Taxine. Part IV.[1] The Constitution of Taxine-I

By J. W. Harrison, R. M. Scrowston, and B. Lythgoe

The n.m.r. data for several derivatives of taxicin-I, particularly for oxonortaxicin-I tetra-acetate, the spectrum of which is considered in some detail, define substantial parts of the structures. Further structural information was obtained from the preparation and examination of 1,2-, 4,5-, and 9,10-seco-taxicin-I derivatives, and also from reactions involving the hydrogenolysis of oxygen functions at positions 5 and 10. The conjugated system in the derivative (IX; R = Ac, R' = Me) was reduced stepwise in a way which shows its simple αβ-unsaturated ketone nature; a feature of these experiments was the remarkable light absorption, $\lambda_{max.}$ *ca.* 225 mμ, found for the unconjugated olefins (XIII).

The results establish for *O*-cinnamoyltaxicin-I the structure (III; R = R' = H) which differs from a tentative earlier proposal [2] only in the position of the exocyclic methylene group.

THE acidic and neutral fragments from the twofold periodate cleavage of *O*-cinnamoyltaxicin-I have been shown [1-3] to have the structures (I) and (II), respectively. The cleavage being assumed to proceed normally, two structures were then possible for the parent molecule, but one of them was ruled out by evidence mentioned below, leaving only the regular isoprenoid structure (III; R = R' = H) for consideration. Since, however, the ultraviolet (u.v.) absorption of taxicin-I ($\lambda_{max.}$ *ca.* 280 mμ), and also some chemical aspects, were not immediately clarified by this structure, we sought in the present work [3] to verify it by other methods.

Of these, n.m.r. measurements were especially useful because of the high content of oxygenated and unsaturated functions in taxicin-I derivatives. Oxonortaxicin-I tetra-acetate [4] (IV; R = Ac) provides the simplest n.m.r. spectrum for initial discussion since its signals were sharp, for the most part free from overlap, and readily identified (see Table) from the spectral effects of variations in structure.

The two doublets at lowest field (τ 3·9 and 4·1) typify signals displayed by a large number of taxicin-I derivatives. The triacetate (III; R = R' = Ac) showed similar doublets (J = 9 c./sec.) near τ 4·0 and 4·4. Protection of the disecondary glycol system with groups less electronegative than acetates, as for instance in the 9,10-*O*-isopropylidene derivative (V; R = Ac) (*vide*

[1] Part III, J. W. Harrison and B. Lythgoe, preceding Paper.
[2] B. W. Langley, B. Lythgoe, B. Scales, R. M. Scrowston, S. Trippett, and D. Wray, *J. Chem. Soc.*, 1962, 2972.
[3] Part of this work has been briefly reported: D. H. Eyre, J. W. Harrison, R. M. Scrowston, and B. Lythgoe, *Proc. Chem. Soc.*, 1963, 271.
[4] J. N. Baxter, B. Lythgoe, B. Scales, R. M. Scrowston, and S. Trippett, *J. Chem. Soc.*, 1962, 2964.

infra), shifted the doublets (J = 9 c./sec.) to higher field (τ 5·05 and 5·6). These and similar data show that the signals are due to the methine protons of a disecondary α-glycol system flanked on both sides by quaternary carbon atoms. It was this observation which excluded one of the two alternative structures for *O*-cinnamoyltaxicin-I mentioned above.

Reaction of *O*-cinnamoyltaxicin-I with acetone and anhydrous copper sulphate gave the isopropylidene derivative (V; R = H), which was acetylated to give the acetate (V; R = Ac). Methyl iodide and silver oxide converted the compound (V; R = H) into the 2-methyl ether (V; R = Me). Surprisingly, attempts to prepare the 2-monoacetate (III; R = H, R′ = Ac) by hydrolysis of the acetate (V; R = Ac) with aqueous acetic acid failed, the compound (III; R = R′ = H) being regenerated. Similar methods were, however, used successfully to prepare the 2-methyl ether (III; R = H, R′ = Me), acetylation of which then provided the diacetate (III; R = Ac, R′ = Me). The β-phenylpropionates (VI; R = Me) and (VIII; R = H, R′ = Me), which were required for work described below, were prepared by controlled hydrogenation of the corresponding cinnamates.

We next consider the coupled doublets (J = 7·5 c./sec.) near τ 4·5 and 6·3 (see Table). Signals corresponding to the low-field member of this pair were given by the 2-monoacetate (V; R = Ac) near τ 4·4 (J = 6·5 c./sec.) and by the 2-hydroxy-compound (V; R = H) at much higher field near τ 6·0 (J = 7 c./sec.). These and similar data identify these signals as due to the methine group at position 2. Since the adjoining position 1 is devoid of hydrogen, position 3 must also be a methine group, responsible for the signal near τ 6·3. Its sharp doublet nature and its chemical shift showed that one of the carbon atoms attached to position 3 is quaternary and the other (position 4) ketonic. Signals due to the C-3 proton were shown by 4(16)-olefins, such as (III; R = R′ = Ac), near τ 6·5 (J = 6·5 c./sec.). By contrast, 4(16)-saturated compounds showed the signal only at much higher fields, where it was overlaid by other signals; thus the compound (IX; R = R′ = Ac) (*vide infra*) did not show it below τ 7·9. These data show that adjacent to the C-3 methine group there is present (at position 4) the isolated methylene double bond of taxicin-I. It was noteworthy that the methine proton at position 3 in the triacetate (III; R = R′ = Ac) (and related compounds) gave a broad unsharp signal which contrasted with the sharp signal from the tetra-acetate (IV; R = R′ = Ac). The broadening was no doubt due to additional allylic coupling [6] with the C-16 methylene group.

Hydrogenation of *O*-β-phenylpropionyltaxicin-I (VII; R = R′ = H) with palladised charcoal in ethyl acetate gave almost exclusively the dihydro-compound (VIII; R = R′ = H).[4] When the same reaction was carried out in aqueous ethanol, much more than the theoretical amount of hydrogen was absorbed, and up to 0·4 mol. of β-phenylpropionic acid was liberated. This reaction gave, in addition to the expected dihydro-compound, a deoxydihydrotaxicin-I (IX; R = R′ = H), which was separated from it by counter-current distribution. The deoxy-compound clearly owed its formation to an allylic hydrogenolysis, so that in the phenylpropionate (VII; R = R′ = H) the expelled ester group must be attached to position 5, adjacent to the ring-terminus of the exocyclic double bond.

Derivatives of the hydrogenolysis product (IX; R = R′ = H) have proved valuable because of their good powers of crystallisation as well as their transparency in some important spectral regions. From the parent tetraol (IX; R = R′ = H) we prepared the

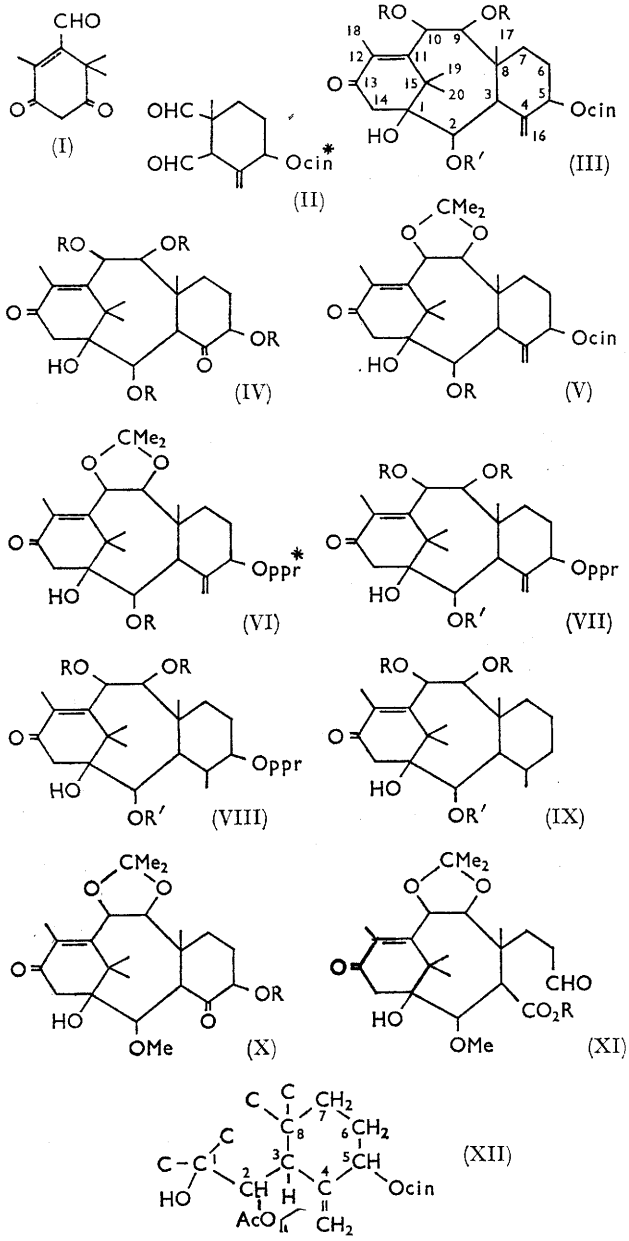
N.m.r. spectrum (60 Mc./sec.) of oxonortaxicin-I tetra-acetate (IV; R = Ac) (in $CDCl_3$)

Position and form of signal		J (c./sec.)	Assignment	Position [5] of proton
τ				
ca. 3·9	Doublet (1H)	11	>C·CH(OAc)·CH(OAc)·C	10 and 9
ca. 4·1	Doublet (1H)	11	>C·CH(OAc)·CH<	2
ca. 4·55	Doublet (1H)	7·5	·CH(OAc)·	5
ca. 5·5	Poorly resolved triplet (1H)	Peak width at half height = 4·5	·CH(OAc)·CH(C<)(CO·)	3
ca. 6·3	Doublet (1H)	7·5	>C·OH	At C-1
ca. 6·9	Singlet (1H)		·CO·CH_2·C<	14
7·25	Singlet (2H)		CH_3–C=C–	18
7·72	Singlet (3H)		CH_3·CO_2–	
7·85	Singlet (3H)		CH_3·CO_2–	
7·90	Singlet (3H)		CH_3·CO_2–	
7·92	Singlet (3H)		CH_3·CO_2–	
7·96	Singlet (3H)		CH_3·CO_2–	
ca. 8·0—8·5	Unresolved multiplet (4H)	?	·CH_2·CH_2·	6 and 7
8·32	Singlet (3H)		CH_3·C<	20
8·75	Singlet (3H)		CH_3·C<	19
9·10	Singlet (3H)		CH_3·C<	17

[5] For the nomenclature and numbering of taxane derivatives, see: B. Lythgoe, K. Nakanishi, and S. Uyeo, *Proc. Chem. Soc.*, 1964, 301.

[6] N. S. Bhacca and D. H. Williams, "Applications of N.M.R. Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, 1964, p. 108.

triacetate (IX; R = R′ = Ac), the isopropylidene derivative (IX; R, R = CMe_2, R′ = H), and its 2-acetate (IX; R, R = CMe_2; R′ = Ac). Heating the latter with aqueous acetic acid gave the 2-monoacetate (IX; R = H, R′ = Ac). The 2-methyl ether (IX;



* In structures in this Paper: cin = CO·CH:CHPh and ppr = CO·CH_2·CH_2Ph

R = H, R′ = Me) was best prepared by hydrogenolysis of the phenylpropionate (VII; R = H, R′ = Me) and separation from the accompanying phenylpropionate (VIII; R = H, R′ = Me). Acetylation of the hydrogenolysis product (IX; R = H, R′ = Me) gave the diacetate (IX; R = Ac, R′ = Me).

