# Taxine. Part VI.[1] The Stereochemistry of Taxicin-I and Taxicin-II

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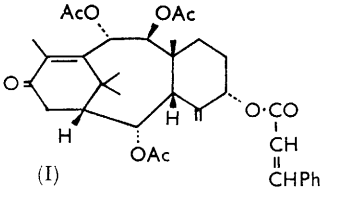
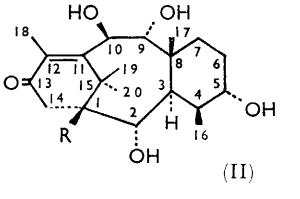
By transforming one of them into a compound of known stereochemistry, configurations are deduced for two cleavage fragments corresponding to ring C of the taxicin-I molecule. Chemical, optical, and n.m.r. observations then show that in the intact taxicin molecule ring C is essentially chair-shaped, and that the eight-membered ring B is in a "boat-chair" conformation. This requires a *trans*-B/C ring-junction, and also permits the configurations at positions 2, 9, and 10 to be deduced from the n.m.r. data, leading to the complete stereostructures for 4,16-dihydrotaxicin-I and 4,16-dihydrotaxicin-II. Some n.m.r. observations on taxicin derivatives are discussed in the light of these results. It is suggested *inter alia* that the effect which causes anomalous differences in the shielding of the α-proton in axial and equatorial α-halogenocyclohexanones may be paralleled in chair-shaped α-acyloxycyclohexanones, of which the oxonortaxicins provide examples.

In earlier Papers we described experiments on *O*-cinnamoyltaxicin-I triacetate [2-6] and *O*-cinnamoyltaxicin-II triacetate [1,2,4] which elucidated their gross structures; the latter compound has also been studied (under the name taxinine) by Japanese workers,[7,8] whose structural conclusions agreed with our own. The first proposals relating to stereochemical aspects were made by Nakanishi, Uyeo, and their associates [9] who, from chemical and n.m.r. studies on taxinine, deduced for it the absolute configuration (I). Our stereochemical studies [10] were conducted mainly with derivatives of taxicin-I, but, by virtue of the relationships established in the preceding Paper,[1] the results obtained apply directly also to derivatives of taxicin-II. They lead to the stereostructure (II; R = OH) for 4,16-dihydrotaxicin-I and (II; R = H) for the corresponding dihydrotaxicin-II.




(I)




(II)

*The Stereochemistry of Isolated Ring* C *Compounds.*—The periodate cleavage [3,5] of suitable compounds gives dialdehydes corresponding to ring C of the taxicin-I molecule; these and their derivatives were used as the starting materials for the work described in this section.

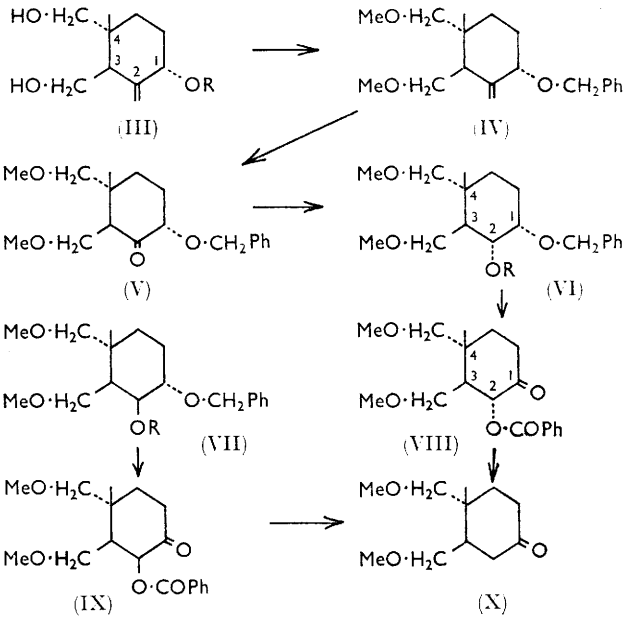
[1] Part V, M. Dukes, D. H. Eyre, J. W. Harrison, R. M. Scrowston, and B. Lythgoe, preceding Paper.
[2] J. N. Baxter, B. Lythgoe, B. Scales, R. M. Scrowston, and S. Trippett, *J. Chem. Soc.*, 1962, 2964.
[3] B. W. Langley, B. Lythgoe, B. Scales, R. M. Scrowston, S. Trippett, and D. Wray, *J. Chem. Soc.*, 1962, 2972.
[4] D. H. Eyre, J. W. Harrison, R. M. Scrowston, and B. Lythgoe, *Proc. Chem. Soc.*, 1963, 271.
[5] J. W. Harrison and B. Lythgoe, *J. Chem. Soc.* (*C*), 1966, 1932.
[6] J. W. Harrison, R. M. Scrowston, and B. Lythgoe, *J. Chem. Soc.* (*C*), 1966, 1933.
[7] M. Kurono, Y. Nakadaira, S. Onuma, K. Sasaki, and K. Nakanishi, *Tetrahedron Letters*, 1963, 2153; K. Nakanishi, M. Kurono, and N. S. Bhacca, *ibid.*, p. 2161.
[8] K. Ueda, S. Uyeo, Y. Yamamoto, and Y. Maki, *Tetrahedron Letters*, 1963, 2167; S. Uyeo, K. Ueda, Y. Yamamoto, and Y. Maki, *J. Pharm. Soc. Japan*, 1964, **84**, 762; 1965, **85**, 404.
[9] M. Kurono, Y. Maki, K. Nakanishi, M. Ohashi, K. Ueda, S. Uyeo, M. C. Woods, and Y. Yamamoto, *Tetrahedron Letters*, 1965, 1917.
[10] M. Dukes, D. H. Eyre, J. W. Harrison, and B. Lythgoe, *Tetrahedron Letters*, 1965, 4765.

The triol (III; R = H) was chosen for initial study. During work in a different field [11] we had synthesised compounds not greatly different in structure from this triol, and of known absolute configuration. Our intention was to convert both series of compounds into a common structure, that of the *trans*-ketone (X), and so determine the absolute configuration of the triol (III; R = H).

Methylation of the cinnamate ester (III; R = CO·CH:CHPh), followed by alkaline hydrolysis and benzylation of the product, gave the dimethyl benzyl ether (IV). This was treated with osmium tetroxide, to yield an α-glycol which was degraded to the nor-ketone (V) by reaction with periodate. This ketone, although amorphous, was shown by thin-layer chromatography to be homogeneous; it was handled with care in order to avoid the risk of epimerisation. Reduction with ethanolic sodium borohydride converted it into a mixture of the epimeric alcohols (VI; R = H) and (VII; R = H) (major product), which were partially separated by chromatography, giving mixtures with the approximate compositions 1 : 1 and 1 : 4 of the above epimers. In the n.m.r. spectra of the corresponding mixed benzoates (VI; R = COPh) and (VII; R = COPh) the signals due to each of the epimers were readily distinguished. The mixed benzoates were hydrogenolysed to remove the benzyl groups, and chromic oxide oxidation then gave mixtures of the ketol benzoates (VIII) and (IX). Their relative proportions were apparent from the n.m.r. spectra. The mixture containing approximately equal amounts of the two was reduced with calcium in liquid ammonia,[12] which gave in good yield a single ketone, as shown by thin-layer and gas chromatography. It was characterised by its chromatographic and spectral properties, by its $[\alpha]_D$ −13·3° ($CHCl_3$), and by its crystalline semicarbazone.

The reactions required to establish that this ketone had the absolute configuration (X) are illustrated in the formulæ (XI)—(XIX). The racemic keto-acid [11] r-(XI) * was converted into its dimethyl ester and then into the dimethyl ketal r-(XII), reduction of which with lithium aluminium hydride gave the diol r-(XIII; R = H). Methylation followed by hydrolysis of the ketal groups then provided the racemic *cis*-ketone r-(XIV). Its properties showed clearly that our specimen of the optically active ketone (X) could not be a *cis*-isomer, or contain any *cis*-isomer as an impurity. We therefore next developed a synthesis of the racemic *trans*-ketone r-(X).

The racemic *cis,cis*-hydroxy-dibasic acid r-(XVI), obtained [11] by reduction of the keto-acid r-(XI), gives a δ-lactone r-(XV). Reaction of the lactone in hot toluene with benzyl chloride and powdered potassium hydroxide, followed by alkaline hydrolysis, gave a mixture of two benzyl ether acids r-(XVIII) and r-(XIX), which were separated by crystallisation. It was clear that partial epimerisation of the secondary carboxyl group had taken place. The *cis*-dibasic acid r-(XIX) was identified by catalytic hydrogenolysis, which converted it into its precursor r-(XV). The *trans*-dibasic acid r-(XVIII) was converted first by lithium aluminium hydride into the diol r-(XVII; R = H) and




then by methylation into the dimethyl ether r-(XVII; R = Me). Hydrogenolytic removal of the benzyl group and oxidation of the alcohol then provided the racemic *trans*-ketone r-(X). Its chromatographic and spectral properties showed that it was the racemic form of the ketone obtained from the degradative work.

