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THE STEREOCHEMISTRY OF TAXICIN-I AND -II

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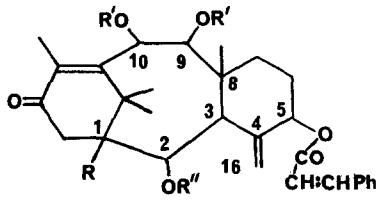
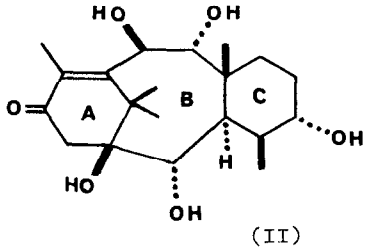
After earlier studies[1] had established its main features, the gross structure of O-cinnamoyltaxicin-I (I; R = OH; R' = R" = H) was completely defined[2] in 1963, and it was then also shown that O-cinnamoyltaxicin-II triacetate has the structure (I; R = H; R' = R" = Ac). We now report evidence that the complete stereochemistry of 4,16-dihydrotaxicin-I[3] corresponds to the structure (II). Chemical and spectral data show that taxicin-I and -II are stereochemically, as well as structurally, analogous, so that this work also defines the configuration of taxicin-II and its derivatives.



(I)



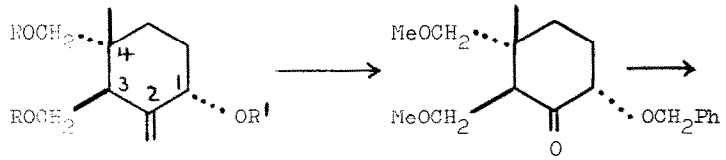
(II)

Periodate cleavage[1] of the 5-esters of taxicin-I or 4,16-dihydrotaxicin-I gives dialdehydes; reduction of the aldehyde groups, followed by hydrolysis, then gives either

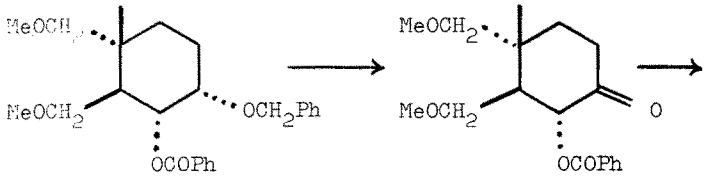
the unsaturated triol (III; R = R' = H), m.p. 112°, or the saturated triol (XII; R = R' = H), m.p. 131°; the latter is one of the products of hydrogenation of the former. We first studied the stereochemistry of these triols.

Methylation of (III; R = H; R' = CO.CH:CHPh), followed by hydrolysis and benzylation, gave the ether (III; R = Me; R' = CH_2Ph). Hydroxylation and glycol cleavage gave the ketone (IV); it was treated with care to avoid change of configuration adjacent to the keto group. Reduction of the keto group gave epimeric alcohols; the corresponding benzoates (V and its 2-epimer)[4] were catalytically debenzylated, and the products oxidised to the α-ketol benzoates (VI and its 2-epimer). Calcium in ammonia reduced both epimers to the same ketone (VII), $[\alpha]_D$ -13·3°[5], semicarbazone, m.p. 185°.

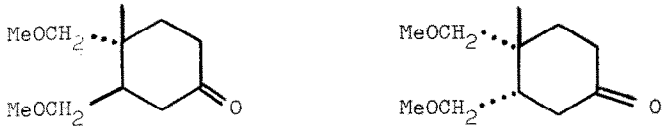
For comparison, the racemate of the cis-analogue (c.f. VIII) of the above ketone was synthesised from the corresponding cis-keto dicarboxylic acid[6]; its properties showed that the ketone (VII) belonged to the trans-series, and was not contaminated by any cis-isomer. Experiments were then undertaken with the δ-lactonic acid (IX), $[\alpha]_D$ -79°, whose absolute configuration is known because its enantiomer has been converted[6] into tachysterol$_3$. Heating (IX) in toluene with benzyl chloride and potassium hydroxide, followed by alkaline hydrolysis, gave mixed benzyloxy di-acids, epimeric at position 2. That corresponding to the lactone (IX) was identified by hydrogenolysis; the other epimer (X) had m.p. 166°, $[\alpha]_D$ +2·6°. It was reduced and the resulting diol was methylated; debenzylation and