We now return to the n.m.r. spectrum of the tetra-acetate (IV; R = Ac) in order to identify the poorly resolved signal near τ 5·5. The triacetate (VIII; R = R′ = Ac) gave a similar but broader signal (τ 5·33), but the 5-deoxy-compound (IX; R = R′ = Ac) showed only three signals, all due to AcO·C*H*< groups, below τ 7. This identifies the above signals near τ 5·5 and 5·33 as due to the methine group at position 5. Chemical and n.m.r. methods thus established the nature and sequence of positions 1—5 in *O*-cinnamoyltaxicin-I triacetate as represented in the structure (III; R = R′ = Ac).

In order to extend this sequence it was necessary to open ring c. Treatment of the phenylpropionate (VI; R = Me) with osmium tetroxide, and cleavage of the resulting 4,16-glycol with lead tetra-acetate, gave the nor-ketone (X; R = CO·CH_2·CH_2Ph). Zemplén methanolysis gave the free α-ketol (X; R = H). It reacted with periodate giving the crystalline 4,5-seco-aldehydo-acid (XI; R = H). The corresponding methyl ester displayed a triplet signal (J = 1 c./sec.) at τ 0·25, and double resonance data showed that the aldehyde proton responsible for this signal was coupled with a methylene group which gave a complex signal near τ 7·37. Thus the nature of position 6 was established.

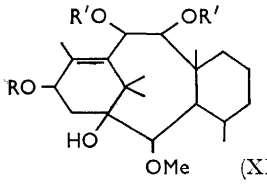
It was clear that the methylene group at position 6 in the above methyl ester was subject to further coupling, and, since the relations of all the other protons were then apparent, those involved were seen to belong to a normal methylene group. Most taxicin-I derivatives showed a complex signal (4H) between τ 8·0 and 8·6, usually partly overlaid by other signals. Where, as in the spectra of the pentaol (IV; R = H) (in hexadeuterio-acetone) and the α-diketone (XX) (*vide infra*), it was free from overlap by other signals, its form was compatible with the presence of an ethano-group (positions 6 and 7). Infrared evidence [4] having shown that ring c is six-membered, positions 3 and 8 must be ring-junctions, and the partial structure (XII) must be present in *O*-cinnamoyltaxicin-I triacetate.

We expected that ring c would conform to the structure (III; R = R′ = H); it was in respect of ring A and its environs that additional evidence was most needed, since hitherto we had been unable to bring its functional groups into chemical reaction. Reduction of neither the keto-group nor the double bond had been satisfactorily effected. Attempts to brominate the 14-methylene group, for example in the tetra-acetate (IV; R = R′ = Ac), had failed. Reactions normally associated with a tertiary β-hydroxy-ketone system, such as dehydration, could not be effected. The behaviour of the 10-hydroxyl group was not typically allylic. However, doubts as to the structural features of ring A were removed by the following observations.

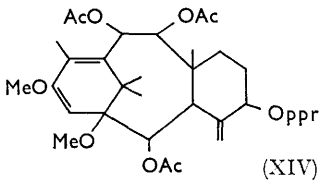
The singlet signal (2H) near τ 7·25 (see Table) was most probably due to a system ·CO·CH_2·C<. Corresponding signals were shown, for example, by the diacetate (III; R = Ac, R′ = Me) as a singlet at τ 7·27, and by the triacetate (IX; R = R′ = Ac) as a quartet (J = 19·5 c./sec.) near τ 7·3. Confirmation was sought by chemical modification of the 13-keto-group.

Although several taxicin-I derivatives previously tried had given unsatisfactory or anomalous results on

attempted reduction with sodium borohydride, we now found the methyl ether diacetate (IX; R = Ac, R′ = Me) to react normally, giving the crystalline secondary alcohol (XIII; R = H, R′ = Ac). As expected from its allylic nature, the alcohol was re-oxidised to its enone



(XIII)



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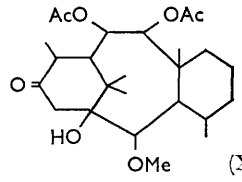
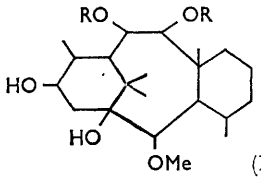


(XV)



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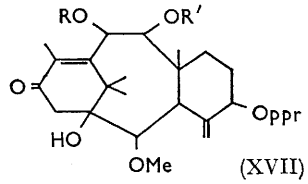
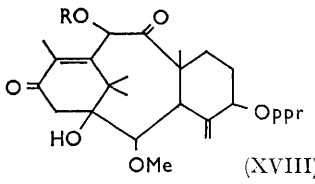
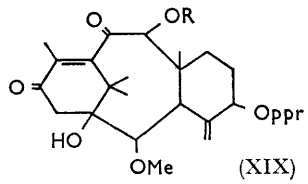


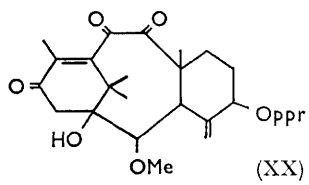
(XVII)



(XVIII)



(XIX)



(XX)

precursor by manganese dioxide in acetone. On the one hand it formed an acetate (XIII; R = R′ = Ac) and on the other it was deacetylated by lithium aluminium hydride to the tetraol (XIII; R = R′ = H), although methanolic sodium methoxide was ineffective for that purpose. Infrared data showed that the tetraol contained no carbonyl groups; its u.v. absorption, $\lambda_{max.}$ 227 mμ (ε 5700) was unique for a mono-olefin; most similar compounds absorb below 205 mμ. The tetraol reacted with acetone in the expected way, acetylation then providing the 9, 10-isopropylidene 13-monoacetate (XIII; R = Ac, R′R′ = CMe_2). Its n.m.r. spectrum showed the C-13 proton signal as a quartet near τ 4·1 with apparent splittings of about 8·5 and 3·5 c./sec., demonstrating the presence of the adjacent methylene group at position 14.

Further evidence on this position was obtained as follows. Methylation of the phenylpropionate (VII; R = R′ = Ac) with methyl iodide and silver oxide in dimethylformamide [7] gave a compound which, as expected, did not contain a free hydroxyl group, but which surprisingly, proved to contain two methoxyl groups. The original keto-group had disappeared, and a new absorption band near 1650 cm.$^{-1}$ indicated an enol ether group. The new compound is therefore regarded as the homoannular diene (XIV), although its u.v. absorption $\lambda_{max.}$ 255 mμ (ε 7300) is anomalous, just as is that of its precursor. Its n.m.r. spectrum supported the above structure. It showed no methylene signal near τ 7·3; instead a new sharp singlet (1H) near τ 3·9 indicated an olefinic proton in the expected environment (position 14).

In earlier experiments, catalytic hydrogenation of the chromophore in many taxicin-I derivatives either proceeded too slowly to be useful, or else gave complex mixtures. Better results were now obtained with the diacetate (IX; R = Ac, R′ = Me) using platinum in acetic acid. From the product, three homogeneous compounds were separated, the first being the secondary alcohol (XIII; R = H; R′ = Ac). The other two were stereoisomeric dihydro-compounds (XV), m. p. 195° and 179°, respectively; they showed $\nu_{max.}$ 1698 cm.$^{-1}$, so that the keto-group had survived, but negligible absorption above 200 mμ, indicating that the conjugated double bond had been reduced. The more abundant isomer, m. p. 195°, was further reduced with sodium borohydride, which gave two epimeric secondary alcohols (XVI; R = Ac); both were re-oxidised to their ketonic precursor by chromic oxide in pyridine. The more abundant of the two alcohols (XVI; R = Ac) was deacetylated with lithium aluminium hydride, which gave the crystalline tetraol (XVI; R = H). It was the first-obtained taxane derivative without any kind of unsaturation, and, as expected, it was free from carbonyl and ethylenic absorption near 6 μ and was transparent above 200 mμ.

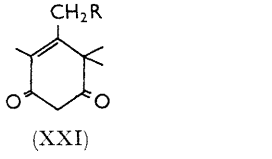
The above results confirmed that the taxicin-I chromophore is a simple αβ-unsaturated ketone system. The n.m.r. data showed that the conjugated double bond is fully substituted, and that one of the substituents is a methyl group. It is this group which causes the 3-proton singlet at τ 7·72 in the spectrum of the tetra-acetate (IV; R = Ac). The diacetate (IX; R = Ac, R′ = Me) showed a similar signal at τ 7·87, but its 11,12-dihydro-compounds (XV) showed instead doublet signals (3H) at higher fields; the more abundant isomer (XV), for example, showed a doublet J = 7 c./sec. near τ 8·6 (>$CH{\cdot}CH_3$), in addition to that (J = 5 c./sec.) at τ 8·87 due to the C-16 secondary methyl group.

We carried out several series of experiments intended to demonstrate the direct attachment of the disecondary glycol system (positions 9 and 10) to the conjugated double bond. In one series, the 2-methyl ether (VII; R = H; R′ = Me) was subjected to partial acetylation, and the products were separated into the expected diacetate (XVII; R = R′ = Ac), and the monoacetates (XVII; R = Ac, R′ = H) and (XVII; R = H, R′ = Ac); the way in which these monoacetates were identified is described below. We hoped that the isomer (XVII; R = H, R′ = Ac) would be oxidised by manganese dioxide in acetone, but no reaction took place. Chromic oxide in pyridine oxidised each of the monoacetates to corresponding α-ketol acetates (XVIII; R = Ac) and (XIX; R = Ac). Somewhat unexpectedly, the spectroscopic data provided little evidence

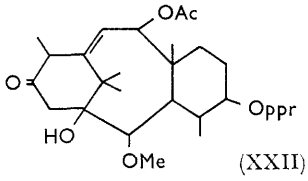
[7] R. Kuhn, H. Trischmann, and I. Löw, *Angew. Chem.*, 1955, **67**, 32.

of conjugation between the new keto-group and the 11,12-double bond in the compound (XIX; R = Ac); it displayed $\lambda_{max.}$ 278 mμ (ε 4500), $\nu_{max.}$ (in KCl) 1705 cm.$^{-1}$ (10-oxo-group). For comparison, the monoacetates (XVII) showed $\lambda_{max.}$ 278 mμ (ε *ca.* 5000), and the ketol acetate (XVIII; R = Ac) showed $\lambda_{max.}$ 270 mμ (ε 4800), $\nu_{max.}$ (in KCl) 1715 cm.$^{-1}$ (9-oxo-group). Configurational studies [8] have recently shown that the shape of the taxicin-I molecule [compare the stereostructure (XXXVII)] is such that a 10-oxo-group is unable to achieve even near-coplanarity with the adjacent double bond; this explains their lack of conjugation.

The α-ketol acetates each showed a sharp singlet due to the methine proton at position 9 or 10; that from the acetate (XIX; R = Ac) occurred at τ 4·37, whereas that from its isomer (XVIII; R = Ac) lay at much lower field, τ 3·35, in agreement with the structures now allocated. The ketol acetates were deacetylated to corresponding α-ketols, which appeared to be strongly internally hydrogen-bonded. Oxidation of each gave the same α-diketone (XX). As expected from its structure, this was a pale yellow non-enolic substance.