The δ-lactonic acid (XV) has been resolved to give both optically pure forms, and the dextrorotatory form has been successfully used as a ring-A component in the synthesis [11] of tachysterol$_3$; this establishes its absolute configuration as (XV). For the present work the more readily available lævorotatory enantiomer e-(XV) * was used. By means of methods earlier employed in the racemic series, this lactonic acid was converted successively into the *trans*-dibasic acid e-(XVIII), the diol e-(XVII; R = H), and the dimethyl ether e-(XVII; R = Me). Hydrogenolysis and oxidation gave an optically active *trans*-ketone e-(X); its properties, and those of its semicarbazone, left no doubt that it was the enantiomer of that obtained from the degradation of *O*-cinnamoyltaxicin-I. This established the absolute configuration at positions 3 and 4 in the unsaturated triol (III; R = H).

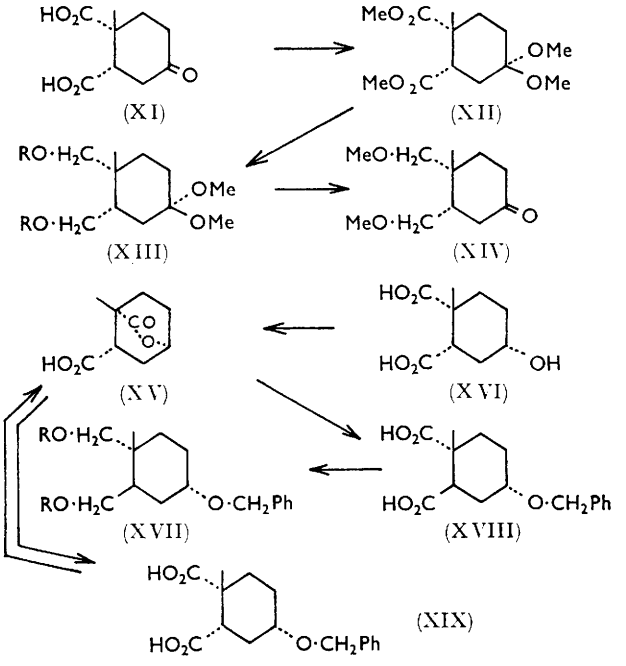
The ketol benzoate (VIII) showed a C(2) proton signal as a doublet ($J$ = 11·5 c./sec.) near τ 4·45, whereas

* All the structures in this Paper represent absolute configurations. For brevity, a racemic form is denoted by putting the prefix r before a formula number; thus, r-(XI) means the racemate corresponding to the structure (XI); an enantiomeric form is similarly denoted by the use of the prefix e.

[11] R. S. Davidson, P. S. Littlewood, T. Medcalfe, S. M. Waddington-Feather, D. H. Williams, and B. Lythgoe, *Tetrahedron Letters*, 1963, 1413.

[12] J. H. Chapman, J. Elks, G. H. Phillipps, and L. J. Wyman, *J. Chem. Soc.*, 1956, 4344.

the isomer (IX) gave a corresponding doublet signal ($J$ = 6 c./sec.) near 4·3. In the spectrum of the benzoate (VI; R = COPh) the C(2) proton signal appeared as a quartet; initial splitting, due to coupling with position 3, was 11 c./sec., and gave doublets near 4·66 and 4·84, the secondary splitting, due to coupling with position 1, being about 2·8 c./sec. In the spectrum of the isomeric benzoate (VII; R = COPh) the C(2) proton signal formed a triplet ($J$ = 4 c./sec.) near 4·43, suggesting an

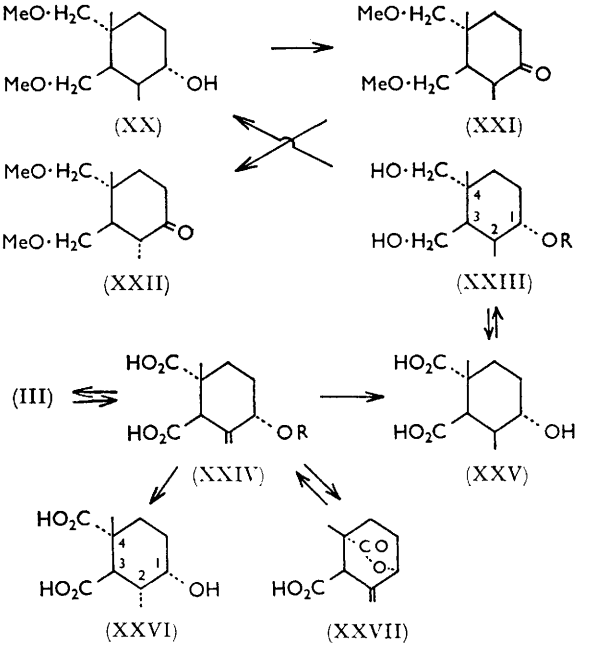



approximately equal degree of coupling with both the adjacent protons. These data require that in the triol (III; R = H) the hydroxyl group at position 1 is *trans* to the hydroxymethyl group at position 3. Thus, the stereochemistry of this unsaturated triol was completely defined.

The saturated triol (XXIII; R = H) can be obtained [3] either from the products of periodate cleavage of dihydrotaxicin-I β-phenylpropionate, or, along with its C(2)-epimer, by hydrogenation of the unsaturated triol (III; R = H). Thus, only its configuration at position 2 was in question. Methylation of the phenylpropionate (XXIII; R = CO·$CH_2$·$CH_2$Ph) and hydrolysis gave the alcohol (XX), careful oxidation of which afforded the corresponding ketone (XXI), characterised as the semicarbazone. Attempted regeneration with pyruvic acid, or treatment of the ketone (XXI) with methanolic sodium methoxide, caused epimerisation to a different ketone (XXII), also characterised as the semicarbazone. Conformational principles therefore suggested that in the triol (XXIII) the methyl groups at positions 2 and 4 were *cis*-related.

Confirmation of this, and also of the other stereochemical features, was obtained by a study of the dibasic acids derived from the diols (III; R = CO·$CH_2$·$CH_2$Ph) and (XXIII; R = CO·$CH_2$·$CH_2$Ph). Oxidation of the dialdehyde corresponding to the former diol gives [5] a crystalline acid (XXIV; R = CO·$CH_2$·$CH_2$Ph); hydrolysis gave a mixture of the hydroxy-acid (XXIV; R = H) and its δ-lactone (XXVII). We have already [2,5] recorded the preparation by similar methods of the saturated hydroxy-acid (XXV). This and its unsaturated counterpart (XXIV; R = H) were formed without change of configuration at position 3 in the oxidation reactions, since reduction with lithium aluminium hydride converted them into the expected triols (XXIII; R = H) and (III; R = H), respectively. When the unsaturated acid (XXIV; R = CO·$CH_2$·$CH_2$Ph) was hydrogenated and the products hydrolysed, two acids were obtained and were separated by crystallisation; they were the hydroxy-acid (XXV) and its C(2)-epimer (XXVI).

The n.m.r. data relating to the hydroxy-acids (XXVI) and (XXV) (in pyridine) permitted an independent deduction of their configurations. The acid (XXVI) showed an unresolved C(1) proton signal (at τ 5·67) of half-height width *ca.* 8 c./sec. (equatorial proton). The C(3) proton signal formed a doublet ($J$ = 11 c./sec.) near 5·9, showing that both this and the adjacent C(2) proton were axially disposed. Since the formation of




the lactonic acid (XXVII) shows the *cis* relationship of the groups involved in the lactone formation, the relative configuration of the acid (XXVI) is completely established. It was of interest that the epimeric acid (XXV) showed a very broad (*ca.* 30 c./sec.) C(1) proton signal (near τ 5·4) (axial proton), whilst the doublet ($J$ = 5 c./sec.) near 6·0 due to the C(3) proton showed that the C(2) methyl group must be equatorially, and the C(3) carboxyl group axially, disposed. The actual conformations of both these acids are those expected from

conformational principles. The above results establish the stereostructure of the triols (XXIII; R = H) and (III; R = H).

