Taxa-4(16),11-diene-5α,9α,10β,13α-tetraol, a New Taxane Derivative from the Heartwood of Yew (*T. baccata* L.): *X*-Ray Analysis of a *p*-Bromobenzoate Derivative

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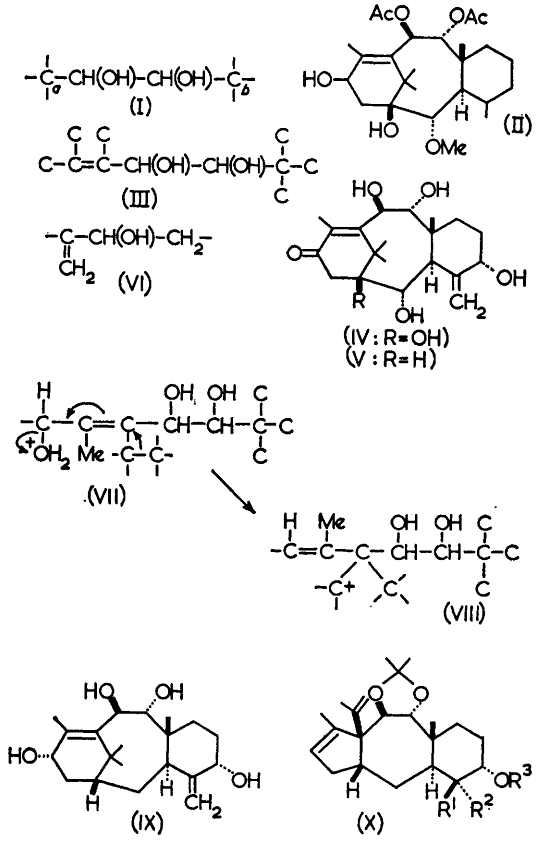
RECENTLY Taylor[1] isolated from the heartwood of yew (*T. baccata* L.) a complex ester $C_{32}H_{44}O_{12}$ which was called baccatin. A different compound, a methoxy-triterpene $C_{31}H_{44}O_4$ isolated from the root of yew by Preuss and Orth,[2] has also been called baccatin. Professor Taylor very generously drew our attention to his baccatin and with his agreement we have examined the heartwood of yew. In addition to his baccatin, now called baccatin-I three other esters have been isolated, baccatins-II ($C_{32}H_{44}O_{14}$), -III (possibly $C_{31}H_{38}O_{11}$), and -IV (M. W. 592) together with β-sitosterol, two tetracyclic triterpenes which will be reported upon later, and a new diterpene tetraol $C_{20}H_{32}O_4$, m.p. 195—198°, $[\alpha]_D + 134°$.

The tetraol gave a tetrakistrimethylsilyl ether ($C_{32}H_{64}O_4Si_4$), a triacetate, and, on treatment with diethyl carbonate and sodium, a $C_{27}H_{38}O_9$ compound which contained a cyclic carbonate grouping and two EtO·CO·O· groups. A band at 1805 cm.$^{-1}$ indicated that the cyclic carbonate grouping was from a 1,2-diol. The n.m.r. spectrum of the $C_{27}H_{38}O_9$ compound with signals at τ 4·78, 4·65, and 4·44 and 4·14 (AB quartet, J, 8·4 c./sec.), showed that all four hydroxyl groups of the tetraol were secondary and that the 1,2-diol group was probably *trans* and of type (I) where carbon atoms *a* and *b* carry no hydrogen atom.

The tetraol contains two double bonds, one being present as a $=CH_2$ group and easily hydrogenated. The other is tetrasubstituted. Both the tetraol and its dihydro-derivative show absorption at 2270 Å (ϵ, 7000) and very striking Cotton effects ($a = +841$ and $+944$; extrema 2400/2006 Å and 2420/2040 Å) [kindly determined by Professor W. Klyne and Dr. S. R. Wallis] due to an isolated double bond. This unusual light-absorption is found in the taxane derivative (II)[3,4] and suggested that the tetraol, especially in view of its occurrence in yew, also had a taxane skeleton. The n.m.r. of the tetraol in $(CD_3)_2SO$ showed four singlet methyl signals (τ 9·25, 9·09, 8·61, and 8·04) one of which was due to a methyl group attached to a double bond. The spectrum of the dihydrotetraol had an additional signal due to $>$CH*Me*.

Oxidation of the tetraol with periodic acid split the glycol grouping and the product, the nature of which will be fully discussed in the detailed Paper, contained a fully substituted $\alpha\beta$-unsaturated aldehyde grouping which permits partial structure (I) to be extended to (III). After allowing for two double bonds the formula of the tetraol indicates that it is tricyclic. These results provided additional evidence for the view that the tetraol was a taxane derivative, the partial grouping (III) being found in taxicin-I (IV)[3–6] and -II (V)[3–11].

