Crystallographic Structure Determination of the Diterpenoid Baccatin-V, a Naturally Occurring Oxetan with a Taxane Skeleton

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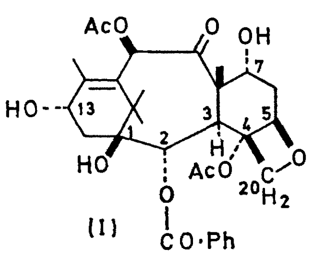
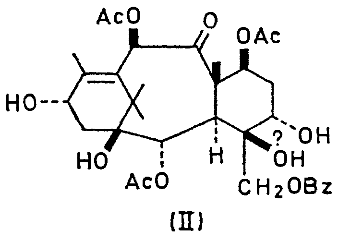
Summary Baccatin-V, $C_{31}H_{38}O_{11}$, a new diterpenoid from *Taxus baccata* L. has been shown by *X*-ray analysis to contain an oxetan ring and to be 5β,20-epoxy-$1\beta,2\alpha,4\alpha$,-$7\alpha,10\beta,13\alpha$-hexahydroxytax-11-en-9-one $4\alpha,10\beta$-diacetate 2α-benzoate (I).

A NEW compound, baccatin-V, $C_{31}H_{38}O_{11}$, m.p. 254—255°, $[\alpha]_D$ − 87°, has been isolated from *Taxus baccata* L. It occurs in fractions of extract near to those containing baccatin-III (II),[1,2] which also has a similar negative rotation, and baccatin-IV.[1] The n.m.r. spectrum indicated two acetate groups and a benzoate group and had four singlets at τ 8·96, 8·90, 8·38, and 8·01 typical of the methyl groups of a taxane derivative. Its low-field region was similar to that of the spectrum of baccatin-III. A singlet at τ 3·17 indicated a proton at C-10 in the grouping ·CHOAc·CO·, the carbonyl group being at C-9. Hydroxy-groups were shown by ν_{max} at 3600 cm^{-1}. One was readily acetylated, when a signal at τ 5·1 shifted to τ 3·82 (broad t, J 8 Hz). This showed the probable presence of a 13α-hydroxy-group.

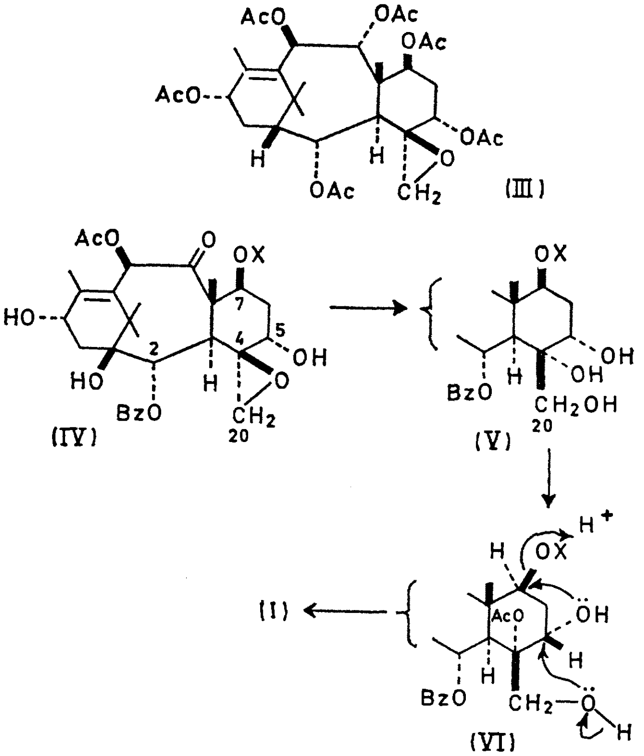


(I)



(II)

An insufficient amount of baccatin-V was available for detailed chemical study, so a structure analysis was attempted directly on baccatin-V.



SCHEME

Baccatin-V crystallised in the non-centrosymmetric orthorhombic space group $P2_12_12_1$ with a = 25·75, b = 9·31, c = 12·34 Å, and Z = 4 for $C_{31}H_{38}O_{11}$. 3364 reflections were collected on a Hilger–Watts linear diffractometer with Mo radiation, 2462 of which were taken as significantly above background. A computer application of the tangent formula of Karle and Hauptman[3] was used to solve the structure. Eight phases were used as a starting set, four of which were fixed[4] and four given 64 different combinations of trial values. After extension of each trial to about 220 phases, one set had a considerably lower "R value"[5] and greater number of interactions in use. An E map calculated on 295 reflections phased by extending this set revealed practically the whole structure, which was completed from an F (obs) map phased on 37 correct, and one incorrect, positions. The structure of baccatin-V so derived is (I). The present value of R is 10·6%.

The structure is interesting in two respects. First it is a naturally occurring oxetan. Secondly the configurations of the oxygen atoms attached to C-5 and C-7 (β and α, respectively) are *opposite* to those found in all other taxane derivatives (*cf.* ref. 6). The reason for this may be associated with the biogenesis of the oxetan ring. This could involve a precursor such as the 4β-20-epoxide (IV) in a sequence of interactions as exemplified in the Scheme. A taxane-4β,20-epoxide, baccatin-I,[7] (III) is already known. The conversion of (VI) into (I) could be acid-catalysed or could be initiated by loss of XO^-.

Oxetan formation by the mechanism suggested may be facilitated by compression between C-20 and the C-2-oxygen. In (I) the interatomic distance between these atoms is only $2{\cdot}6_8$ Å. The C-2-oxygen is also very close ($2{\cdot}6_0$ Å) to that at C-1. The importance of release of non-bonding strain in the oxetan formation has been discussed in the case of 3α,5α-epoxycholestane.[8]

The n.m.r. signal of the β-proton at C-7 appears at τ 6·32 as a sextet being split by the C-6 methylene group and the hydroxylic proton of the 7α-hydroxyl. On deuterium exchange, the signal collapses to a triplet. This hydroxylic proton is involved in a strong hydrogen bond with the acyl oxygen of the 4α-acetate group, the distance between this oxygen and that of the 7α-hydroxyl being $2{\cdot}7_7$ Å. The 2α-proton gives a doublet at τ 4·26, being coupled with the 3-proton resonating at τ 5·98 (J 6 Hz). This latter proton is very near the double bond, being separated from it by only 2·7—2·8 Å. The 3-proton is enclosed within a globular-shaped carbon framework.

The methylene group of the oxetan ring resonates at τ 5·62 as a singlet in baccatin-V and its 13α-acetate, but in the hexa-hydro-derivative of the acetate (benzoate group reduced) it is split into an AB system at τ 5·43 and 5·64 (J 6 Hz). The C-5 oxetan proton gives a signal at τ 5·1 (m).

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