Before leaving the subject of hydroxy-acids we may mention that, whereas the acid (XVI) showed a tendency to form the δ-lactone spontaneously, especially in the presence of acids, none was observed for the acid obtained by debenzylation of (XVIII). Likewise, although the acid (XXIV; R = H) spontaneously formed the δ-lactone, neither (XXV) nor (XXVI) did so. Conformational factors which may be responsible for these contrasts are as follows. In the δ-lactone corresponding to (XVI) the secondary carboxyl group at position 3 has unfavourable *gauche* interactions with two groups at the ring junction (position 4), and also eclipses one hydrogen atom at position 2. In a δ-lactone derived from a debenzylated form of (XVIII), the secondary carboxyl group would have similar unfavourable *gauche* interactions with two groups at position 4, an eclipsing interaction with one hydrogen atom at position 2, and also a *cis*-1,3-interaction with a hydrogen atom at position 5. In the δ-lactone corresponding to (XXIV; R = H), the *gauche* interaction of the secondary carboxyl group with two groups at position 4 is present as in the previous case, and so also is the *cis*-1,3-interaction with a hydrogen atom at position 5; but the eclipsing interaction with the hydrogen atom at position 2 is absent. A δ-lactone corresponding to the acid (XXVI) would have all the unfavourable interactions present in a lactone corresponding to (XVIII) and also others due to the methyl group at position 2.

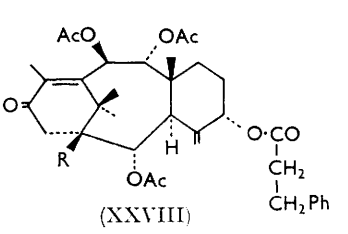
*Stereochemistry and Conformation of Taxicin-I and Taxicin-II.*—The results of the previous section establish the configurations at positions 4, 5, and 8 in the stereostructure (II; R = OH) for 4,16-dihydrotaxicin-I. They also point to a *trans*-B/C junction and an α-configuration * at C(3); but in the ring-C dialdehydes which arise by periodate cleavage it is in theory possible for configurational change to take place at the site of the secondary aldehyde group. Although we consider it unlikely that such change has occurred in the formation of the compounds discussed in the preceding section, we propose in the present section to rest our conclusions regarding the configuration at C(3) upon other evidence.

* For denoting configurations in the taxicin-II molecule the Japanese authors [cf. 9, 21] used an α,β-notation which, although nowhere explicitly described, is based on that used in steroid chemistry. It is, however, not fully consistent; thus, the methyl group which they designate 15α is *cis* in ring B to both the 8β-methyl group and the 1β-hydrogen atom. In our work the following notation is adopted. Groups attached to rings B or C are denoted α or β according to their relationship to the C(17) (= 8β) methyl group, as in steroid notation. Groups attached to positions 12, 13, and 14 (ring A) are denoted *exo* or *endo* in relation to the C(15) bridge. Thus, the C(14) proton in taxicin-II compounds which is coupled by about 6·5 c./sec. to the C(1) proton is designated the *exo*-C(14) proton; its twin, which is only weakly coupled, is the *endo*-C(14) proton (see preceding Paper.

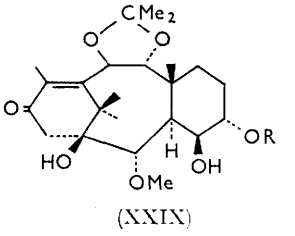
It should be noted that, because of the formal way in which taxicin structures are represented in planar formulæ, the group attached to C(15) by a dotted line has (at first sight surprisingly) the β configuration.

We first consider the conformation of ring C in the intact taxicin-I and taxicin-II. In typical derivatives such as (XXVIII; R = OH) (see Figure) the C(5) proton signal shows a small and approximately equal degree of coupling with both C(6) protons. It must therefore make nearly equal angles with them, suggesting that it has an equatorial disposition.

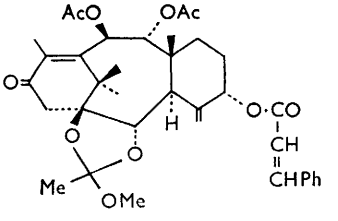
The 4β,5α-diol (XXIX; R = H) can be prepared by reducing the corresponding 4-keto-compound [5] with sodium borohydride. It behaved [13] as a *trans*-diaxial diol in that it failed to undergo glycol cleavage with lead tetra-acetate or sodium metaperiodate, although its α-ketol precursor was readily split. It was also clear



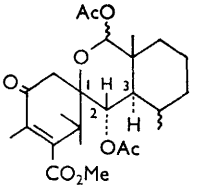

(XXVIII)



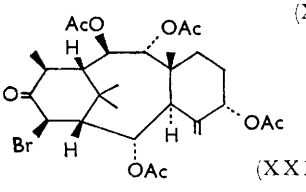

(XXIX)




(XXXII)




(XXXIII)




(XXXIV)

that in the diol the 4β-hydroxy and 8β-methyl groups stood in a *cis*-1,3-diaxial relationship. Mild acetylation of the diol gave only the 5-monoacetate (XXIX; R = Ac), which reflects steric hindrance due to the methyl group, whilst, as discussed in the following section, the n.m.r. signal of the methyl group suffered a displacement of 0·25—0·30 p.p.m. towards lower fields due to the action of the 4β-hydroxyl group. The relationships thus deduced between the groups situated at positions 4, 5, 6, and 8 show that the shape of ring C in the taxicin molecule is not greatly different from a normal cyclohexane chair.

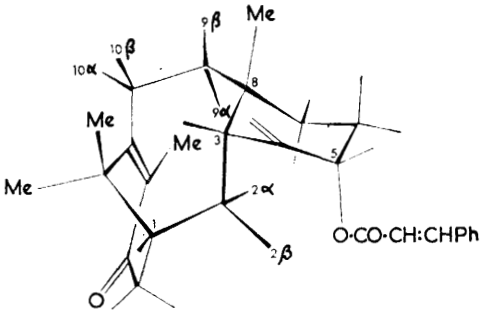
The conjugated enone system in ring A of *O*-β-phenylpropionyltaxicin-I triacetate (XXVIII; R = OH) and the corresponding taxicin-II compound (XXVIII; R = H) forms a right-handed helix, as shown by the high-amplitude positive Cotton effect curves,[14] which resemble those of a normal steroid 4-en-3-one.[15] In some compounds the helicity so determined may not permit an

[13] S. J. Angyal and R. J. Young, *J. Amer. Chem. Soc.*, 1959, **81**, 5467, 5251.

[14] W. Klyne, personal communication.

[15] C. Djerassi, R. Records, E. Bunnenberg, K. Mislow, and A. Moscowitz, *J. Amer. Chem. Soc.*, 1962, **84**, 870.

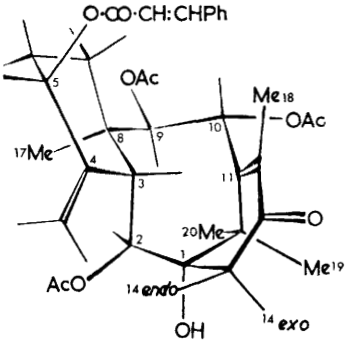
unambiguous assignment of absolute configuration,[16] but in the taxicin molecules the rigidity in ring A which is induced by the fusion with ring B relates the helicity unequivocally to the absolute configuration at position 1, and defines the latter as shown in the stereostructures (XXVIII) and (II).




(XXX)

Given the configurations at positions 1 and 8 determined above, and an essentially chair-shaped ring C, only two types of conformation for the eight-membered ring B are possible. In the first type, shown in the perspective (XXX), the B/C junction is *cis*; there are two variants, either the α-C(9) and β-C(10) valencies being antiparallel, as illustrated, or the β-C(9) and α-C(10) valencies being so. In both variants the steric relationships between positions 1, 2, and 3 are closely similar; the β-C(1) and α-C(2) valencies make a large dihedral angle (*ca.* 150—180°), whilst the β-C(1) and β-C(2) valencies make a small dihedral angle (*ca.* 30—60°). These relationships are incompatible with the observed properties of taxicin derivatives. Thus, methylation of *O*-cinnamoyltaxicin-I triacetate with methyl iodide and silver oxide converted it into a crystalline mixture of two orthoacetates (XXXII), stereoisomeric at the orthoacetate carbon atom. Their structure was apparent from the analytical and n.m.r. data, and also from their hydrolysis with very dilute acid to give the normal triacetate precursor. If the taxicins had a stereostructure of the type (XXX), this orthoacetate formation would require a β-C(2) acetoxy group; in this event, the β-C(1) and α-C(2) protons in *O*-cinnamoyltaxicin-II triacetate would form a dihedral angle of *ca.* 150—180°, and should have a large (*ca.* 10 c./sec.) coupling constant. The observed value is *ca.* 2 c./sec., so conformations of the type (XXX) must be dismissed. They are further unacceptable because they fail to account for some especially striking effects in the n.m.r. spectrum of the 9-oxotaxicin-I derivative (XXXIX), which are, however, as shown in the final section of the Paper, very satisfactorily accounted for by the second type of conformation of ring B, discussed below.