(XXI)



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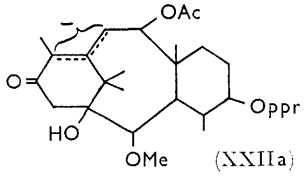
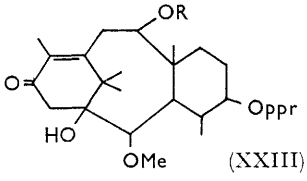
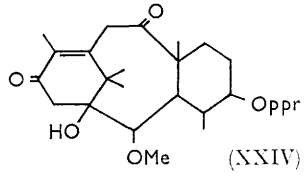


(XXIIa)



(XXIII)



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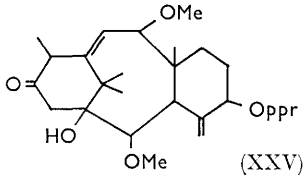

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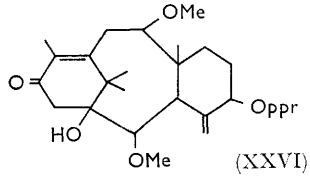

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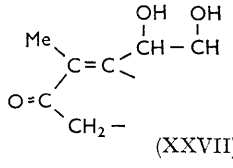


(XXVII)

During work described in Part II,[2] the allylic disposition of the primary hydroxyl group in the compound (XXI; R = OH) was demonstrated by reduction with zinc and acetic acid to the deoxy-compound (XXI; R = H). It was of interest to apply this reaction to intact derivatives of taxicin-I. Its course was found to depend on the nature of the compound used. The triacetate (VII; R = R′ = Ac), for example, gave a product of the expected composition, suggesting the replacement of an acetoxy-group by hydrogen, but, unexpectedly, the chromophore in the product was a new one, $\lambda_{max.}$ 244 mμ (ε 14,000). We propose to discuss this abnormal reaction mode elsewhere. In contrast, compounds containing a 2-methoxy-group reacted with zinc and acetic acid in the expected manner, and provided useful structural information.

Treatment of the diacetate (VIII; R = Ac, R′ = Me) with zinc and acetic acid gave the monoacetate (XXII), as shown by the analytical data and also by the following evidence. It showed no high-intensity absorption in the near-ultraviolet region; its keto-group showed $\nu_{max.}$ 1700 cm.$^{-1}$; it was clearly unconjugated. The methyl group at position 12 showed a doublet signal (J = 7 c./sec.) near τ 8·8, whilst the olefinic proton at position 10 and the methine proton at position 9 showed doublets, J = 10·5 c./sec., near τ 4·25 and 4·7. This compound was thus formed under kinetic control by protonation of the intermediate carbanion (XXIIa) at position 12 rather than at position 10. It was apparently not the more stable of the two possible isomers. Zemplén deacetylation with 0·025N-methanolic sodium methoxide moved the double bond back into conjugation with the keto-group, giving the amorphous hydroxy-compound (XXIII; R = H). This showed $\lambda_{max.}$ near 280 mμ (ε 4500) and provided on acetylation the crystalline acetate (XXIII; R = Ac). The acetate had the normal u.v. and i.r. spectral characteristics [4] of the taxicin-I chromophore. Features of its n.m.r. spectrum were the singlet signal (3H) at τ 8·05 due to the 18-methyl group, and a quartet signal (1H) near τ 4·65 due to the methine proton at position 9, which was coupled to both the protons of the adjacent C-10 methylene group. Chromic oxide in pyridine oxidised the alcohol (XXIII; R = H) to the diketone (XXIV) which, in spite of its vinylogous β-diketone structure, was non-enolic. Its $\lambda_{max.}$ 278 mμ (ε 5700) was normal for the taxicin-I chromophore; the keto-group at position 9 showed $\nu_{max.}$ 1690 cm.$^{-1}$, in marked contrast to the value found for the 10-acetoxy-derivative (XVIII; R = Ac). Attempts to move the double bond into conjugation with the keto-group at position 9 were unsuccessful. The above reactions show not only that position 10 is allylic to the conjugated double bond of taxicin-I, they also show that the methyl group attached to this double bond must be located at the position adjacent to the keto-group, rather than at that remote from it.

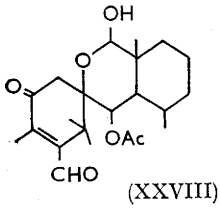
Treatment of the monoacetate (XVII; R = Ac, R′ = H) with methyl iodide and silver oxide gave the dimethyl ether (XVII; R = Ac, R′ = Me). With zinc and acetic acid this gave the dimethyl ether (XXV). Its structure was apparent from the analytical and spectra data, and also from its isomerisation to the conjugated ketone (XXVI) by methanolic sodium methoxide. This provides additional evidence for the identity of the monoacetate (XVII; R = Ac, R′ = H).

Prolonged reduction of the diketone (XXIV) with zinc and acetic acid gave an amorphous product in which

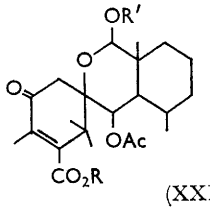
[8] M. Dukes, D. H. Eyre, J. W. Harrison, and B. Lythgoe, *Tetrahedron Letters*, 1965, 4765.

the conjugated double bond had been reduced, as was apparent from the lack of absorption in the near-ultraviolet region, and from the carbonyl absorption $\nu_{max.}$ 1695 cm.$^{-1}$. This is a known effect of zinc and acetic acid. It was shown most strikingly by the action of these reagents on the diacetate (IX; R = Ac, R′ = Me) which gave, *inter alia*, about 10% of the dihydro-compound (XV) (minor isomer, m. p. 179°).

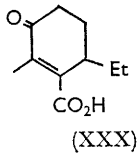
The foregoing results show that the part-structure (XXVII) is present in taxicin-I, and is attached by three quaternary carbon atoms. The latter were identified in the course of experiments on the partial periodate cleavage of ring B, undertaken in order to confirm the normality of the dual cleavage described in Part II.



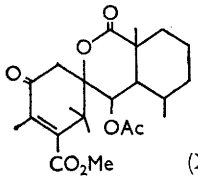
(XXVIII)



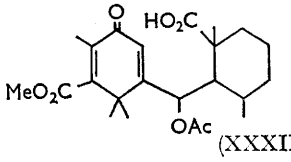
(XXIX)



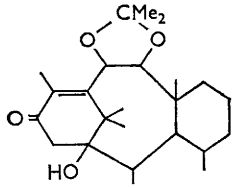
(XXX)



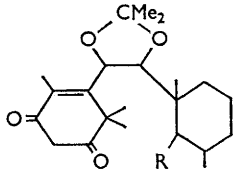
(XXXI)



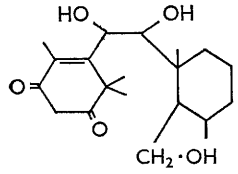
(XXXII)



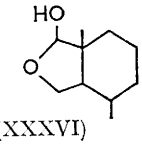
(XXXIII)



(XXXIV)



(XXXV)



(XXXVI)

Reaction of the 2-monoacetate (IX; R = H, R′ = Ac) with periodate might be expected to give a dialdehyde; instead, cyclisation between one of the aldehyde groups and the tertiary hydroxyl group of the initial product resulted in the isolation of a formyl-hemiacetal (XXVIII), $\lambda_{max.}$ 256 mμ (ε 6800). Its solutions were unstable in air, the free aldehyde group autoxidising rapidly to give the acid (XXIX; R = R′ = H). The acid showed $\lambda_{max.}$ 247 mμ (ε 6500), the change in absorption providing evidence that the free aldehyde group in the precursor (XXVIII) was conjugated. At this stage we were able to confirm the identity of the chromophore of the acid (XXIX; R = R′ = H) by reference to the model compound (XXX),[9] which was known to have $\lambda_{max.}$ 246 mμ. Methylation of the acid (XXIX; R = H), followed by acetylation of the methyl est vided the diacetate (XXIX; R = Me, R′ = A expected, its n.m.r. spectrum displayed no al proton signal; instead, a singlet (1H) at τ 4·1, the proton at position 9, confirmed the hemiacetal structure. The observation that hemiacetal fo occurred initially indicates either a γ- or a δ- between the participating functions; in fact, the possibility was excluded by careful oxidation hemiacetal (XXIX; R = Me, R′ = H) with oxide in pyridine, when a lactone (XXXI), show i.r. spectral properties to be a δ-lactone, was ob This established the direct union of the disec glycol system of taxicin-I with the quaternary pos

Warming the δ-lactone in pyridine caused an i elimination, yielding the dienone carboxyli (XXXII). Whereas the diacetate (XXIX; R R′ = Ac) showed a characteristic signal (2H) at due to the methylene group at position 14, t (XXXII) gave a dimethyl ester which showed signal, but instead a new sharp singlet (1H) at due to the olefinic proton at position 14. These show the nature and connection of the groups tions 1, 14, and 13, and define the manner in wh part-structures (XII) and (XXVII) are united cinnamoyltaxicin-I. Four carbon atoms then re be placed; the n.m.r. data show that three are as tertiary methyl groups, and the last as a qua carbon atom. This leads uniquely to the structu R = R′ = H).

The mild conditions required for the elimina the C-1 oxygen function in the δ-lactone (XX trast with our failure to effect an analogous rea intact derivatives of taxicin-I. We attribu difficulty here chiefly to the fact that taxicin-I, bridgehead double bond, is already on the limits formity with Prelog's[10] extension of Bredt Introduction of a second bridgehead double bon no doubt cause prohibitive strain.

In further partial cleavage studies, the (XXXIII) reacted with 1 mol. of periodate, giv acidic monoaldehyde (XXXIV; R = CHO). i.r., and n.m.r. spectral properties fully suppor structure. Reduction to the primary alcohol (X R = CH_2·OH) and acidic hydrolysis gave the (XXXV). This reacted further with periodate, gi acidic fragment (I) and the hemiacetal (XXX this way the overall result of the twofold cleava taxicin-I molecule reported in Part II was accon stepwise, leaving no doubt as to the correctnes structure (III; R = R′ = H).

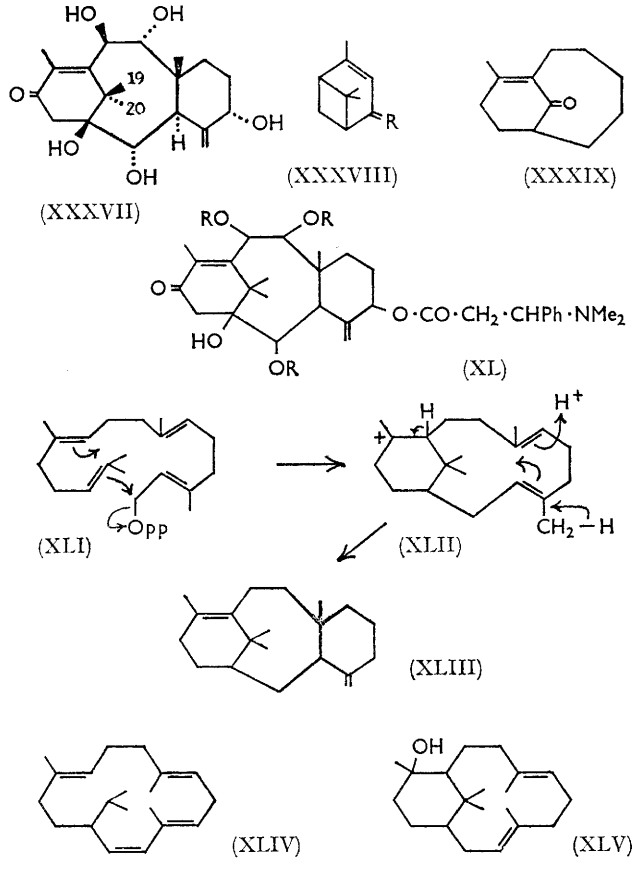
The cleavage of 1,2- and 9,10-glycols in the t series, for example that of (XXXIII) and R = H, R′ = Ac), was most conveniently effe the use of manganese dioxide in acetone rath periodate. The work-up was simpler and the

[9] G. Büchi and E. W. Warnhoff, *J. Amer. Chem. Soc.*, 1959, **81**, 4433.