When the tetraol was treated with acetone and a few drops of perchloric acid it afforded an anhydro-acetonide $C_{23}H_{34}O_3$ (84% yield) which formed a monoacetate and a di- and tri-epoxide. The anhydro-acetonide could be oxidised to a *cisoid*-$\alpha\beta$-unsaturated ketone, ν_{max} 1698 and 1623 cm.$^{-1}$ Similar treatment of the dihydro-tetraol gave a corresponding anhydro-acetonide $C_{23}H_{36}O_3$ which was characterised as a *p*-bromobenzoate, m.p. 143—145°. It was oxidised to a saturated monoketone (ν_{max} 1705 cm.$^{-1}$) which formed a monobenzylidene derivative and it took up one mole of hydrogen to give a product characterised as its monoacetate $C_{25}H_{40}O_4$. These results indicate the presence of partial structure (VI) in the acetonide. The tetrahydro-anhydro-acetonide monoacetate contains a methyl group on a *tri*-substituted double bond and it was concluded that during the formation of the acetonide rearrangement accompanied dehydration. The most likely possibility appeared to be dehydration of an allylic alcohol grouping as indicated [(VII) → (VIII)]. If the partial structure (VII) (unprotonated) together with the partial structure (VI) found in the acetonide are present in the tetraol then structure (IX) [absolute stereochemistry assumed to be the same as that in taxicin-I and -II (IV and V)][4,11] appeared probable for the tetraol.



(I) (II) (III) (VI) (IV: R=OH) (V: R=H) (VII) (VIII) (IX) (X)

The nature of the acetonide was not immediately clear. The third double bond introduced by dehydration had two olefinic protons. A methylene group ($=CH_2$) was considered but the infrared spectrum of the dihydro-acetonide had no band apparently indicative of $=CH_2$. A structure containing a disubstituted ethylene can be formulated but the rearrangement leading to it could not be concerted.

The problem was, however, unambiguously solved by the determination of the crystal structure of the *p*-bromobenzoate of the dihydro-anhydro-acetonide which clearly establishes the structure as (X; R^1 = Me, R^2 = H, R^3 = *p*-$BrC_6H_4{\cdot}CO$). The dihydro-anhydro-acetonide thus has the constitution and stereochemistry defined by (X; R^1 = Me, $R^2 = R^3$ = H) although there is no infrared evidence for the $>C=CH_2$ group. The anhydro-acetonide must be formulated as (X; R^1, R^2 = $H_2C=$; R^3 = H) and structure (IX) is correct for the tetraol, the rearrangement involved in the formation of the acetonide involving a type of *cis*-S_N2' substitution in the protonated allylic system.

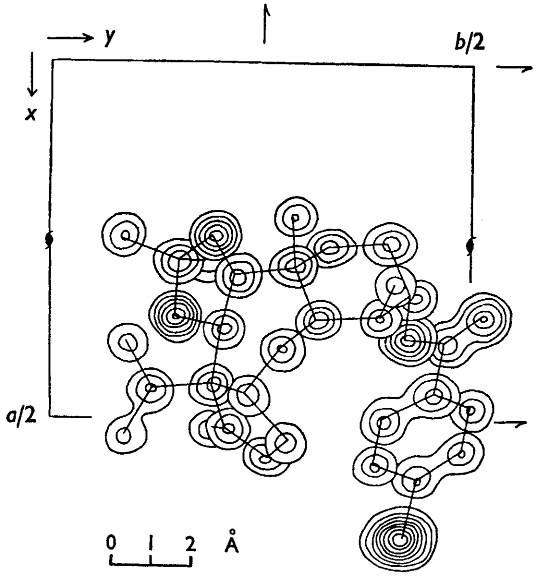


FIGURE. *Superimposed sections of the three-dimensional electron density distribution drawn parallel to* (001). *Contours start at the* 2e $Å^{-3}$ *level and continue at* 1e $Å^{-3}$ *intervals except around the bromine atom where the intervals are at* 3e $Å^{-3}$.

The *p*-bromobenzoate of the dihydro-anhydro-acetonide crystallises in the orthorhombic space group $P2_12_12_1$ (D_2) with 4 molecules of $C_{30}H_{39}BrO_4$ in the unit cell defined by a = 17·48, b = 20·62, c = 7·76 Å. From equi-inclination Weissenberg photographs 1580 three-dimensional independently measured reflections were obtained. The crystal structure analysis which proceeded by the phase determining heavy-atom method was complicated initially by the presence of pseudo-mirror planes due to the heavy atom being in a special position with z = 0. Acceptance of the phenyl ring of the *p*-bromobenzoate served to destroy the pseudo-mirror symmetry and three further rounds of structure-factor and Fourier calculations revealed the entire structure.

The atomic parameters were refined by Fourier and least-squares methods. R is at present 12% and further refinement is in progress.

The conformation of the molecule in the crystal is illustrated in the Figure.

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