This conformation, illustrated in the perspective (XXXI), requires a *trans*-B/C junction (*i.e.*, α-hydrogen at position 3), and is characterised by an approximately antiparallel disposition of the β-C(9) and α-C(10) valencies. The β-C(1) valency makes a dihedral angle




(XXXI)

of about 60° with both the α-C(2) and the β-C(2) valencies, so this model is compatible with the formation of the orthoacetates (XXXII) and also with the small coupling constant, $J_{1,2} = 2$ c./sec., observed for taxicin-II derivatives. Clearly the taxicins are modelled on this conformation. It is of interest that, very recently, the same " boat-chair " conformation of the eight-membered ring has been shown [17] to exist in crystalline cyclo-octane-1,2-*trans*-dicarboxylic acid, and it seems possible that this, and not the crown-shaped conformation, may prove to be the most stable form for cyclo-octanes in general.

Periodate cleavage of 5-deoxy-4,16-dihydrotaxicin-I 2-acetate yields [6] an aldehydo-hemiacetal which is readily converted into the methyl ester diacetate (XXXIII). In the n.m.r. spectrum of this compound the C(2) proton signal formed a doublet near τ 4·76, with $J_{2,3} = ca.$ 11 c./sec. (*trans*-diaxial protons). In taxicin-I compounds, therefore, since the C(3) proton is α-oriented, the C(2) proton must be β- and the C(2) hydroxyl group α-oriented.

It is clear that the antiparallel valencies at positions 9 and 10 in the perspective (XXXI) must be occupied by protons, since in both taxicin-I and taxicin-II derivatives the C(9) and C(10) protons normally show coupling constants of about 10 c./sec. The acetone derivatives formed at these positions show 9,10-coupling of a similar magnitude, and are clearly formed by *trans*-hydroxyl groups. This arrangement, uncommon in smaller rings, is known [18] to occur in cyclo-octane-1,2-diols. This completed the evidence for the stereostructure (II; R = OH) for 4,16-dihydrotaxicin-I.

The analogous structure (II; R = H) for 4,16-dihydrotaxicin-II is in agreement with the original Japanese [9] proposals so far as positions 1, 2, 5, and 8 are concerned, but it differs from their structure (I) in respect of positions 3, 9, and 10; they did not define the configuration at position 4 in 4,16-dihydrotaxicin-II

[16] C. Djerassi and J. E. Gurst, *J. Amer. Chem. Soc.*, 1964, **86**, 1755.
[17] J. D. Dunitz and A. Mugnoli, *Chem. Comm.*, 1966, 166.
[18] A. C. Cope, S. W. Fenton, and C. F. Spencer, *J. Amer. Chem. Soc.*, 1952, **74**, 5884.

derivatives. The correctness of our stereostructure (II) has recently been confirmed by an *X*-ray crystallographic study of 2,5,9,10-tetra-*O*-acetyl-14-bromotaxinol by the Japanese authors;[19] they deduced for it the stereochemistry (XXXIV).

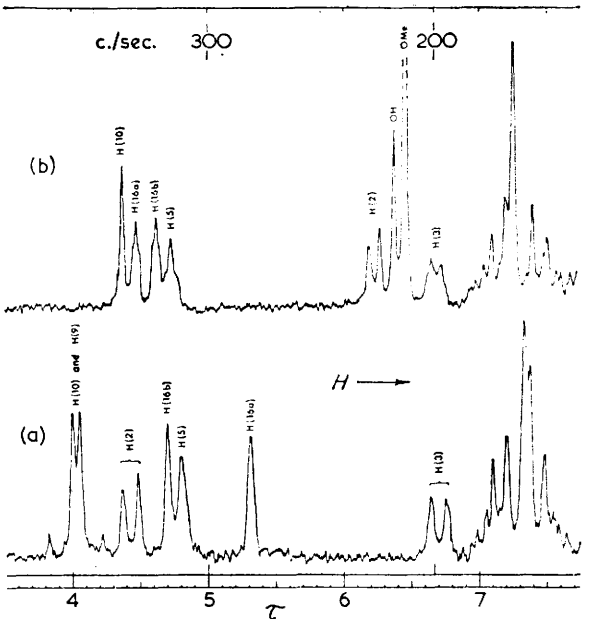
*Some N.m.r. Spectral Observations.*—This section is concerned with some n.m.r. observations which either give support to, or are illuminated by, the conclusions of the previous section. First we consider the signals of the three saturated quaternary *C*-methyl groups in taxicin-I derivatives. Typical values, selected from observations on some 35 compounds, are shown in the Table.

For each of the listed compounds, with one possible exception, referred to below, the signal at highest field is also the narrowest and, in the absence of overlap by other signals, the highest of the three signals under discussion; that is, it is least subject to secondary or long-distance coupling. It is therefore probable that it represents in each case the same methyl group. This signal is assigned to the 17-methyl group because of its high-field position, as this position was little changed in the compounds (XXXV) and (XXXVI), where one or other of the two unsaturated units in ring A is reduced, and also because its position was little affected when the usual taxicin ring-system was broken and transformed into the hemiacetal structure (XXXIII). Normally the signal lay in the range $\tau$ 8·90—9·10; its position was noticeably affected by the nature of the protecting group at C(9), whereas that at C(10) had less influence. Thus, isopropylidene derivatives, *e.g.*, (XXXVII; R = Ac), and 9-methyl ethers, *e.g.*, (XXXVIII; R = Ac, R′ = Me), showed values near $\tau$ 8·92, whereas 9-acetates, *e.g.*, (XXVIII; R = H), showed higher values (9·0—9·1), whilst 9-hydroxy-compounds, *e.g.*, (XXXVIII; R = Ac, R′ = H), showed considerably lower values (8·8—8·9). Deshielding was also observed in 9-oxo-compounds; thus the ketol acetate (XXXIX) showed the signal at 8·83, whereas the 10-oxo-isomer (XL) showed it at 8·90. The most striking compound in respect of deshielding was the 4β-hydroxy-compound (XXIX; R = Ac). Its 17-methyl signal is probably that at $\tau$ 8·70, although it is just possible that this represents the signal from C(19); in that case the 17-methyl signal would be that at 8·62. Whichever is the case the 17-methyl group is strongly and specifically deshielded by the 4β-hydroxyl group, an effect clearly parallel to that which, in 5α-steroids with a β(axial)-hydroxyl group at position 2, 4, 6, 8, or 11, causes the 19-methyl group to resonate at values up to 0·27 p.p.m. lower than the normal.[20] This emphasises the *cis*-diaxial relationship of the 4β and 8β valencies in 4-tetrahedral taxicin-I derivatives.

An oxo group at position 9 exerted a particularly striking effect on one of the two methyl groups attached to C(15). That group which resonated at lower field normally gave a signal in the range $\tau$ 8·31—8·53 in taxicin-I derivatives, and whereas 10-oxo-compounds such as (XL) were normal in this respect all the 9-oxo-compounds observed showed rather high values, usually above 8·58; thus, the ketol acetate (XXXIX) had the value 8·75. The same effect was observed in the taxicin-II series. Whereas *O*-cinnamoyltaxicin-II triacetate showed the signal at 8·22, the α-ketol acetate (XLI) showed it at 8·75. It was clear that the signal in question was due to a methyl group which falls within the shielding cone of the 9-oxo group. Reference to a model [compare the perspective (XLII)] based on the conclusions of the previous section identified this as the group at 15β; we propose to refer to this group as C(20), whilst its 15α counterpart becomes C(19). Woods, Nakanishi, and Bhacca[21] assigned the methyl signal near $\tau$ 8·3 (in the taxicin-II series) to the group which they denote as 15α; although they used the incorrect stereostructure (I) as their basis, their different notation should not be allowed to obscure the fact that their

Positions ($\tau$) of $\geq$C–Me resonances of taxicin-I derivatives (in $CDCl_3$)

| | C(20) | C(19) | C(17) |
|---|---|---|---|
| Tetra-acetate (XLIII) | 8·32 | 8·75 | 9·10 |
| 5-Deoxy-4,16-dihydrotaxicin-I 2,9,10-tri-triacetate | 8·33 | 8·80 | 9·15 |
| Isopropylidene derivative (XXXVII; R = Ac) | 8·31 | 8·67 | 8·92 |
| 9-Acetate (XXXVIII; R = H; R′ = Ac) | 8·36 | 8·70 | 9·06 |
| 10-Acetate (XXXVIII; R = Ac; R′ = H) | 8·56 | 8·82 | 8·88 |
| 9-Oxo-derivative (XXXIX) | 8·75 | 8·75 | 8·83 |
| 4-Hydroxy-derivative (XXIX; R = Ac) | 8·43 | 8·62 | 8·70 |
| 13-Hydroxy-derivative (XXXV) | 8·42 | 8·89 | 9·02 |
| 11,12-Dihydro-compound (XXXVI) | 8·53 | 8·92 | 8·97 |
| 9,10-Seco-compound (XXXIII) | 8·4 | 8·5 | 8·93 |



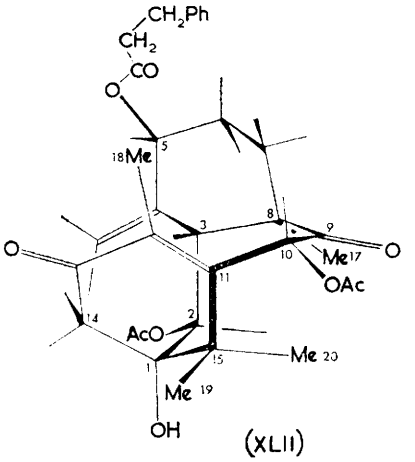

Part of the n.m.r. spectra (60 Mc./sec.) of (a) compound (XXVIII; R = OH) and (b) compound (XL), in deuteriochloroform

[19] M. Shiro, T. Sato, H. Koyama, Y. Maki, K. Nakanishi, and S. Uyeo, *Chem. Comm.*, 1966, 97.

