturally occurring taxane derivative which lacks the exocyclic double bond at C-4. The n.m.r. spectrum of baccatin-III showed the signals of the four methyl groups for a taxane system at τ 7·75, 8·35, 8·91, and 8·91. The presence of three acetate and one benzoate groups was shown by spectroscopic data. An n.m.r. signal at τ 3·66 (s, 1H) and the absence of the pair of doublets associated with the 9,10-dioxy-grouping, together with the large negative rotation and the position of the bands due to the methyl groups, indicated a 9-oxo-10β-acetoxy-grouping analogous to that found in the ketol acetates (II)[2] and (III)[3]. The presence of two secondary hydroxy-groups was shown by n.m.r., and one of them was readily acetylated to give baccatin-III monoacetate (IV). Two tertiary hydroxy-groups accounted for the remaining oxygen atoms. No signals, however, were found due to two olefinic protons at C-20. Instead the presence of an AB system at τ 5·70 and 5·83 (J 8 Hz) suggested the presence of a C–CH_2–O·CO·Ph grouping. A doublet at τ 4·38 (J 7 Hz) was found to be coupled with a doublet at τ 6·14. This latter signal was assigned to the C-3 proton which indicated that the signal at τ 4·38 was due to a proton on C-2 which carried an α-acetoxy-group. It also follows that there is no proton at C-1, which must be substituted with a tertiary hydroxy-group. The low τ value of the C-3 proton supported the presence of a 9-oxo-group which causes deshielding of this proton similar to that observed for the compound (II).[4]

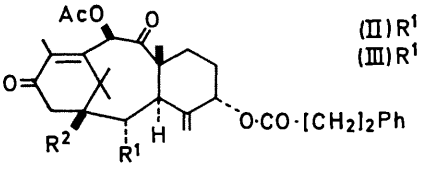
When baccatin-III monoacetate (IV) was hydrogenated with Adams catalyst in acetic acid, the n.m.r. spectrum of the product (V) showed the absence of a signal for one

proton at τ 5·15 indicating the loss of one allylic secondary hydroxy-group from C-13. This was confirmed by prolongated treatment of baccatin-III with sodium metaperiodate when oxidation of the allylic hydroxy-group occurred with the formation of an $\alpha\beta$-unsaturated ketone (VI) (λ_{max} 275 nm, ϵ 6800) which showed the abnormal light adsorption associated with the 13-oxo-11-ene system of the taxanes. Although no fission of a glycol group occurred under these conditions, baccatin-III gave a positive result for an α-glycol group with Fiegel's periodic acid oxidation test.[5] Since the C-3 proton is only coupled to one proton at C-2, there must be a hydroxy-group at C-4 and this group together with a secondary hydroxy-group at C-5 would account for the α-glycol structure. The C-5 hydroxy-group was the one which was acetylated, and when this took place the τ signal for the C-5 proton shifted from τ 5·54 (q, J 10·5, 6 Hz) to τ 4·36 (q, J 10, 6 Hz). The remaining acetoxy-group is placed at C-7, the proton geminal with it having a signal at τ 5·01 (q, J 10, 4 Hz).

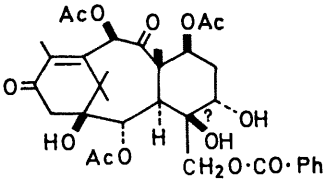
If the substituents in baccatin-III have the same stereochemistry as in other taxane derivatives[2] the C-7 acetoxy-group should be β and the C-5 hydroxy-group α. The coupling constant of the proton at C-7 is consistent with the values given for other taxane derivatives,[6,7] but that of the proton at C-5 is different from that usually found, and indicated that it is axial rather than equatorial. Inspection of models indicates, however, that with a 5α-hydroxy-group there is a favourable conformation of baccatin-III with ring C present as a boat with C-5 and C-8 as the bow and stern, and this conformation gives dihedral angles which account for the coupling constants for both the 5β- and 7α-protons. Finally there is the question of the stereochemistry at C-4. The most likely biogenetic route to the C-4, C-20 dioxy-system is *via* epoxidation of the C-4, C-20 double bond and opening of the oxide ring. If so the α-epoxide is the more likely to be formed. Assuming *trans*-opening of the epoxy-group, this would lead to 4β-hydroxy-group. This stereochemistry would give a *trans*-α-glycol grouping in baccatin-III which could account for the resistance to oxidation with sodium metaperiodate.



(I) R^1 = OH, R^2 = H
(IV) R^1 = OH, R^2 = Ac
(V) R^1 = H, R^2 = Ac



(II) R^1 = OAc, R^2 = H
(III) R^1 = OMe, R^2 = OH



(VI)

One of us (D. P. D. C. de M) thanks the Consejo de Desarrollo de la Universidad Central de Venezuela for a Scholarship. We thank the S.R.C. for financial support.

(*Received, December 15th*, 1969; *Com.* 1884.)

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