[10] V. Prelog, P. Barman, and M. Zimmermann, *He Acta*, 1949, **32**, 1284.

cleaner. Examples of glycol cleavage by manganese dioxide have been recorded.[11] It was noteworthy that the hemiacetal (XXVIII) was not further oxidised by the manganese dioxide used in its formation; the reagent frequently oxidises hemiacetals to lactones.[12] We also used manganese dioxide as the most convenient method of oxidising the α-ketols (XVIII; R = H) and (XIX; R = H) to the α-diketone (XX); it may prove generally effective as a reagent for this kind of oxidation.

There remain for assignment the three singlet *C*-methyl signals at τ 8·32, 8·75, and 9·10 in the spectrum of the tetra-acetate (IV; R = Ac). They typify signals given by the majority of the taxicin-I derivatives with all three rings intact; that at lowest field is regarded as due to the group attached in the β-configuration at position 15; this we shall refer to as C-20. The second is due to C-19, *i.e.*, the group in the α-configuration at position 15; the highest field signal is regarded as due to C-17. These assignments require detailed consideration of the stereochemistry (XXXVII) of taxicin-I, and will be discussed in a later Paper.



The ultraviolet maxima of the taxicin-I derivatives here described lay normally in the region 275—285 mμ, that is, some 25 mμ higher than the value (*ca.* 255 mμ) expected [13] for enones of the same type. Exaltations of the same kind, although not the same magnitude, are known to occur in some enones where the double bond occupies a strained position; thus verbenone (XXXVIII; R = O) has $\lambda_{max.}$ 253 mμ (ε 6840)[14] (expected, *ca.* 239 mμ). In such cases the corresponding olefin often shows abnormal absorption; thus α-pinene (XXXVIII; R = H_2) has $\lambda_{max.}$ 210 mμ [15] (expected [16]: *ca.* 195 mμ). This feature is also present in the taxicin-I series; the tetraol (XIII; R = R′ = H) had $\lambda_{max.}$ 227 mμ (expected: *ca.* 202 mμ), thus showing an exaltation of the same magnitude as that of the parent enone. The causes of the anomalies in taxicin-I and verbenone may therefore be analogous. Two points must, however, be made; first, taxicin-I is not strained in the sense that verbenone is; models of the stereostructure (XXXVII) can be constructed with relatively little strain; secondly, the enone (XXXIX),[10] in which the double bond is situated in an environment apparently very similar to that in taxicin-I, shows normal light-absorption at 250 mμ (ε 5600). The differences are not due to the presence of an oxygen function at position 10, since the deoxy-compound (XXVI) had $\lambda_{max.}$ 282 mμ; but the hydroxyl group at position 1 was partly responsible, since taxicin-II derivatives were found to show $\lambda_{max.}$ *ca.* 7 mμ lower than the corresponding taxicin-I compounds; for example, the triacetate (VII; R = R′ = Ac) had $\lambda_{max.}$ 276 mμ, the corresponding taxicin-II compound 268 mμ. It was of interest that opening ring C caused little change; the compound (XI; R = H) had $\lambda_{max.}$ 276 mμ. It seems likely that the *gem*-dimethyl group in the taxicin molecule may be the most important feature in causing the abnormally long-wave light absorption in relation to the enone (XXXIX).

Taxine-I, the major alkaloid of *Taxus baccata* L., is an acetylated form of the tetraol (XL; R = H); how many acetate groups are present? Taxine-B, isolated by Graf,[17] was undoubtedly a monoacetate. We have obtained substantial amounts of the triacetate (III; R = R′ = Ac) by direct crystallisation of some samples of desdimethylaminotaxine [4] from methanol, so that a triacetate (XL; R = Ac) must occur naturally. In all cases, however, acetylation of desdimethylaminotaxine increased the yield of the triacetate, and it is probable that a mixture of acetates of the compound (XL; R = H) is usually present.

It seems possible [18] that the taxicin-I skeleton may arise biogenetically from geranylgeraniol by cyclisation reactions such as (XLI) ⟶ (XLII) ⟶ (XLIII). A similar biogenesis was earlier suggested [19] for the monocyclic diterpene cembrene (XLIV), and, more recently, it has been suggested [20] that the bicyclic diterpene alcohol

[11] P. N. Ras, *J. Org. Chem.*, 1961, **26**, 2149.
[12] R. J. Highet and W. C. Wildman, *J. Amer. Chem. Soc.*, 1955, **77**, 4399.
[13] R. B. Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76.
[14] R. G. Moore and G. S. Fisher, *J. Amer. Chem. Soc.*, 1956, **78**, 4362.
[15] D. W. Turner, *J. Chem. Soc.*, 1959, 30.
[16] P. S. Ellington and G. D. Meakins, *J. Chem. Soc.*, 1960, 697.
[17] E. Graf, *Arch. Pharm.*, 1958, **291**, 443.
[18] J. W. Harrison, Ph.D. Thesis, Leeds, 1964.
[19] W. G. Dauben, W. E. Thiessen, and P. Resnick, *J. Amer. Chem. Soc.*, 1962, **84**, 2015.
[20] H. Erdtman, T. Norin, M. Sumimoto, and A. Morrison, *Tetrahedron Letters*, 1964, 3879.

verticillol (XLV?) may form a third member of the same biogenetic group.

EXPERIMENTAL

Except where otherwise specified, specific rotation data relate to 1—2% solutions in chloroform, i.r. spectral data to solutions in chloroform, u.v. data to solutions in ethanol, and n.m.r. data to solutions in deuteriochloroform. Unless otherwise specified, " light petroleum " means the fraction of b. p. 60—80°. For describing n.m.r. signals the following abbreviations are used: s. (singlet), d. (doublet), t. (triplet), q. (quartet), m. (multiplet); coupling constants are given in c./sec., and skeletal positions of responsible protons are italicised.

9,10-O-*Isopropylidene*-5-O-*cinnamoyltaxicin-I* (V; R = H).—*O*-Cinnamoyltaxicin-I (220 mg.) and anhydrous copper sulphate (2 g.) were shaken in dry acetone (20 c.c.) for 80 hr. Filtration and evaporation gave a residue which was kept together with benzene (10 c.c.), the starting material which then separated being removed. Evaporation to low volume gave the *isopropylidene derivative*, which separated from benzene–hexane as needles, m. p. 142—144·5°, $[\alpha]_D^{20}$ +242° (Found: C, 71·65; H, 7·6. $C_{32}H_{40}O_7$ requires C, 71·6; H, 7·5%).

Acetylation with acetic anhydride and pyridine gave the 2-*acetate* (V; R = Ac), which separated from aqueous ethanol, m. p. 141—142° (Found: C, 70·2; H, 7·25. $C_{34}H_{42}O_8$ requires C, 70·55; H, 7·3%). It showed *inter alia* the following n.m.r. signals: τ 4·36, d. J = 6·5, 1H, *2*; τ 4·64, broad s., 2H, *5* and *16*; τ 5·05, d. J = 9, 1H, *10*; τ 5·27, broad s., 1H, *16*; τ 5·6, d. J = 9, 1H, *9*; τ 6·62, broad d. J = 6·5, 1H, *3*; τ 7·22, q. J = 20, 2H, *14*; τ 7·85, s., 3H, *18*; τ 8·30, s., 3H, *20*; τ 8·67, s., 3H, *19*; τ 8·92, s., 3H, *17*.

2-O-*Methyl*-5-O-*cinnamoyltaxicin*-I (III; R = H, R′ = Me).—The isopropylidene derivative (V; R = H) (5 g.) and freshly prepared silver oxide [21] (14 g.) were refluxed together for 2 days in methyl iodide (100 c.c.) with exclusion of light. Filtration, evaporation, and crystallisation from ether–light petroleum (b. p. 40—60°) gave the *methyl ether* (V; R = Me) (2·5 g.) as needles, m. p. 180°, $[\alpha]_D^{18}$ +295° (Found: C, 72·05; H, 7·75. $C_{33}H_{42}O_7$ requires C, 71·95; H, 7·7%). More of the same product was obtained by chromatography of the mother-liquors on alumina.

The methyl ether (1 g.) was heated to 80° for 2 hr. with glacial acetic acid (50 c.c.) and water (50 c.c.). After the solution had been diluted with water the product was extracted with ether. Crystallisation from ethyl acetate–light petroleum (b. p. 40—60°) gave the *methyl ether* (III; R = H, R′ = Me) (750 mg.) as needles, m. p., 212·5—213·5° (Found: C, 70·65; H, 7·55. $C_{30}H_{38}O_7$ requires C, 70·55; H, 7·5%).

The *diacetate* (III; R = Ac, R′ = Me), obtained by reaction with acetic anhydride and pyridine for 7 days at 35°, separated from ethyl acetate–light petroleum as prisms, m. p. 194—195°, $[\alpha]_D^{19}$ +233° (Found: C, 68·7; H, 7·05. $C_{34}H_{42}O_9$ requires C, 68·7; H, 7·1%).

2-O-*Methyl*-5-O-β-*phenylpropionyltaxicin-I* (VII; R = H, R′ = Me).—(*a*) The methyl ether (V; R = Me) (800 mg.) was hydrogenated in ethyl acetate (15 c.c.) with 5% palladised charcoal (200 mg.), the reaction being terminated after 1·0 mol. of hydrogen had been taken up (15 min.). Isolation in the usual manner gave the *phenylpropionate* (VI; R = Me) which separated from ether–light petroleum (b. p. 40—60°) as needles (780 mg.), m. p. 150—151°, $[\alpha]_D^{20}$ +218°, $\lambda_{max.}$ 278 mμ (ε 6000) (Found: C, 71·55; H, 8·05. $C_{33}H_{44}O_7$ requires C, 71·7; H, 8·0%).

Reaction with hot 50% aqueous acetic acid, isolation in the usual manner, and crystallisation from benzene–hexane gave the *methyl ether* (VII; R = H, R′ = Me) (80%) as needle clusters, m. p. 182—183° (Found: C, 70·45; H, 7·75. $C_{30}H_{40}O_7$ requires C, 70·3; H, 7·85%). It showed $\lambda_{max.}$ 275 mμ (ε 5400).

(*b*) Hydrogenation of the methyl ether (III; R = H; R′ = Me) with 5% palladised charcoal in ethyl acetate and 1 mol. of hydrogen gave the above methyl ether nearly quantitatively.