[20] R. F. Zürcher, *Helv. Chim. Acta*, 1963, **46**, 2054.

[21] M. C. Woods, K. Nakanishi, and N. S. Bhacca, *Tetrahedron*, 1966, **22**, 243.

conclusion agrees with our own. It is, however, doubtful if their reason was valid; they pointed out that the group in question (15β, on our notation) is not far from the plane of the C(13) keto group, and hence would be



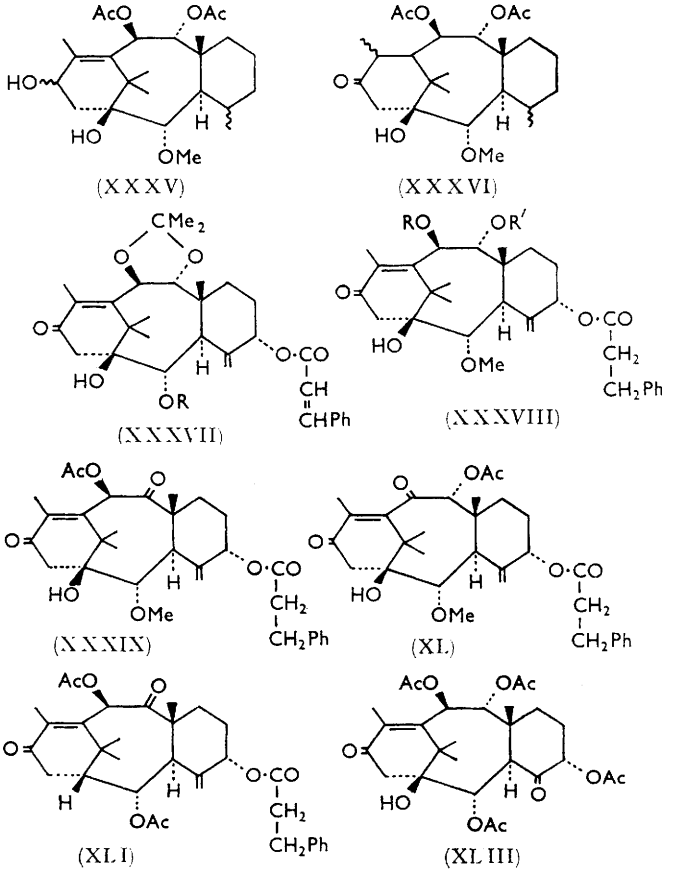

(XLII)

expected to be more strongly deshielded than its twin. In fact, reduction of the keto group, as in the compound (XXXV), has little effect on the position of the 15β (our notation) methyl signal, but instead strongly shields the 15α protons (see Table).

A 9-oxo group also affected the protons at positions 2 and 3. In the 2-methyl ether (XXXVII; R = Me) these protons resonated at τ 6·45 and 6·83, respectively, which may be regarded as typical. The corresponding values for the 10-oxo-compound (XL) were 6·23 and 6·67; that is, both protons were deshielded, that at C(2) more than that at C(3); this would be expected from the appropriate model, since in it the C(2) proton lies close to the line of the C=O bond. In the 9-oxo-compound (XXXIX) the C(2) and C(3) proton resonances have changed their relative positions; they now lie at τ 6·82 and 6·33, respectively. The 9-oxo group has thus the effect of shielding the C(2) proton and deshielding the C(3) proton, and the reason for this is made clear by the model [compare the perspective (XLII)]. In it the C(3) proton is close to the line of the C=O bond, but the C(2) proton stands in a relationship to this group rather similar to that of the 20-methyl group, so shielding would be expected. Similar effects were observed in the taxicin-II derivative (XLI). Its C(2) and C(3) proton resonances lay at τ 4·75 and 6·30, respectively, whilst those of *O*-cinnamoyltaxicin-II triacetate lay at 4·43 and 6·57. These considerations provide striking confirmation of the boat-chair conformation of ring B here proposed, and of the *trans*-B/C ring junction; they also provided additional evidence for the α configuration of the acetoxy group at position 2.

The signal of the C(19) methyl group in taxicin-I compounds lay normally between τ 8·66 and 8·82, Substantial deviations occurred only when one of the units of the conjugated system in ring A was saturated; thus, the compounds (XXXV) and (XXXVI) showed this signal at 8·92.

Next we consider signals due to the protons at positions 3, 5, and 16. In the spectrum of the acetate (XXVIII; R = OH) (see Figure) and in those of other 2-acetates, one of the two protons at position 16 (proton 16a) resonates well above τ 5 (in the example named, near 5·3) whereas the other proton, at 16b, resonates near 4·7. In compounds such as (XXXVII; R = H or Me) or (XL) (see Figure), where no 2-acetate group is present, both the 16a and 16b protons resonate near 4·5—4·7. Clearly the 2-acetate group strongly shields the 16a proton, and proximity considerations suggest that this proton is the one which lies *cis* to position 3. The signals due to the protons at 5 and 16b usually lay close together, as in the spectrum of the triacetate (XXVIII; R = OH), or overlapped, as in that of the ketol acetate (XXXIX).




As mentioned earlier,[6] allylic coupling[22] occurs between positions 3 and 16 in taxicin-I compounds. The extent of involvement of position 3 is apparent by comparing the heights of the C(2) and C(3) proton signals. The C(16) proton signals for the compound (XL) are seen to be much shorter than the true singlet given by the C(9) proton, and to show incipient resolution

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

into triplets. Part of this shortening is due presumably to geminal coupling, the rest to allylic coupling with position 3. The 16a proton appears to be rather more strongly involved in the allylic coupling than that at 16b; *i.e.*, cisoid coupling is here stronger than transoid. The extent of the allylic coupling of the C(3) proton is, particularly in the ketol acetates (XL) and (XXXIX), considerable, and, from the known steric requirements of such coupling,[22] it seemed probable that the C(3) proton occupies a pseudo-axial position. Other workers [21] have used spin-decoupling methods to show that, in taxicin-II derivatives, the proton at position 5, the other position allylic to the exocyclic double bond, is not subject to allylic coupling. This situation is very easily interpreted in terms of the B/C-*trans* stereochemistry here proposed, in which the C(3) proton is pseudo-axial and the C(5) proton pseudo-equatorial, but not in terms of the B/C-*cis*-stereostructure [9] which Nakanishi and his colleagues [21] used as the basis for discussion of their n.m.r. results.

In comparison with the values observed for 4,16-dihydrotaxicin-I compounds, 4,16-unsaturated compounds showed C(3) and C(5) proton resonances displaced to lower field; in the triacetate (XXVIII; R = OH), for example, these resonances occurred at $\tau$ 6·68 and 4·78, respectively. It might be expected that a carbonyl group at position 4 would have the same kind of effect as a double bond, and this expectation was realised so far as the C(3) resonance was concerned; thus, in oxonortaxicin-I tetra-acetate (XLIII) this signal was found near $\tau$ 6·3. The corresponding C(5) signal, however, lay near 5·5, *i.e.*, at even higher field than the corresponding signal (at 5·35) from 4,16-dihydrotaxicin-I β-phenylpropionate triacetate. In α-halogenocyclohexanones it is known [23] that, when the halogen is equatorial, normal deshielding of the α-methine proton is observed, but when the halogen atom is axial the deshielding is much less than expected. Although two pairs of steroidal α-acetoxy-ketones have been reported [24] in which, as in the α-halogenocyclohexanones, the equatorial proton in the axial acetoxy-compound is less strongly deshielded than the axial proton in the isomeric equatorial acetoxy-compound, it has not apparently been suggested so far that an axial acyloxy group adjacent to the keto group in a chair-shaped cyclohexanone may produce effects similar to those which an axial halogen atom exerts. We now make the suggestion that such an effect may be found to operate widely, and that it is responsible for the high $\tau$-value of the C(5) proton signal in taxicin compounds such as (XLIII) where the α-acyloxy group is known to be axially disposed.

