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The Structure of the Diterpenoid Baccatin-I, the 4β,20-Epoxide of 2α,5α,7β,9α,10β,13α-Hexa-acetoxytaxa-4(20),11-diene

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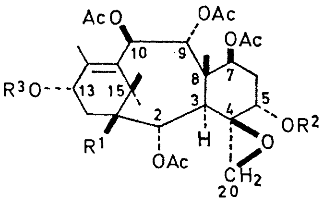
Summary Baccatin-I has been shown to be the 4β,20-epoxide of 2α,5α,7β,9α,10β,13α-hexa-acetoxytaxa-4(20),11-diene (I), and 5α-deacetylbaccatin-I (III) and 1β-hydroxybaccatin-I (IV) have also been isolated.

In 1964 Taylor[1] isolated a complex ester formulated as $C_{32}H_{44}O_{12}$ from the heartwood of *Taxus baccata* L. It was called baccatin, but on re-isolation[2] was subsequently renamed baccatin-I to avoid confusion with a methoxy-triterpene lactone isolated by Preuss and Orth[3] which had also been called baccatin.

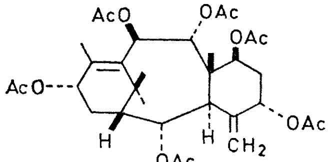
Baccatin-I is very difficult to obtain free of related esters but careful purification has afforded a sample, m.p. 298°, $[\alpha]_D$ + 86° which has been shown to have the molecular formula $C_{32}H_{44}O_{13}$ with one more oxygen atom than the formula originally suggested. Its structure (I) has now been established as the 4β,20-epoxide of the hexa-acetate of taxa-4(20),11-diene-2α,5α,7β,9α,10β,13α-hexaol.

The n.m.r. spectrum showed that it was a taxane derivative having the four typical methyl signals at τ 8·86, 8·76, 8·28, and 7·75. Together with an analysis of the mass spectrum it also indicated that baccatin-I was a 2α,5α,7β,9α,10β,13α-hexa-acetate. The u.v. absorption maximum at 217 nm (ε 6900) indicated[4,5] the Δ^{11} double bond but the lack of signals due to olefinic protons in the n.m.r. spectrum showed the absence of the 4(20)-methylene group. The β-proton at C-5 which carries an α-acetoxy-group appeared at an unusually high τ-value (5·77, *J* 3 Hz) suggesting a shielding effect by a neighbouring group such as a 4,20-epoxide which would account for the additional oxygen atom.

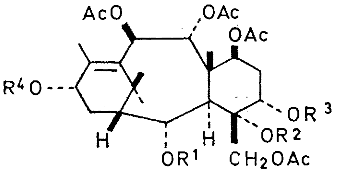
The presence of the epoxide group and the structure of baccatin-I were proved by epoxidising with monoperphthalic acid the taxadiene hexa-acetate (V) previously isolated from *T. baccata* L.[4] Both the 4α,20- and 4β,20-epoxides were obtained, together with a little diepoxide. The α-epoxide was formed in higher yield in agreement with easier 'equatorial' attack from the less hindered side of the double bond.[6] The β-epoxide (I) was identical with baccatin-I. The β-epoxy-group not only explains the high τ-value for the 5β-proton but also the low τ-value (8·76) for the 8-methyl, an effect found with other taxane derivatives having a 4β-substituent.[7] The signals of the C-20 protons of the epoxide ring are at τ 6·43 and *ca.* 7·5.



	R¹	R²	R³
(I)	H	Ac	Ac
(II)	H	H	H
(III)	H	H	Ac
(IV)	OH	Ac	Ac



(V)



	R¹	R²	R³	R⁴
(VI)	H	Me	H	H
(VII)	Ac	H	H	Ac
(VIII)	Ac	H	Ac	Ac

With methanolic sodium hydroxide baccatin-I afforded a methoxy-tetra-acetate, formulated as (VI) because of its n.m.r. spectrum, which *inter alia* shows signals of a new AB system at τ 5·81 and 6·18 (*J* 10 Hz) similar to those given by other ·CH_2OAc groups in the taxane series and by the $\cdot CH_2\cdot OBz$ group of baccatin-III,[8] and its likely mode of formation. This involves acetyl transfer from the C-2 acetate to the epoxide oxygen during opening of the epoxide to generate a C-4 carbonium ion which is then attacked by methoxide ion. Transfer from the C-5 acetate is excluded since the 5α,13α-diol (II) reacts similarly.

Treatment of baccatin-I with boron trifluoride–ether complex in acetic anhydride gave the hexa- and hepta-acetates (VII) and (VIII), probably by mechanisms involving an acetoxonium ion and an orthoacetate.

In addition to baccatin-I its 5-deacetyl derivative (III), m.p. 256—258°, and 1β-hydroxybaccatin-I (IV), $C_{32}H_{44}O_{14}$, m.p. 273° (d), $[\alpha]_D + 102°$ have also been isolated. In compound (IV) the C-2 proton is only coupled with that at C-3 and gives in pyridine–$CDCl_3$ (1 : 1) a doublet at τ 4·18 (*J* 3·5 Hz).

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