9,10-O-*Isopropylidene*-2-O-*methyl*-5-O-β-*phenylpropionyldihydrotaxicin-I* (VIII; R = CMe_2, R′ = Me).—*O*-β-Phenylpropionyldihydrotaxicin-I (1 g.) was shaken with acetone (30 c.c.) and anhydrous copper sulphate (4 g.) for 2 days, and the amorphous product (1 g.), after isolation in the usual manner, was methylated with methyl iodide and silver oxide in the usual manner. Chromatography on alumina (Grade II) and elution with benzene containing 0·1—0·2% ethanol gave the *methyl ether* as needles (520 mg.), m. p. 145—146° (from ethyl acetate–light petroleum), $[\alpha]_D^{19}$ +202°, $\lambda_{max.}$ 280 mμ (ε 5300) (Found: C, 71·75; H, 8·35. $C_{33}H_{46}O_7$ requires C, 71·45; H, 8·35%).

5-Deoxydihydrotaxicin-I (IX; R = R′ = H).—*O*-Cinnamoyltaxicin-I (16 g.) in methanol (100 c.c.) and water (2 c.c.) containing 5% palladised charcoal (8 g.) was shaken with hydrogen for 16 hr. (uptake 2·47 mol.). The product, isolated in the usual way, was dissolved in ether. The ether was washed with aqueous sodium hydrogen carbonate and then with water; acidification of the combined aqueous phases yielded β-phenylpropionic acid (2·08 g.). Evaporation of the ether gave an amorphous product (13·8 g.) which was subjected to counter-current distribution (150 transfers) in the system methanol–water–ethyl acetate–light petroleum (4 : 6 : 5 : 5). Tubes 118—138 furnished material which separated from aqueous methanol giving *O*-β-phenylpropionyldihydrotaxicin-I (5·4 g.). Tubes 65—90 furnished material which separated from aqueous methanol as prisms (4·0 g.) of the *deoxy-compound* (IX; R = R′ = H), m. p. 206—208° (decomp.), $[\alpha]_D^{20}$ +299° (*c*, 1% in ethanol) (Found: C, 68·3; H, 9·0. $C_{20}H_{32}O_5$ requires C, 68·15; H, 9·15%). It showed $\lambda_{max.}$ 283 mμ (ε 5700), $\nu_{max.}$ (in KCl) 1664 (conj. C=O), 1597 (conj. C=C) cm.$^{-1}$.

Acetylation with pyridine and acetic anhydride at 18° for 5 days gave the *triacetate* (from acetone–light petroleum), m. p. 218—219°, $[\alpha]_D^{20}$ + 192° (*c*, 1 in acetone), $\lambda_{max.}$ 279 mμ (ε 5700), $\nu_{max.}$ 1675 (conj. C=O) cm.$^{-1}$ (Found: C, 65·2; H, 8·0. $C_{26}H_{38}O_8$ requires C, 65·25; H, 8·0%). It showed *inter alia* the following n.m.r. signals: τ 4·09, s., 2H, *9* and *10*; τ 4·54, d., J = 4, 1H, *2*; τ 7·22, q., J = 19·5, 2H, *14*; τ 7·93, s., 3H, *18*; τ 8·33, s., 3H, *20*; τ 8·80, s., 3H, *19*; τ 9·02, d., J = 4, 3H, *16*; τ 9·15, s., 3H, *17*.

2-O-*Acetyl*-5-*deoxy*-4,16-*dihydrotaxicin-I* (IX; R = H; R′ = Ac).—5-Deoxydihydrotaxicin-I (4·8 g.), anhydrous copper sulphate (10 g.), and acetone (75 c.c.) were shaken together for 16 hr. Filtration, evaporation, and crystallisation from chloroform–light petroleum gave the *isopropylidene derivative* (4·1 g.) as needles, m. p. 223—224°, $[\alpha]_D^{20}$ +309° (*c*, 1 in acetone), $\lambda_{max.}$ 282 mμ (ε 5200), $\nu_{max.}$ (in KCl) 1669 (conj. C=O) cm.$^{-1}$ (Found: C, 70·25; H, 9·2. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·2%).

[21] B. Helferich and W. Klein, *Annalen*, 1926, **450**, 219.

The 2-*monoacetate* (IX; R, R = CMe_2, R′ = Ac), prepared in the usual way, separated from aqueous ethanol as prisms, m. p. 123—124° (Found: C, 69·0; H, 8·7. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

The above monoacetate was heated to 75° for 2 hr. with 50% aqueous acetic acid. Dilution, isolation with ether, and crystallisation from acetone–light petroleum gave the 2-*acetate* (IX; R = H; R′ = Ac) as needles, m. p. 203—204°, $[\alpha]_D^{20}$ +233° (*c*, 0·7 in acetone), $\lambda_{max.}$ 283 mμ (ε 5300) (Found: C, 67·15; H, 8·6. $C_{22}H_{34}O_6$ requires C, 67·0; H, 8·7%).

Hydrogenolysis of the Methyl Ether (III; R = H, R′ = Me).—The methyl ether (6·7 g.) and 5% palladised charcoal (3 g.) in methanol (50 c.c.) and water (1 c.c.) were shaken with hydrogen for 16 hr. (uptake, 2·81 mol.). Working up in the usual manner, and extraction with sodium hydrogen carbonate solution removed β-phenylpropionic acid (1·51 g.). Crystallisation of the remaining material from chloroform–light petroleum gave 2-O-*methyl*-5-*deoxydihydrotaxicin-I* (IX; R = H; R′ = Me) as rosettes of needles (2·2 g.), m. p. 260—265° (decomp.), $[\alpha]_D^{20}$ +270° (*c*, 1·0 in methanol), $\lambda_{max.}$ 281 mμ (ε 5800), $\nu_{max.}$ 1665 (conj. C=O) cm.$^{-1}$ (Found: C, 69·1; H, 9·4. $C_{21}H_{34}O_5$ requires C, 68·8; H, 9·35%).

The *diacetate* (IX; R = Ac, R′ = Me) separated from chloroform–light petroleum as prisms, m. p. 223—224°, $[\alpha]_D^{20}$ +220° (*c*, 2 in acetone), $\lambda_{max.}$ 279 mμ (ε 5600), $\nu_{max.}$ 1672 (conj. C=O) cm.$^{-1}$ (Found: C, 66·7; H, 8·45. $C_{25}H_{38}O_7$ requires C, 66·6; H, 8·5%). It showed *inter alia* the following n.m.r. signals: τ 3·9, d., *J* = 11, 1H, *10*; τ 4·1, d., *J* = 11, 1H, *9*; τ 6·45, s., 3H (OCH_3); τ 7·17, q., *J* = 19·5, 2H, *14*; τ 7·87, s., 3H, *18*; τ 8·30, s., 3H, *20*; τ 8·69, s., 3H, *19*; τ 8·95, s., 3H, *17*; τ 8·98, d., *J* = 3·5, 3H, *16*.

Hydrogenation of the Methyl Ether (III; R = H; R′ = Me).—The methyl ether (5·0 g.) and 5% palladised charcoal (2·5 g.) in ethyl acetate (50 c.c.) were shaken with hydrogen for 12 hr. (uptake, 2·13 mol.). Filtration, evaporation, and crystallisation from chloroform–light petroleum gave 2-O-*methyl*-5-O-β-*phenylpropionyldihydrotaxicin-I* (VIII; R = H; R′ = Me) as rosettes of needles, m. p. 190—191°, $\lambda_{max.}$ 281 mμ (ε 6200) (Found: C, 70·05; H, 8·1. $C_{30}H_{42}O_7$ requires C, 70·0; H, 8·2%). Chromatography of the mother-liquor material afforded a small amount (255 mg.) of the deoxy-compound (IX; R = H, R′ = Me).

Acetylation of the above phenylpropionate in the usual way gave the *diacetate* (VIII; R = Ac, R′ = Me) as prisms (from acetone–light petroleum) m. p. 164° (Found: C, 69·3; H, 7·4. $C_{34}H_{46}O_9$ requires C, 69·4; H, 7·45%).

The Nor-ketone (X; R = H).—The phenylpropionate (VI; R = Me) (1·0 g.) and osmium tetroxide (480 mg.) were kept together in dry ether (150 c.c.) and pyridine (0·5 c.c.) for 16 hr. at 0°. Slow evaporation to low volume (*ca.* 10 c.c.) precipitated the osmiate, which was collected, washed with ether, and dissolved in pyridine (8 c.c.). A solution of sodium hydrogen sulphite (1 g.) in water (15 c.c.) and pyridine (10 c.c.) was added slowly with shaking, which was continued (40 min.) until a clear orange solution was formed. It was extracted with chloroform, the chloroform extract was washed with 2N-hydrochloric acid and then with water, dried, and evaporated. Crystallisation from ethyl acetate–light petroleum gave the 4,16-*glycol* as needles (720 mg.), m. p. 181—182°, $[\alpha]_D^{21}$ +198°, $\lambda_{max.}$ 276 mμ (ε 5400) (Found: C, 67·55; H, 7·8. $C_{33}H_{46}O_9$ requires C, 67·55; H, 7·9%).

The glycol (100 mg.) in dry chloroform (15 c.c.) was kept with 0·1M-chloroformic lead tetra-acetate (1·05 equiv.) for 30 min.; the solution was diluted with chloroform, washed with dilute hydrochloric acid and then with water, and then dried and evaporated. Crystallisation from ethyl acetate–hexane gave the *nor-ketone* (X; R = $CO{\cdot}CH_2{\cdot}CH_2Ph$) as needles (80 mg.), m. p. 202—203°, $[\alpha]_D^{20}$ +206°, $\lambda_{max.}$ 275 mμ (ε 5600) (Found: C, 69·0; H, 7·45. $C_{32}H_{42}O_8$ requires C, 69·3; H, 7·6%).

The above nor-ketone (800 mg.) was kept overnight at 0° with 0·025N-methanolic sodium methoxide (40 c.c.), and then the solution was neutralised with glacial acetic acid and evaporated under reduced pressure. Dilution with water and isolation with ether gave the *ketol* (X; R = H), which separated from ethyl acetate–hexane as needles (210 mg.), m. p. 235—237° (decomp.), $[\alpha]_D^{18}$ +284°, $\lambda_{max.}$ 275 mμ (ε 5700), $\nu_{max.}$ 1675 (conj. C=O), 1715 (unconj. C=O) cm.$^{-1}$ (Found: C, 65·35; H, 8·05. $C_{23}H_{34}O_7$ requires C, 65·35; H, 8·1%).

The Formyl-acid (XI).—The ketol (X; R = H) (100 mg.) and 0·25M-sodium metaperiodate solution (3 mols.) were kept together for 4 hr. (uptake of oxidant, 1·0 mol.). The product was extracted with ether, and the ethereal solution was extracted with sodium hydrogen carbonate solution. Acidification and isolation of the acidic product with ether gave the *formyl-acid* (XI). It separated from ethyl acetate–light petroleum as needles (80 mg.), m. p. 206—208°, $[\alpha]_D^{20}$ +242°, $\lambda_{max.}$ 276 mμ (ε 6200) (Found: C, 62·9; H, 7·65. $C_{23}H_{34}O_8$ requires C, 63·0; H, 7·8%). The amorphous methyl ester was obtained by reaction with diazomethane in the usual manner.