## EXPERIMENTAL

For general directions, see the preceding Paper.

*The Optically Active Ketone* (X).—The diol (III; R = CO·CH:CHPh) [3] (6·2 g.) was heated under reflux in methyl iodide (150 c.c.) with silver oxide (50 g.) with exclusion of moisture and light; further amounts of silver oxide (total, 50 g.) and methyl iodide (total, 80 c.c.) were added during 4 days, after which chloroform (200 c.c.) was added and the silver oxide was filtered off. The solvents were removed and the residual gum was chromatographed on Grade II alumina, elution with benzene giving the dimethyl ether cinnamate as an oil (3·9 g.). A portion (1·53 g.) was kept at 40° for 17 hr. with methanol (100 c.c.) containing sodium hydroxide (4·43 g.). Dilution with water and isolation with ether gave the dimethyl ether alcohol as a colourless oil (0·96 g.) which showed one spot on thin-layer chromatography. The alcohol (0·97 g.) and sodium hydride (0·6 g.) were stirred together in toluene (50 c.c.) under nitrogen for 30 min., benzyl chloride (2 c.c.) was added, and the mixture was refluxed under nitrogen for 2 hr., cooled, filtered, and evaporated. The excess of benzyl chloride was removed by repeated evaporation of the residue with toluene, after which the residue was chromatographed on Grade II alumina (80 g.). The column was first eluted with light petroleum (b. p. 60—80°); further elution with benzene–light petroleum (1 : 1) gave the benzyl ether (IV) (1·06 g.). It was homogeneous to thin-layer chromatography and showed no hydroxylic absorption near 3 μ. Its n.m.r. spectrum showed *inter alia* the following signals: $\tau$ 9·13, s (>C–$CH_3$); 6·69, s ($OCH_3$); 6·71, s ($OCH_3$).

The benzyl ether (800 mg.), pyridine (3·5 c.c.), ether (50 c.c.), and osmium tetroxide (1·15 g.) were kept together at 18° for 22 hr. The solvent was evaporated, sodium hydrogen sulphite (3·3 g.) in water (55 c.c.) and pyridine (45 c.c.) was added, and the mixture was shaken for 1 hr., diluted with water, and extracted with chloroform. The chloroform extract was washed with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried and evaporated. The residue (900 mg.) showed no ethylenic absorption near 1650 $cm.^{-1}$, and showed two spots of about equal intensity on thin-layer chromatography, believed to be due to diastereoisomeric α-glycols. A portion (520 mg.) and sodium metaperiodate (990 mg.) were kept together in methanol (10 c.c.) and water (10 c.c.) for 3 hr., the solution was then filtered, and the filtrate diluted with water and extracted with ether. The ether extract was washed with water, dried, and evaporated, to give the ketone (V) as an oil (455 mg.) which was homogeneous to thin-layer chromatography. It showed no hydroxylic absorption near 3 μ, but showed $\nu_{max.}$ 1718 $cm.^{-1}$ (cyclohexanone); its n.m.r. spectrum (in carbon tetrachloride) included the following signals: $\tau$ 9·29, s (>C–$CH_3$); 6·73, s ($OCH_3$); 6·79, s ($OCH_3$).

The above ketone (455 mg.) and sodium borohydride (250 mg.) were kept together in ethanol (35 c.c.) at 18° for 3½ hr., and then glacial acetic acid (5·5 c.c.) was added, followed by water (100 c.c.). The product was isolated with ether and chromatographed on alumina (Grade II; 16 g.), using for development mixtures of benzene and light petroleum (b. p. 60—80°), and finally benzene alone. Benzene–light petroleum (1 : 10) eluted an approximately equimolecular mixture of the epimeric alcohols (VI; R = H) and (VII; R = H) the former showed a singlet signal (>C–$CH_3$) at $\tau$ 9·27, the latter a corresponding signal at 8·97. The final eluate, obtained with benzene alone, was

[23] A. Nickon, M. A. Castle, R. Harada, C. E. Berkoff, and R. O. Williams, *J. Amer. Chem. Soc.*, 1963, **85**, 2185.

[24] K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, 1961, **83**, 4623.

a 1 : 4 mixture of the alcohols (VI; R = H) and (VII; R = H).

Benzoylation of the above 1 : 4 mixture (120 mg.) with benzoyl chloride in pyridine in the usual way gave a corresponding mixture of benzoates, of which (VI; R = COPh) gave n.m.r. signals *inter alia* near $\tau$ 4·75 (q; splittings of 11 and 2·8 c./sec.) [C(2) proton] and 9·05, s ($\rangle$C–$CH_3$), whilst the epimer (VII; R = COPh gave corresponding signals near 4·43 (t; $J$ = 4 c./sec.) and 8·88, s ($\rangle$C–$CH_3$). An equimolecular mixture of these two benzoates was similarly obtained.

The 1 : 4 mixture (140 mg.) of the benzoates (VI; R = COPh) and (VII; R = COPh) in ethyl acetate (20 c.c.) containing a trace of concentrated hydrochloric acid and 5% palladised charcoal (200 mg.) was shaken with hydrogen (uptake, 1 mol.) for 15 min. Isolation in the usual way gave a mixture of two alcohols (which could be resolved by thin-layer chromatography). This material (315 mg.) was dissolved in ether (1·6 c.c.) and shaken with chromic reagent (0·92 c.c.) [made by mixing sodium dichromate dihydrate (5 g.), sulphuric acid (3·75 c.c.), and water (21·25 c.c.)] for 3 hr. Ether (50 c.c.) was then added, and the solution was washed with water, aqueous sodium hydrogen carbonate, and water, and then dried and evaporated. The 1 : 4 mixture (300 mg.) of the ketol benzoates (VIII) and (IX) showed one spot on thin-layer chromatography, and had $\nu_{max.}$ (film) 1720 (cyclohexanone) cm.$^{-1}$. The minor component (VIII) showed signals near $\tau$ 4·45, d ($J$ = 11·5 c./sec.) (position 2) and 8·81, s ($\rangle$C–$CH_3$). The major component (IX) showed corresponding signals near 4·3, d ($J$ = 6 c./sec.) and 8·84, s. An approximately equimolar mixture of the ketol benzoates (VIII) and (IX) was similarly prepared.

Freshly cleaned calcium turnings (100 mg.) were stirred for 2 min. with liquid ammonia (20 c.c.), atmospheric moisture being excluded, and a 1 : 1 mixture (100 mg.) of the ketol benzoates (VIII) and (IX) in dry toluene was then added during 3 min. Vigorous stirring was continued for a further 5 min., after which the ammonia was removed at room temperature. Methanol (2 c.c.) and then 2N-hydrochloric acid (20 c.c.) were added to the cooled (0°) residual mixture, which was then extracted with ether. The extract was washed with water, aqueous sodium carbonate, and water, and then dried and evaporated. The residue was chromatographed on Grade II alumina using light petroleum (b. p. 60—80°) as the eluant, and controlling the elution by thin-layer chromatography. The major reaction product was thus obtained pure as an oil (70 mg.) $[\alpha]_D^{22}$ −13·3° (*c* 1·2 in chloroform), $\nu_{max.}$ (film) 1710 (cyclohexanone), 1120 (ether) cm.$^{-1}$; no hydroxylic absorption. On a 4-ft. gas chromatography column with 1% polyethylene glycol on Celite at 99° and a flow rate of 40 c.c./min. the ketone was homogeneous and had retention time 15·7 min. It showed (in carbon tetrachloride) the following n.m.r. singlet signals: $\tau$ 9·03 (3H; $\rangle$C–$CH_3$), 6·80 (3H; OMe), and 6·76 (3H; OMe).

The *semicarbazone* separated from ethanol as plates, m. p. 185°, $[\alpha]_D^{24}$ +5·6°, $[\alpha]_{364\ m\mu}^{23}$ −75° (in chloroform) (Found: C, 55·9; H, 9·3; N, 16·25. $C_{12}H_{23}N_3O_3$ requires C, 56·0; H, 9·0; N, 16·3%).

*The Racemic Diol* r-(XIII; R = H).—The racemic keto acid (XI) [11] (5 g.), suspended in ether (50 c.c.), was treated with ethereal diazomethane until all had dissolved and the solution was yellow. Acetic acid was then added, and the dimethyl ester was isolated in the usual way; it formed an oil (5·35 g.). The *oxime* separated from benzene–light petroleum (b. p. 60—80°), m. p. 100° (Found: C, 53·95; H, 6·9; N, 5·75. $C_{11}H_{17}NO_5$ requires C, 54·3; H, 7·05; N, 5·72%).