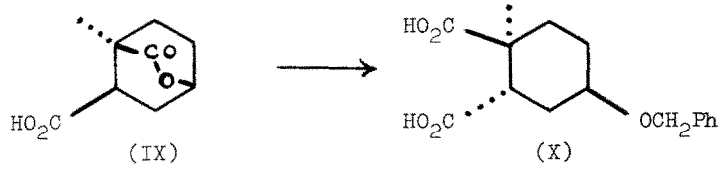
(III) (IV)



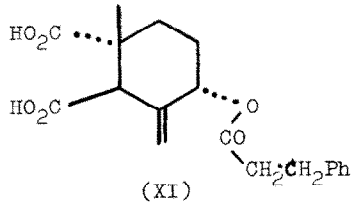
(V) (VI)



(VII) (VIII)



(IX) (X)



(XI) (XII)

oxidation then gave a ketone, $[\alpha]_D$ +13·4° (semicarbazone, m.p. 183°) enantiomeric with (VII). This fixed the configurations at positions 3 and 4 in the triol (III; R = R' = H).

The proton at position 2 in the benzoate (V) gave a quartet signal near τ 4·75 with couplings of 3 c.p.s. (axial-equatorial) with the proton at position 1, and 11 c.p.s. (trans-diaxial) with that at position 3; the corresponding signal in the ketone (VI) was a doublet, $J_{2,3}$ = 12 c.p.s. Thus in the triol (III; R = R' = H) the groups at positions 1 and 3 are trans-related. In confirmation, the dibasic acid (XI), obtained by oxidising (III; R = H; R' = $CO.CH_2.CH_2Ph$), gave on hydrolysis and acidification a δ-lactone, m.p. 181°. This establishes the stereostructure (III).

Mild oxidation of (XII; R = Me; R' = H) gave a ketone (XIII), semicarbazone $[\alpha]_D$ +21·5°. Acid or alkaline treatment converted the ketone into its 2-epimer (XIV), semicarbazone $[\alpha]_D$ +44°. In the less stable epimer (XIII) the groups at positions 2 and 3 are clearly cis-related, indicating the stereochemistry (XII; R = R' = H) for the triol. Confirmation was obtained from a study of the epimeric acids (XV) and (XVI). Catalytic reduction of (XI), followed by hydrolysis, gave a mixture of the two acids from which (XV), m.p.s 142° and 171°, was separated. The epimer (XVI), m.p. 197°, was obtained by oxidation of (XII; R = H; R' = $CO.CH_2.CH_2Ph$) followed by hydrolysis; it gave the triol (XII; R = R' = H) on reduction. The n.m.r. data showed

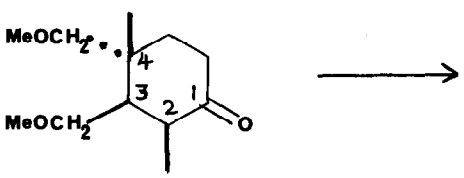
that in (XV) the hydroxyl group was axial and the substituents at positions 2 and 3 both equatorial ($J_{2,3}$ = 11 c.p.s.); in (XVI) the hydroxyl group was equatorial and the groups at positions 3 and 2 axial and equatorial ($J_{2,3}$ = 5 c.p.s.). These results confirm the stereochemistry (XII; R = R' = H). At first sight it appears possible that this triol could arise from a cis-dialdehyde (XVII) by a change of configuration at the secondary aldehyde group. This is improbable for two reasons; first, because of the mildness of the conditions used; secondly, because of the lack of conformational driving force. In (XVII) all the substituents except the tertiary aldehyde group can be equatorial, so that this aldehyde would be more stable than that corresponding to the triol (XII; R = R' = H). Dihydrotaxicin-I and the triol (XII; R = R' = H) must therefore have the same stereochemistry, and this defines the configurations at positions 3, 4, 5, and 8 in the structure (II). Since a trans-junction between rings B and C is present, ring C must be chair-shaped; only in this way can the proton at position 5 (equatorial) form approximately equal dihedral angles with those at position 6, as indicated by the small coupling constant between them (ca. 2-3 c.p.s.).

Periodate cleavage of 5-deoxy-4,16-dihydrotaxicin-I 2-acetate gave a hemiacetal containing one free aldehyde group. Oxidation of this group and conversion of the acid to its methyl ester, followed by acetylation, gave a diacetate (XVIII), m.p. 195°, in which the proton at position 2 gave a doublet signal at τ 4·75 with $J_{2,3}$

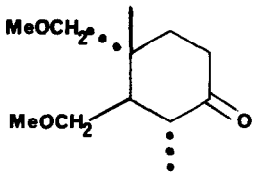
= 12 c.p.s. (trans-diaxial protons). The hydroxyl group at position 2 in (II) must therefore have the α-configuration.