Reduction of the Methyl Ether (IX; R = Ac, R′ = Me) *with Sodium Borohydride*.—A saturated solution (20 c.c.) of sodium borohydride in ethanol was added to a solution of the methyl ether (1·4 g.) in ethyl acetate (3 c.c.) and the mixture was kept for 18 hr. and then cooled to 0° whilst the excess of reducing agent was decomposed by the dropwise addition of dilute sulphuric acid. After the solution had been diluted with water the product was isolated with ether and chromatographed on alumina (Grade V; 130 g.). Elution with benzene gave the *alcohol* (XIII; R = H, R′ = Ac) which separated from chloroform–light petroleum as needles (1·1 g.), m. p. 207°, $[\alpha]_D^{20}$ +141° (*c*, 1·0 in acetone), $\lambda_{max.}$ 224 mμ (ε 6400), $\nu_{max.}$ 1730 (acetate) cm.$^{-1}$ (Found: C, 66·4; H, 8·8. $C_{25}H_{40}O_7$ requires C, 66·3; H, 8·9%).

Acetylation in the usual manner gave the *triacetate* (XIII; R = R′ = Ac) which separated from chloroform–light petroleum as fine needles, m. p. 225—226°, $[\alpha]_D^{20}$ +149°, $\lambda_{max.}$ 221 mμ (ε 6400), $\nu_{max.}$ 1732 (acetate) cm.$^{-1}$ (Found: C, 65·45; H, 8·35. $C_{27}H_{42}O_8$ requires C, 65·6; H, 8·6%).

The Tetraol (XIII; R = R′ = H).—Lithium aluminium hydride (500 mg.) was added to a solution of the diacetate (XIII; R = H, R′ = Ac) (300 mg.) in dry tetrahydrofuran (5 c.c.). After 30 min., the excess of hydride was destroyed by the cautious addition of ethyl acetate to the cooled mixture. Following acidification with dilute sulphuric acid and dilution with water, the product was isolated with ether. The *tetraol* separated from acetone–light petroleum as cubes, m. p. 263—265° (decomp.), $\lambda_{max.}$ 227 mμ (ε 5700) (Found: C, 68·3; H, 9·75. $C_{21}H_{36}O_5$ requires C, 68·4; H, 9·85%).

The isopropylidene derivative, which was prepared in the usual manner, gave on acetylation the 13-*acetate*, which formed needles (from dilute ethanol), m. p. 170—171°, $[\alpha]_D^{20}$ +169° (Found: C, 69·5; H, 9·4. $C_{26}H_{42}O_6$ requires C, 69·3; H, 9·4%).

The Dimethyl Ether (XIV) (with Dr. Brian Scales).—*O*-β-Phenylpropionyltaxicin-I triacetate (125 mg.) and freshly

prepared silver oxide (500 mg.) were shaken together with methyl iodide (0·75 c.c.) and dimethylformamide (2·5 c.c.) at 18° for 72 hr. The solution was diluted with chloroform (100 c.c.), filtered, and evaporated to a pale yellow oil (135 mg.). Chromatography on alumina (Grade II; 8 g.) and elution with benzene gave material which crystallised from light petroleum, giving the *dimethyl ether* (15 mg.), m. p. 162—163·5° (Found: C, 68·2; H, 7·55; OMe, 9·35. $C_{37}H_{48}O_{10}$ requires C, 68·15; H, 7·4; OMe, 9·5%).

Catalytic Hydrogenation of the Methyl Ether (IX; R = Ac; R′ = Me).—The methyl ether (2 g.) and Adams platinum catalyst (700 mg.) in glacial acetic acid (20 c.c.) were shaken with hydrogen at 18° for 2 hr. (uptake, 2·2 mol.). The product, isolated in the usual way, was amorphous. It was chromatographed on alumina (Grade II; 100 g.). Benzene eluted a crystalline fraction which fractional crystallisation from acetone–light petroleum resolved into the major *dihydro-compound* (XV) (560 mg.), m. p. 194—195°, $[\alpha]_D^{20}$ +47° (*c*, 2·0 in acetone), $\nu_{max.}$ 1698 (unconj. C=O) cm.$^{-1}$ (Found: C, 66·25; H, 8·75. $C_{25}H_{40}O_7$ requires C, 66·3; H, 8·9%) and the minor *dihydro-compound* (XV) (310 mg.), m. p. 179°, $[\alpha]_D^{20}$ +21° (*c*, 2·0 in acetone), $\nu_{max.}$ 1698 (unconj. C=O) cm.$^{-1}$ (Found: C, 66·55; H, 8·75. $C_{25}H_{40}O_7$ requires C, 66·3; H, 8·9%). Continued elution with benzene containing 0·25% ethanol gave the secondary alcohol (XIII; R = H; R′ = Ac) (290 mg.), m. p. and mixed m. p. 207°.

The dihydro-compound (XV), m. p. 194—195°, showed *inter alia* the following n.m.r. signals: τ 4·25, d., *J* = 11·5, 1H, *10*; τ 4·9, d., *J* = 11·5, 1H, *9*; τ 6·45, s., 3H, OCH_3; τ 7·27, q., *J* = 20, 2H, *14*; τ 8·52, s., 3H, *20*; τ 8·62, d., *J* = 7, 3H, *18*; τ 8·87, d., *J* = 5, 3H, *16*; τ 8·92, s., 3H, *19*; τ 8·98, s., 3H, *17*.

The Tetraol (XVI; R = H).—A saturated solution of sodium borohydride in ethanol (5 c.c.) was added to a solution of the dihydro-compound (XV) of m. p. 194—195° (150 mg.); the mixture was kept overnight at 18°, and the crude product, isolated in the usual manner, was chromatographed on alumina (Grade V; 10 g.). Elution with benzene, and fractional crystallisation from acetone–light petroleum gave two pure epimeric secondary *alcohols* (XVI; R = Ac). The major component (95 mg.) had m. p. 212° (Found: C, 66·0; H, 9·2. $C_{25}H_{42}O_7$ requires C, 66·05; H, 9·3%). The minor component (24 mg.) had m. p. 222—223° (Found: C, 65·95; H, 9·3%). Both epimers showed no high-intensity absorption in the near-ultraviolet region and only $\nu_{max.}$ (in KCl) 1740 (acetate) cm.$^{-1}$ in the carbonyl region of the infrared spectrum.

Lithium aluminium hydride (100 mg.) and the epimer m. p. 212° (50 mg.) were kept together in dry tetrahydrofuran at 18° for 30 min. The product was isolated in the usual manner and crystallised from methanol–chloroform–light petroleum, giving the *tetraol* (XVI; R = H) (40 mg.), m. p. 257—259° (decomp.), $[\alpha]_D^{20}$ +64° (*c*, 2·0 in methanol) (Found: C, 67·95; H, 10·2. $C_{21}H_{38}O_5$ requires C, 68·1; H, 10·3%).

Partial Acetylation of the Methyl Ether (VII; R = H; R′ = Me).—The methyl ether (3 g.) was kept with acetic anhydride (0·8 c.c.) and pyridine (10 c.c.) at 18° for 12 hr. The product, isolated in the usual way, was subjected to counter-current partition (75 transfers) in the system methanol–water–ethyl acetate–light petroleum (60 : 40 : 35 : 65). Tubes 5—15 gave back starting material (240 mg.); tubes 55—70 gave the *diacetate* (XVII; R = R′ = Ac) (350 mg.), m. p. 194—194·5° (Found: C, 68·4; H, 7·45. $C_{34}H_{44}O_9$ requires C, 68·4; H, 7·4%). Tubes 30—50 gave a mixture (2·2 g.); crystallisation from chloroform–light petroleum gave the *monoacetate* (XVII; R = Ac, R′ = H) (1·2 g.), m. p. 191—191·5°, $[\alpha]_D^{20}$ +187° (*c*, 0·5 in acetone), $\lambda_{max.}$ 278 mμ (ε 5000) (Found: C, 69·3; H, 7·6. $C_{32}H_{42}O_8$ requires C, 69·3; H, 7·6%). From the mother-liquors was obtained the isomeric *monoacetate* (XVII; R = H; R′ = Ac) (510 mg.), which separated from ether–light petroleum at −40° as long needles, m. p. 84—86°, $[\alpha]_D^{20}$ +187° (*c*, 0·5 in acetone) (Found: C, 69·1; H, 7·7). It had $\lambda_{max.}$ 278 mμ (ε 5800).

The α-Ketol (XVIII; R = H).—The monoacetate (XVII; R = Ac; R′ = H) (500 mg.) was kept for 7 days at 18° with the complex from chromic oxide (360 mg.) and pyridine (8 c.c.). The solution was filtered and the precipitate washed with ether; the combined filtrates were diluted to 100 c.c. with ether, and washed successively with water, dilute sulphuric acid, aqueous sodium hydrogen carbonate, and water, and dried. Evaporation gave the *ketol acetate* (XVIII; R = Ac) which separated from chloroform–light petroleum as needles (410 mg.), m. p. 145—146°, $[\alpha]_D^{20}$ −31° (*c*, 1 in acetone) (Found: C, 69·3; H, 7·5. $C_{32}H_{40}O_8$ requires C, 69·5; H, 7·3%). It showed *inter alia* the following n.m.r. signals: τ 3·35, s., 1H, *10*; τ 4·43, broad s., 1H, *16*; τ 4·70, broad s., 2H, *5* and *16*; τ 6·33, broad d., *J* = 4·5, 1H, *3*; τ 6·57, s., 3H, OCH_3; τ 6·82, d., *J* = 4·5, 1H, *2*; τ 7·77 and 7·82, s.s., 3H and 3H, *18* and OAc; τ 8·75, s., 6H, *19* and *20*; τ 8·83, s., 3H, *17*.

Reaction with hydroxylamine hydrochloride in pyridine gave the *oxime* as needles (from chloroform–light petroleum), m. p. 208°, $[\alpha]_D^{20}$ +65° (*c*, 0·5 in acetone) (Found: C, 67·85; H, 7·25; N, 2·2. $C_{32}H_{41}NO_8$ requires C, 67·75; H, 7·3; N, 2·4%).

For deacetylation, the ketol acetate (500 mg.) and 0·004N-methanolic sodium methoxide (75 c.c.) were kept together at 0° for 15 hr. Acetic acid (0·05 c.c.) was added, and the solvents were removed under reduced pressure. The residue was treated with ether (50 c.c.) and water (3 × 10 c.c.), and the ether layer was evaporated. Crystallisation from chloroform–light petroleum gave the α-ketol (XVIII; R = H) as needles (355 mg.), m. p. 149—150°, $[\alpha]_D^{20}$ −6° (*c*, 0·77 in acetone), $\lambda_{max.}$ 275 mμ (ε 5900) (Found: C, 70·65; H, 7·4. $C_{30}H_{38}O_7$ requires C, 70·6; H, 7·5%).

The α-Ketol (XIX; R = H).—The monoacetate (XVII; R = H; R′ = Ac) (1·45 g.) was oxidised for 2 days at room temperature with chromic oxide in pyridine in the manner employed for its isomer (XVII; R = Ac; R′ = H). The amorphous reaction product (1·41 g.) in ether was washed with sodium hydrogen carbonate and then with water; evaporation of the ether then gave a neutral oil (1·07 g.). Chromatography on alumina (Grade V; 70 g.) and elution with benzene gave the *ketol acetate* (XIX; R = Ac) (140 mg.), which separated from chloroform–light petroleum as needles, m. p. 126—127°, $[\alpha]_D^{20}$ +61° (*c*, 1 in acetone) (Found: C, 69·25; H, 7·3. $C_{32}H_{40}O_8$ requires C, 69·5; H, 7·3%). It showed *inter alia* the following n.m.r. signals: τ 4·37, s., 1H, *9*; τ 4·45, broad s., 1H, *16*; τ 4·62, broad s., 1H, *16*; τ 4·72, broad s., 1H, *5*; τ 6·23, d., *J* = 4·5, 1H, *2*; τ 6·45, s., 3H, OCH_3; τ 6·67, broad d., *J* = 4·5, 1H, *3*; τ 7·78, 8·08, s., s., 3H, 3H, *18* and OAc; τ 8·48, s., 3H, *20*; τ 8·64, s., 3H, *19*; τ 8·89, s., 3H, *17*.