The dimethyl ester (4·01 g.) and methyl orthoformate (4·8 c.c.) were kept together in dry methanol (150 c.c.) containing concentrated sulphuric acid (0·18 g.) at 20° for 22 hr., and the solution was then neutralised by the addition of 0·36N-methanolic sodium methoxide (10 c.c.) and most of the methanol was removed by evaporation. After the addition of 0·1N-aqueous sodium hydrogen carbonate the mixture was extracted with ether; the extract was washed with water, and then dried and evaporated. The dimethyl ketal r-(XII) formed an oil (4·84 g.), $\nu_{max.}$ (film) 1730 (ester) cm.$^{-1}$. Its n.m.r. spectrum in carbon tetrachloride showed singlets at $\tau$ 8·72 ($\rangle$C–$CH_3$), 6·92 ($OCH_3$), 6·89 ($OCH_3$), and 6·38 (two $OCH_3$).

A solution of the above ketal (4·84 g.) in dry ether (125 c.c.) was added dropwise during 20 min. to a stirred solution of lithium aluminium hydride (1·36 g.) in ether (125 c.c.); after stirring had been continued for a further 1 hr. ethyl acetate (15 c.c.) was added cautiously followed by sodium potassium tartrate (20 g.) in water (100 c.c.). The product, isolated by continuous extraction with ether for 16 hr., separated from ether–light petroleum (b. p. 40—60°) giving the racemic *diol* (2·16 g.), m. p. 79° (Found: C, 60·55; H, 9·95. $C_{11}H_{22}O_4$ requires C, 60·5; H, 10·15%). Its n.m.r. spectrum in $D_2O$ showed singlets at $\tau$ 8·96 ($\rangle$C–$CH_3$), 6·78 ($OCH_3$), and 6·72 ($OCH_3$).

*The* cis-*Di(methoxymethyl)cyclohexanone* r-(XIV).—The above diol (200 mg.) and sodium hydride (176 mg.) were mixed in dry tetrahydrofuran under nitrogen, and the mixture was then stirred with methyl iodide (5 c.c.) at 18° for 18 hr. The filtered solution was diluted with chloroform, refiltered, and evaporated to an oil (200 mg.) which showed no hydroxylic absorption near 3 $\mu$. It was kept for 2 hr. at 20° with methanol (4·8 c.c.) and water (1·2 c.c.), the mixture being made 2N with respect to sulphuric acid. The product was isolated in the usual way, and chromatographed on Grade II alumina using light petroleum (b. p. 60—80°) as the eluant. The cyclohexanone (94 mg.) was a colourless liquid, $\nu_{max.}$ 1715 cm.$^{-1}$, which gave a single spot on thin-layer chromatography. It was homogeneous on gas chromatography under the conditions described for the ketone (X), and, in contrast to the latter, showed a retention time of 13·5 min. Its n.m.r. spectrum (in carbon tetrachloride) showed marked differences to that of the ketone (X); it showed singlets at $\tau$ 8·83 ($\rangle$C–$CH_3$), 6·73 ($OCH_3$), and 6·67 ($OCH_3$). The *semicarbazone* formed plates (from ethanol), m. p. 173·5° (Found: C, 56·25; H, 8·85; N, 16·3. $C_{12}H_{23}N_3O_3$ requires C, 56·0; H, 9·0; N, 16·3%).

*Benzylation of the Lactonic Acid* (XV).—The racemic lactonic acid [10] (1 g.), benzyl chloride (12 c.c.), powdered potassium hydroxide (12 g.), and dry toluene (14 c.c.) were stirred vigorously together and refluxed in an apparatus provided with a Dean and Stark water separator for 22 hr. The cooled mixture was then diluted with water and the toluene phase was discarded. The aqueous phase was boiled under reflux for 6 hr., cooled, and extracted with ether. The aqueous phase was acidified, and the crystalline acidic product (1·55 g.) was isolated with ether. On recrystallisation from acetone–light petroleum (b. p. 60—80°) the racemic trans-*di-acid* r-(XVIII) (0·6 g.) separated first; after recrystallisation it formed needles, m. p. 192°

(Found: C, 65·95; H, 6·75. $C_{16}H_{20}O_5$ requires C, 65·75; H, 6·9%). Its n.m.r. spectrum (in alkaline $D_2O$) showed singlet signals at τ 8·82 (>C–$CH_3$), 5·54 (–O–$CH_2$–), and 2·66 ($C_6H_5$). On thin-layer chromatography on Kieselgel G (Merck) with 2% acetic acid in di-isopropyl ether it had $R_F$ 0·41.

Evaporation of the mother-liquors, and crystallisation from acetone–light petroleum (b. p. 80—100°), afforded the racemic cis-*di-acid* r-(XIX) (100 mg.) as prisms, m. p. 164° (Found: C, 66·0; H, 7·05%). Its n.m.r. spectrum (in alkaline $D_2O$) showed singlet signals at τ 8·70 (>C–$CH_3$), 5·52 (–O–$CH_2$–), and 2·70 ($C_6H_5$). On thin-layer chromatography on Kieselgel G with 2% acetic acid in di-isopropyl ether it had $R_F$ 0·2.

For identification, the *trans*-di-acid r-(XVIII) (200 mg.) was hydrogenated in ethyl acetate with 5% palladised charcoal and a trace of concentrated hydrochloric acid. The resulting *hydroxy*-trans-*di-acid* [as r-(XVIII), but H in place of $CH_2Ph$] formed plates (100 mg.) (from methanol–benzene), m. p. 151° (Found: C, 53·8; H, 6·8. $C_9H_{14}O_5$ requires C, 53·5; H, 7·0%). Similar hydrogenolysis of the *cis*-di-acid r-(XIX) (200 mg.) gave the racemic δ-lactonic acid r-(XV) (30 mg.), m. p. 145°.

Benzylation of the optically pure [11] δ-lactonic acid e-(XV) by the method used in the racemic series gave the trans-*di-acid* e-(XVIII) as needles, m. p. 166·5°, $[\alpha]_D^{22}$ +2·6° (Found: C, 65·95; H, 6·75%).

*The Ketones* r-(X) *and* e-(X).—Tetrahydrofuran (40 c.c.) containing the *trans*-di-acid r-(XVIII) (800 mg.) was added dropwise to lithium aluminium hydride (800 mg.) in tetrahydrofuran (40 c.c.) at 0°, and the mixture was boiled under reflux for 9 hr., and then cooled to −10° while ethyl acetate (8 c.c.) was added cautiously. After 2N-sulphuric acid (80 c.c.) had been added the oily diol (737 mg.) was isolated with ether. It showed one spot on thin-layer chromatography. Methylation with methyl iodide and silver oxide in the manner described for the diol (III; R = CO·CH:CHPh) gave the dimethyl ether (546 mg.) as an oil. It gave one spot on thin-layer chromatography. Its n.m.r. spectrum showed singlet signals at τ 9·20 (>C–$CH_3$), 6·82 ($OCH_3$), 6·78 ($OCH_3$), 5·62 (O·$CH_2$–), and 2·85 ($C_6H_5$). Hydrogenolysis in ethyl acetate (25 c.c.) containing a trace of concentrated hydrochloric acid with 5% palladised charcoal was carried out in the usual way, and gave the racemic di(methoxymethyl)cyclohexanol (378 mg.) as an oil which showed one spot on thin-layer chromatography. This alcohol (201 mg.) dissolved in acetone (7·8 c.c.) was oxidised at 0° with chromic reagent (0·247 c.c.) in the way described for the preparation of the ketol benzoates (VIII) and (IX). This gave the racemic ketone r-(X) (186 mg.) as an oil, $\nu_{max.}$ (film) 1710 cm.$^{-1}$, which showed one spot on thin-layer chromatography. Its n.m.r. spectrum, and gas chromatography characteristics were identical with those described for the optically active ketone (X), but considerably different from those of the racemic ketone r-(XIV). The *semicarbazone* separated from ethanol as plates, m. p. 173° (Found: C, 56·35; H, 8·85; N, 16·3. $C_{12}H_{23}N_3O_3$ requires C, 56·0; H, 9·0; N, 16·3%).

Operations with the optically active *trans*-di-acid e-(XVIII) were conducted exactly as described for the racemic material, and gave products which had infrared and n.m.r. characteristics identical with those obtained from the latter. The final optically active cyclohexanone e-(X) gave one spot on thin-layer chromatography and showed $R_F$ value, infrared, and n.m.r. spectra, and gas chromatography characteristics identical with those of the ketones (X) and r-(X); it had $[\alpha]_D^{20}$ +13·4°. The *semicarbazone* separated from ethanol as plates, m. p. 186°, $[\alpha]_D^{24}$ −5·9°, $[\alpha]_{364\ m\mu}^{25}$ +72·7° (Found: C, 55·8; H, 9·1. $C_{12}H_{23}N_3O_3$ requires C, 56·0; H, 9·0%). Its infrared spectrum (KCl disc) was identical with that of the semicarbazone of the ketone (X).