Two steric relationships were found between positions 1 and 2. Firstly, the oxygen functions at these positions in taxicin-I must be sterically close, in order to account, for example, for the formation of an orthoacetate (XIX) when O-cinnamoyltaxicin-I triacetate reacts with methyl iodide and silver oxide. Secondly, the dihedral angle between the protons at positions 1 and 2 in taxicin-II must be compatible with the small degree of coupling (ca. 2-3 c.p.s.) between them. Models of taxicin-I and -II with the steric features already established, and with the α-configuration at position 1, show dihedral angles of ca. 160-180° between the α-C(1) and β-C(2) valencies, and so fail to satisfy this second criterion. Position 1 must therefore have the β-configuration. In confirmation, O.R.D. measurements[7] on O-β-phenylpropionyltaxicin-I triacetate showed that its conjugated enone system has the same chirality as that of a normal steroid 4-en-3-one.[8]

The glycol system at positions 9 and 10 readily forms acetone derivatives[2]; these, like other derivatives of taxicin-I, show $J_{9,10}$ = ca. 10 c.p.s. Clearly the protons at these positions are trans-related and form a dihedral angle of about 150-180°. In conjunction with the features already established, this can only be achieved with a 9α,10β-glycol system. This completes the evidence for the stereostructure (II); Dreiding models can be constructed without undue strain.



(XIII)



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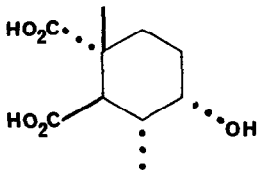
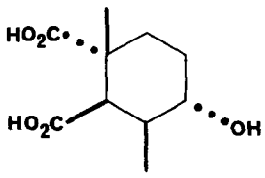
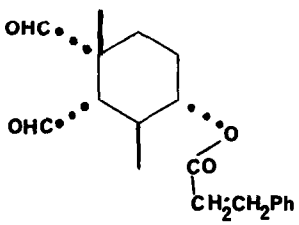


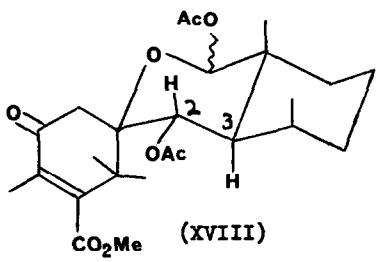
(XV)



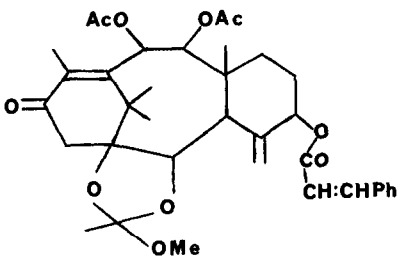
(XVI)



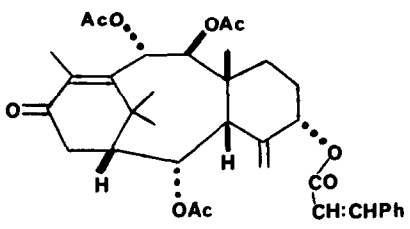
(XVII)



(XVIII)



(XIX)



(XX)

Relevant to the above work are studies on taxinine[9] (obtained from the Japanese yew) which, as previously suggested[10], has proved identical with O-cinnamoyltaxicin-II triacetate.[11] Groups headed by K. Nakanishi[12] and by S. Uyeo[13] have studied taxinine, and arrived, by independent methods, at the structure (I; R = H; R' = R" = Ac) which had been established[2] for O-cinnamoyltaxicin-II triacetate not long before. Recently these authors investigated the stereochemistry of taxinine and summarised their results in the stereostructure (XX).[14] Our present conclusions, although based on different compounds and methods, agree with theirs on positions 1, 2, 5, and 8. They differ from theirs, however, in respect of positions 3, 9, and 10; the Japanese authors did not determine the configuration at position 4 in their dihydro compounds.

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5. Rotations relate to solutions in chloroform.

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7. We are most grateful to Professor W. Klyne and Dr. D.N. Kirk (Westfield College, University of London) for these measurements, and for helpful comments on them.

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11. We thank Professor S. Uyeo for supplying a sample of taxinine, which made the direct comparison possible.

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