Deacetylation with 0·004N-methanolic sodium methoxide, in the way described for its isomer, yielded the α-ketol (XIX; R = H) as an amorphous solid, $\lambda_{max.}$ 275 mμ (ε 5900), $\nu_{max.}$ 1727 (ester), 1679 (C=O) cm.$^{-1}$.

The α-Diketone (XX)—(*a*). The α-ketol (XVIII; R = H)

(105 mg.) and bismuth oxide (45 mg.) were shaken together at 100° in acetic acid (7 c.c.) for 1 hr. The solvent was removed under reduced pressure, benzene was added, and the solution was passed through alumina (Grade V; 5 g.), elution with benzene giving the α-*diketone* as pale yellow needles (95 mg.) (from chloroform–light petroleum), m. p. 180—181°, $[\alpha]_D^{20}$ −117° (*c*, 1·0 in acetone), $\lambda_{max.}$ 275 mμ (ε 5200), $\nu_{max.}$ 1701 (C=O), 1675 (conj. C=O) cm.$^{-1}$ (Found: C, 70·7; H, 7·0. $C_{30}H_{36}O_7$ requires C, 70·8; H, 7·1%).

(*b*). The α-ketol (XVIII; R = H) (1 g.) and active manganese dioxide [22] (3·5 g.) were shaken together in acetone (20 c.c.) for 2 hr. Filtration and evaporation gave the α-diketone (850 mg.), m. p. and mixed m. p. 180—181°.

(*c*). The amorphous α-ketol (XIX; R = H) (40 mg.), oxidised with active manganese dioxide as described above, furnished the α-diketone (35 mg.) (as needles from chloroform–light petroleum), m. p. and mixed m. p. 180—181°.

The 4,16-*Dihydro-derivative of* (XX)—(*a*). The diketone (XX) (450 mg.) was hydrogenated with 5% palladised charcoal (150 mg.) in ethyl acetate (10 c.c.) for 6 hr. (uptake, 1·3 mol.). The product was chromatographed on alumina (Grade V; 50 g.); after elution with benzene had removed starting material, further elution with ethanol–benzene (0·75% EtOH) gave the dihydrodiketone (210 mg.) as pale yellow needles (from chloroform–light petroleum), m. p. 192—193°, $[\alpha]_D^{20}$ −82° (*c*, 1·0 in acetone), $\lambda_{max.}$ 281 mμ (ε 4800) (Found: C, 70·5; H, 7·35. $C_{30}H_{38}O_7$ requires C, 70·6; H, 7·5%).

(*b*). Partial acetylation of the dihydro-compound (VIII; R = H; R′ = Me) (4·8 g.) gave the *dihydro-derivative* of the monoacetate (XVII; R = H, R′ = Ac) (1·3 g.), m. p. 101—102°, $[\alpha]_D^{20}$ + 199° (*c*, 0·8 in acetone) (Found: C, 69·0; H, 8·0. $C_{32}H_{44}O_8$ requires C, 69·0; H, 8·0%), and the *dihydro-derivative* of the monoacetate (XVII; R = Ac; R′ = H) (1·45 g.), m. p. 194—195°, $[\alpha]_D^{20}$ +199° (*c*, 0·67 in acetone) (Found: C, 68·9; H, 7·9%).

Oxidation of the latter with chromic oxide in pyridine gave the α-*ketol acetate*, m. p. 185—186°, $[\alpha]_D^{20}$ −11° (*c*, 1·0 in acetone) (Found: C, 69·1; H, 7·6. $C_{32}H_{42}O_8$ requires C, 69·3; H, 7·6%). Deacetylation with 0·004N-methanolic sodium methoxide gave the α-*ketol* (from chloroform–light petroleum), m. p. 176°, $[\alpha]_D^{20}$ +5° (*c*, 1·0 in acetone) (Found: C, 70·1; H, 7·7. $C_{30}H_{40}O_7$ requires C, 70·30; H, 7·9%). Oxidation of the α-ketol with manganese dioxide in acetone gave the dihydro-diketone, m. p. and mixed m. p. 192—193°.

Reaction of the Triacetate (VII; R = R′ = Ac) *with Zinc and Acetic Acid.*—A solution of the triacetate (500 mg.) in glacial acetic acid (10 c.c.) was stirred efficiently with zinc dust (5 g.) at 100° for 1 hr. After filtration and dilution with water the product was isolated with ether, and subjected to counter-current partition (50 transfers) in the system methanol–water–ether–light petroleum (7·5 : 7·5 : 2 : 13). Tubes 7—33 contained material (350 mg.) which separated from benzene–hexane giving the *reduction product* as large prisms (315 mg.), m. p. 165°, $[\alpha]_D^{21}$ +79°, $\lambda_{max.}$ 244 mμ (ε 14100) (Found: C, 70·0; H, 7·55; OAc, 21·1. $C_{33}H_{42}O_8$ requires C, 69·95; H, 7·5; 2 OAc, 20·9%).

Reaction of the Diacetate (VIII; R = Ac, R′ = Me) *with Zinc and Acetic Acid.*—To the diacetate (300 mg.) in glacial acetic acid (6 c.c.) at 100° zinc dust (3 g.) was added in small portions over 2 hr. with vigorous stirring. The solution was filtered, and the solvent removed from the filtrate under reduced pressure. The residue was extracted with ether and the solution was washed with water, dried, and evaporated. Chromatography of the residue on alumina (Grade II; 30 g.) and elution with benzene gave the *monoacetate* (XXII) (210 mg.) which separated from acetone–light petroleum as hexagonal plates, m. p. 173—174°, $[\alpha]_D^{20}$ −40°, $\nu_{max.}$ 1703 (C=O) cm.$^{-1}$ (Found: C, 71·25; H, 7·8. $C_{32}H_{42}O_7$ requires C, 71·35; H, 7·9%). It showed *inter alia* the following n.m.r. signals: τ 4·25, d., *J* = 10·5, 1H, *10*; τ 4·7, d., *J* = 10·5, 1H, *9*; τ 5·33, m., width at half-height 7 c./sec., 1H, *5*; τ 6·67, d., *J* = 4·5, 1H, *2*; τ 8·32, s., 3H, *20*; τ 8·57, s., 3H, *19*; τ 8·8, d., *J* = 7, 3H, *18*; τ 8·92, s., 3H, *17*; τ 8·95, d., *J* = 7, 3H, *16*.

Similar reduction of the corresponding 9-acetoxy-10-hydroxy-compound furnished the same product.

The Diketone (XXIV).—The above monoacetate (500 mg.) was kept with 0·1N-methanolic sodium methoxide at 15° for 16 hr. The product was isolated in the usual manner and chromatographed on alumina (Grade V; 25 g.), from which benzene eluted the amorphous alcohol (XXIII; R = H) (385 mg.). It was homogeneous on a thin-layer chromatogram (ethanol–benzene, 1 : 10), and had $\lambda_{max.}$ 282 mμ (ε 4500), $\nu_{max.}$ 1660 (conj. C=O), 1720 (ester); no acetate band near 1235 cm.$^{-1}$. The *acetate* (XXIII; R = Ac) (295 mg.) separated from chloroform–light petroleum and had m. p. 122°, $[\alpha]_D^{20}$ +200°, $\lambda_{max.}$ 282 mμ (ε 6000) $\nu_{max.}$ 1662 (conj. C=O) cm.$^{-1}$ (Found: C, 70·9; H, 8·05. $C_{32}H_{44}O_7$ requires C, 71·1; H, 8·2%). It showed *inter alia* the following n.m.r. signals: τ 4·63, q., *J* = 8 and 7·5, 1H, *9*; τ 5·28, broad s., 1H, *5*; τ 6·63, d., *J* = 4·5, 1H, *2*; τ 7·90 and 8·05, s., s., 3H and 3H, OAc and *18*; τ 8·45, s., 3H, *20*; τ 8·73, s., 3H, *19*; τ 8·92, d., *J* = 8·5, 3H, *16*; τ 9·00, s., 3H, *17*.

When the alcohol (XXIII; R = H) (500 mg.) was kept with chromic oxide (1 g.) in pyridine (10 c.c.) at 18° for 14 hr., the product, isolated in the usual way, separated from chloroform–light petroleum giving the *diketone* (XXIV) (435 mg.) m. p. 159—160°, $[\alpha]_D^{20}$ −48°, $\lambda_{max.}$ 278 mμ (ε 5700), $\nu_{max.}$ 1665 (conj. C=O), 1690 (C=O) cm.$^{-1}$ (Found: C, 72·4; H, 8·05. $C_{30}H_{40}O_6$ requires C, 72·55; H, 8·1%).

The Dimethyl Ether (XXV).—The monoacetate (XVII; R = Ac, R′ = H) (1·5 g.) was heated under reflux in the dark with methyl iodide (total 60 c.c.) and silver oxide (total 10 g.), half the reagents being freshly added in small portions over 3 days. Filtration and evaporation gave 2,9-*di*-O-*methyl*-10-O-*acetyl*-5-O-β-*phenylpropionyltaxicin-I* (1·2 g.) which separated from chloroform–light petroleum as needles, m. p. 184·5—185·5°, $[\alpha]_D^{20}$ +180° (*c*, 1·0 in acetone), $\lambda_{max.}$ 276 mμ (ε 6300), $\nu_{max.}$ 1681 (conj. C=O) cm.$^{-1}$ (Found: C, 69·8; H, 7·9. $C_{33}H_{44}O_8$ requires C, 69·7; H, 7·8%).

The above monoacetate (500 mg.) was treated with zinc dust in acetic acid in the way described for the diacetate (VIII; R = Ac; R′ = Me). The crude product was chromatographed on alumina (Grade II; 50 g.); benzene–light petroleum (80 : 20) eluted the *dimethyl ether* (XXV) (175 mg.). It separated from ether–light petroleum as needles, m. p. 126—127°, $[\alpha]_D^{20}$ −27° (*c*, 1·0 in acetone), $\nu_{max.}$ 1700 (unconj. ketone) cm.$^{-1}$ (Found: C, 72·95; H, 8·05. $C_{31}H_{42}O_6$ requires C, 72·9; H, 8·3%).

Isomerisation with 0·1N-methanolic sodium methoxide (10 c.c.) at 16° for 16 hr. converted the above dimethyl ether into the *isomer* (XXVI) (186 mg.); after crystallisation

[22] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.

from chloroform–light petroleum it had m. p. 223—224°, $\lambda_{max.}$ 282 mμ (ε 5600), $\nu_{max.}$ 1660 (conj. C=O) cm.$^{-1}$ (Found: C, 72·8; H, 8·25. $C_{31}H_{42}O_6$ requires C, 72·9; H, 8·3%).

The Acid (XXIX; R = R′ = H).—The monoacetate (IX; R = H, R′ = Ac) (540 mg.) and manganese dioxide [22] (2 g.) were shaken together under nitrogen in acetone (15 c.c.) for 1 hr. Filtration, evaporation under reduced pressure, and crystallisation under nitrogen from acetone–light petroleum, gave the *aldehyde* (XXVIII) (310 mg.) as pale yellow needles, m. p. 150—151°, $\lambda_{max.}$ 256 mμ (ε 6800), $\nu_{max.}$ 1678 (conj. ketone), 1698 (conj. aldehyde) cm.$^{-1}$ (Found: C, 67·3; H, 8·05. $C_{22}H_{36}O_6$ requires C, 67·3; H, 8·2%). Identical material was obtained by using periodate as the oxidant instead of manganese dioxide.

Reduction of the above aldehyde with ethanolic sodium borohydride afforded the corresponding primary alcohol which, although amorphous, was shown by thin-layer chromatography to be homogeneous. It showed $\lambda_{max.}$ 249 mμ (ε 7900), $\nu_{max.}$ 1666 (conj. ketone) and 1738 (acetate) cm.$^{-1}$, but no aldehydic absorption. Manganese dioxide in acetone converted it back into the crystalline aldehyde (XXVIII).

For oxidation, the aldehyde (XXVIII) (310 mg.) was dissolved in acetone (20 c.c.) through which oxygen was passed for *ca.* 1 hr., when the yellow colour was discharged. Removal of the solvent and crystallisation from ether–light petroleum gave the *acid* (XXIX; R = R′ = H), m. p. 195·5°, $[\alpha]_D^{20}$ −36° (*c*, 1·0 in ethanol), $\lambda_{max.}$ 247 mμ (ε 6500), $\nu_{max.}$ (in KCl) 1678 (conj. ketone), 1709 (conj. acid), and 1724 (acetate) cm.$^{-1}$ (Found: C, 64·6; H, 7·9. $C_{22}H_{32}O_7$ requires C, 64·7; H, 7·9%). A solution of the sodium salt in deuterium oxide showed no aldehyde proton signal.

The *methyl ester* (XXIX; R = Me, R′ = H), obtained by reaction with diazomethane in ether, separated from aqueous ethanol as crystals, m. p. 187—189°, $[\alpha]_D^{20}$ −30° (*c*, 2·0 in acetone), $\lambda_{max.}$ 245 mμ (ε 7200) (Found: C, 65·2; H, 8·0. $C_{23}H_{34}O_7$ requires C, 65·4; H, 8·1%). Acetylation gave the *diacetate* (XXIX; R = Me, R′ = Ac) which separated from ether–light petroleum as dense cubes, m. p. 194—195°, $[\alpha]_D^{20}$ −40° (*c*, 2·0 in acetone) (Found: C, 64·5; H, 7·6. $C_{25}H_{36}O_8$ requires C, 64·6; H, 7·8%). It showed *inter alia* the following n.m.r. signals: τ 4·10, s., 1H, *9*; τ 4·76, d., *J* = 11, 1H, *2*; τ 7·14, 2H, *14*; τ 8·36, s., 3H, *18*; τ 8·40, 8·50, s. and s., 3H and 3H, *19* and *20*; τ 8·93, s., 3H, *17*; τ 9·13, d., *J* = 4, 3H, *16*.

The Acid (XXXII).—Oxidation of the methyl ester (XXIX; R = Me, R′ = Ac) (500 mg.) with chromic oxide (1 g.) in pyridine (20 c.c.) for 16 hr., and isolation in the usual manner, gave the *lactone* (XXXI) (390 mg.). After crystallisation from acetone–light petroleum it had m. p. 173—174°, $[\alpha]_D^{20}$ −21° (*c*, 2·0 in acetone), $\lambda_{max.}$ 244 mμ (ε 9300), $\nu_{max.}$ 1730 (acetate and δ-lactone), 1680 (conj. ketone) cm.$^{-1}$ (Found: C, 65·8; H, 7·6. $C_{23}H_{32}O_7$ requires C, 65·7; H, 7·7%).

A solution of the lactone (380 mg.) in pyridine (10 c.c.) was kept at 90° for 4 hr. Removal of the solvent under reduced pressure and crystallisation from aqueous ethanol gave an ethanol solvate; it was boiled with benzene to remove the ethanol, after which the benzene was evaporated and the residue crystallised from acetone–light petroleum. The *acid* (XXXII) (280 mg.) had m. p. 139—140°, $\lambda_{max.}$ 246 mμ (ε 16,100), $\nu_{max.}$ 1633 (conj. double bond), 1659 (conj. ketone), 1696 (carboxylic acid) and 1734 (ester) cm.$^{-1}$ (Found: C, 65·9; H, 7·8. $C_{23}H_{32}O_7$ requires C, 65·7; H, 7·7%). It showed *inter alia* the following n.m.r. signals: τ 3·58, s., 1H, *14*; τ 4·25 unresolved, 2; τ 8·18, s., 3H, *18*; τ 8·45, s., 3H, *19* or *20*; τ 8·56, s., 3H, *19* or *20*; τ 8·83, s., 3H, *17*; τ 9·15, d., *J* = 6·5, 3H, *16*.

The Aldehyde (XXXIV; R = CHO).—The isopropylidene derivative (XXXIII) (100 mg.) and manganese dioxide [22] (500 mg.) were shaken together in acetone (5 c.c.). After 1 hr. the solvent was removed from the filtered solution. The *aldehyde* crystallised from chloroform–light petroleum as fine needles (45 mg.) of the chloroform solvate. Evaporation with ethanol and recrystallisation from aqueous ethanol gave unsolvated material, m. p. 256—258°, $[\alpha]_D^{20}$ −163° (*c*, 0·8 in acetone) (Found: C, 70·7; H, 8·6. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%). The aldehyde (in pyridine) showed a doublet signal (1H; *J* = 3 c./sec.) near τ −0·08, $\lambda_{max.}$ 246 mμ (ε 11,300) and 291 mμ (ε 5500) in 50% ethanol 0·1N in HCl; $\lambda_{max.}$ 246 mμ (ε 5200) and 329 mμ (ε 8600) in 50% ethanol 0·1N in KOH; these values may be compared with those [2] of the alcohol (XXI; R = OH). It showed $\nu_{max.}$ 1600, 1653, 1678, (1,3-dione) and 1718 (aldehyde) cm.$^{-1}$.

The same aldehyde was obtained by using sodium metaperiodate in 50% aqueous ethanol as the oxidant instead of manganese dioxide. It was extractable from an ethereal solution with aqueous sodium hydrogen carbonate.

The aldehyde (400 mg.) was kept at 0° for 30 min. with sodium borohydride (120 mg.) in ethanol (10 c.c.). The product, isolated in the usual way, crystallised from aqueous ethanol giving rectangular plates (350 mg.) of the primary *alcohol* (XXXIV; R = CH_2OH), m. p. 241—243°, $[\alpha]_D^{20}$ −17° (*c*, 2·0 in ethanol), $\lambda_{max.}$ 246 mμ (ε 11,100) and 286 mμ (ε 5500), $\nu_{max.}$ (in KCl) 1608, 1656, 1681 (1,3-dione) cm.$^{-1}$; no band at 1718 cm.$^{-1}$ (Found: C, 70·3; H, 9·15. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·2%). The alcohol could be extracted from an ethereal solution with aqueous sodium hydrogen carbonate.

Further treatment with saturated ethanolic sodium borohydride during 4 hr. converted the primary alcohol by reduction of both the keto-groups into a neutral *alcohol*, which separated from aqueous ethanol as needle clusters, m. p. 252—253° (decomp.), $\lambda_{max.}$ *ca.* 205 mμ (ε 9200), no $\nu_{max.}$ 1500—1800 cm.$^{-1}$ (Found: C, 69·6; H, 10·1. $C_{23}H_{40}O_5$ requires C, 69·7; H, 10·2%).

The Acidic Triol (XXXV).—Dilute(2N) sulphuric acid (10 c.c.) was added over 3 hr. to a solution of the alcohol (XXXIV; R = CH_2OH) (500 mg.) in ethanol (5 c.c.) at 75°. The product was separated in the usual way into acidic and neutral components. Crystallisation of the acidic material from aqueous ethanol gave the *acidic triol* (XXXV) (345 mg.), m. p. 140—145° (decomp.), $[\alpha]_D^{20}$ −17° (*c*, 1·0 in acetone), $\lambda_{max.}$ 246 mμ (ε 11,900), 286 mμ (ε 5100), $\nu_{max.}$ 1580, 1644 (1,3-dione) cm.$^{-1}$ (Found: C, 67·9; H, 9·3. $C_{20}H_{32}O_5$ requires C, 68·15; H, 9·15%).

The neutral component (55 mg.) was an *enol ether* which separated from chloroform–light petroleum as needles, m. p. 177—178°, $[\alpha]_D^{20}$ −13° (*c*, 1·0 in acetone), $\lambda_{max.}$ 279 mμ (ε 6900), $\nu_{max.}$ 1640 (enol ether) cm.$^{-1}$ (Found: C, 69·25; H, 9·45. $C_{22}H_{36}O_5$ requires C, 69·45; H, 9·5%).

A solution of the triol (XXXV) (250 mg.) in ethyl acetate (8 c.c.) was shaken vigorously for 85 min. with sodium metaperiodate (180 mg.) in water (8 c.c.). The ethyl acetate was diluted with ether (50 c.c.) and washed with aqueous sodium hydrogen carbonate. Acidification of the washings provided the acidic fragment (I) (102 mg.; 82% yield). The neutral material from the ether layer formed

an oil (112 mg.) which showed hydroxylic ($\nu_{max.}$ 3395 cm.$^{-1}$) but no carbonyl absorption, and which appeared to be homogeneous on thin-layer chromatography. Oxidation with chromic oxide in pyridine gave a neutral oil, $\nu_{max.}$ 1770 (γ-lactone) cm.$^{-1}$; no hydroxylic absorption. Reduction with lithium aluminium hydride in tetrahydrofuran gave an amorphous diol. The bis-3,5-dinitrobenzoate, although homogeneous on thin-layer chromatography, was also amorphous (Found: C, 51·7; H, 4·5; N, 9·9. $C_{24}H_{24}O_{12}N_4$ requires C, 51·4; H, 4·3; N, 10·0%).

The Triacetate (III; R = R′ = Ac) [4] showed *inter alia* the following n.m.r. signals: τ 3·9, d., J = 10, 1H, *10*; τ 4·1, d., J = 10, 1H, *9*; τ 4·4, d., J = 6·5, 1H, *2*; τ 4·67, broad s., 2H, *5* and *16*; τ 5·3, broad s., 1H, *16*; τ 6·47, broad d., J = 6·5, 1H, *3*; τ 7·23, q., J = 19, 2H, *14*; τ 7·73, s., 3H, *18*; τ 8·30, s., 3H, *20*; τ 8·77, s., 3H, *19*; τ 9·05, s., 3H, *17*.

The Triacetate (VIII; R = R′ = Ac) [4] showed *inter alia* the following n.m.r. signals: τ 4·0, d., J = 10, 1H, *10*; τ 4·25, d., J = 10, 1H, *9*; τ 4·55,d., J = 6, 1H, *2*; τ 5·33 unresolved m. (half-height width 6·5 c./sec.), 1H, *5*; τ 7·83, s., 3H, *18*; τ 8·35, s., 3H overlaid by other signals, *20*; τ 8·81, s., 3H, *19*; τ 9·07, s., 3H, *17*; near τ 9·07, d., J = 7, 3H, *16*.

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