*The Cyclohexanol* (XX).—The diol (XXIII; R = CO·$CH_2$·$CH_2$Ph) (2·4 g.) was methylated in the usual way for 3 days with silver oxide (total, 30 g.) and methyl iodide (total, 100 c.c.); chromatography of the product on Grade II alumina (200 g.) and elution with benzene–light petroleum (1 : 1) then gave the corresponding dimethyl ether (1·22 g.), which showed one spot on thin-layer chromatography. It was hydrolysed at 20° with methanol (100 c.c.) containing sodium hydroxide (4·3 g.); isolation of the neutral material in the usual way gave the cyclohexanol (XX) as an oil (690 mg.). The 3,5-*dinitrobenzoate* separated from chloroform–light petroleum (b. p. 60—80°) as needles, m. p. 152°, $[\alpha]_D^{24}$ +54° (Found: C, 55·35; H, 6·25; N, 6·8. $C_{19}H_{26}N_2O_8$ requires C, 55·6; H, 6·4; N, 6·8%).

*The Cyclohexanones* (XXI) *and* (XXII).—The alcohol (XX) (386 mg.), purified by regeneration from its 3,5-dinitrobenzoate, was shaken for 2¼ hr. at 18° with ether (1·9 c.c.) and chromate reagent (1·2 c.c.) [made by mixing sodium dichromate dihydrate (5 g.), concentrated sulphuric acid (3·75 c.c.), and adding water to 25 c.c.]. After dilution with water (20 c.c.) and ether (20 c.c.) the ethereal layer was washed with aqueous sodium hydrogen carbonate and then with water, dried, and evaporated, giving the ketone (XXI) as an oil (350 mg.), $\nu_{max.}$ 1710 cm.$^{-1}$. The *semicarbazone* separated from chloroform–light petroleum (b. p. 60—80°) as needles, m. p. 150—152°, $[\alpha]_D^{24}$ +22° (Found: C, 57·7; H, 9·4; N, 15·45. $C_{13}H_{25}N_3O_3$ requires C, 57·75; H, 8·95; N, 15·5%). It showed the following n.m.r. signals: τ 9·03, s (>C–$CH_3$); 8·90, d $J$ = 7 c./sec. (>CH–$CH_3$); 6·79, s ($OCH_3$); 6·70, s ($OCH_3$).

The above semicarbazone (284 mg.), acetic acid (3 c.c.), and freshly distilled pyruvic acid (1·57 c.c.) were heated together at 100° for 50 min., and the cooled solution was then diluted with ether. The solution was washed with aqueous sodium carbonate and then with water, and then dried and evaporated, giving the ketone (XXII) as an oil (220 mg.). It showed $\nu_{max.}$ (film) 1708 cm.$^{-1}$, and its infrared spectrum was in general similar to that of the ketone (XXI), but it lacked bands at 795, 970, and 1070 cm.$^{-1}$ which were present in the latter. The *semicarbazone* separated from aqueous ethanol as needles, m. p. 121—123°, $[\alpha]_D^{22}$ +44° (Found: C, 57·7; H, 9·4; N, 15·45%). Its n.m.r. spectrum showed signals at τ 9·06, s (>C–$CH_3$); 8·85, d $J$ = 6·5 c./sec. (>CH–$CH_3$); 6·73, s (two $OCH_3$).

*Hydrolysis of the Acid* (XXIV; R = CO·$CH_2$·$CH_2$Ph).—The acid [5] (500 mg.) was kept for 22 hr. at 40° with methanol (20 c.c.) containing sodium hydroxide (1·01 g.). The mixture was cooled to 0°, acidified with 2N-hydrochloric acid, and most of the methanol was evaporated under reduced pressure. After the addition of water, the product was isolated with ether. It was rinsed with light petroleum (b. p. 60—80°; 3 × 2 c.c.) to remove β-phenylpropionic acid, which left a crystalline mass (204 mg.); thin-layer chromatography showed the presence of two compounds. Recrystallisation from water (*ca.* 4 c.c.) gave the *lactonic acid* (XXVII) (96 mg.), m. p. 181° (decomp.), $[\alpha]_D^{22}$ +41°, $\nu_{max.}$ (in KCl) 1722 (δ-lactone), 1709 (carboxyl) cm.$^{-1}$ (Found: C, 60·7; H, 6·15. $C_{10}H_{12}O_4$ requires C, 61·2; H,

6·2%). Whereas the lactonic acid showed $R_F$ 0·33 (Kieselgel G; 1% acetic acid in di-isopropyl ether), the second component showed $R_F$ 0·17. This component was more conveniently isolated by hydrolysing the lactonic acid with aqueous alkali followed by careful acidification and continuous extraction with ether. Crystallisation from acetone–light petroleum (b. p. 60—80°) gave the *dibasic hydroxy-acid* (XXIV; R = H), m. p. 180—182° (decomp.) (Found: C, 56·2; H, 6·6. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·6%).

*Reduction of the Acid* (XXIV; R = $CO{\cdot}CH_2{\cdot}CH_2Ph$) *with Lithium Aluminium Hydride*.—The acid (350 mg.) in dry tetrahydrofuran (20 c.c.) was added to lithium aluminium hydride (500 mg.) in tetrahydrofuran (20 c.c.), and the mixture was refluxed for 21 hr. After the excess of hydride had been destroyed with ethyl acetate, 2N-sulphuric acid (40 c.c.) was added, and the mixture was extracted with ether (3 × 40 c.c.) to remove the phenylpropanol. Continuous ether extraction of the aqueous phase gave an oil (179 mg.) which crystallised from benzene, giving the unsaturated triol (III; R = H), m. p. 111°. Its thin-layer chromatographic behaviour and its infrared spectrum were identical with those of authentic material.

Similar reduction of the acid (XXV) yielded the saturated triol (XXIII; R = H) (experiment by Mr. M. Dukes).

*Hydrogenation of the Unsaturated Acid* (XXIV; R = $CO{\cdot}CH_2{\cdot}CH_2Ph$).—The acid (400 mg.) was hydrogenated (uptake, 1 mol.) with 5% palladised charcoal (200 mg.) in ethyl acetate (60 c.c.) during 17 hr.; the product, isolated in the usual manner, showed the presence of two components in about equal amounts (thin-layer chromatography). This mixture (500 mg.) was hydrolysed with methanolic sodium hydroxide, and, after neutralisation with acetic acid and evaporation of the methanol, water (30 c.c.) and 2N-hydrochloric acid (9 c.c.) were added. Ether extraction gave a mixture (338 mg.) containing mainly β-phenylpropionic acid and the acid (XXV). The phenylpropionic acid was removed by washing with light petroleum (b. p. 60—80°) (3 c.c.); recrystallisation of the residue (141 mg.) from water then gave the acid (XXV), m. p. 195°. Its infrared spectrum was identical with that of authentic material.

The aqueous phase from the ether extraction was continuously extracted with ether, which gave material (194 mg.) consisting mainly of the acid (XXVI). Recrystallisation from ether and then from acetone–benzene gave the *acid*, which showed a double m. p., 142 and 171°, $[\alpha]_D^{20}$ +21·2° (*c* 2 in ethanol) (Found: C, 55·75; H, 7·55. $C_{10}H_{16}O_5$ requires C, 55·5; H, 7·5%).

*The Diol* (XXIX; R = H) (with Dr. R. M. Scrowston).—The corresponding 4-keto-5α-ol (60 mg.) and sodium borohydride (4·1 mg.) were kept together in dry ethanol (4 c.c.) and ethyl acetate (2 c.c.) at 0° for 3 hr. Isolation of the product in the usual manner gave the *diol* (XXIX; R = H) (35 mg.) as needles (from ethyl acetate–hexene), m. p. 246°, $\lambda_{max.}$ 276 mμ (ε 4950) (Found: C, 65·25; H, 8·6. $C_{23}H_{36}O_7$ requires C, 65·1; H, 8·55%).

When treated with an excess of acetic anhydride in pyridine for 2 days at 18° the diol gave the *5-monoacetate* (XXIX; R = Ac), which formed needles (from ethyl acetate–hexane), m. p. 271° (Found: C, 64·5; H, 8·25. $C_{25}H_{38}O_8$ requires C, 64·35; H, 8·2%).

*The Orthoacetates* (XXXII) (with Dr. R. M. Scrowston).—*O*-Cinnamoyltaxicin-I triacetate (1 g.), silver oxide (9 g.), and methyl iodide (100 c.c.) were heated together under reflux with exclusion of moisture and light for 24 hr. Filtration, evaporation of the solvent, and crystallisation from ethanol gave the mixed orthoacetates, m. p. 226—227° (Found: C, 67·55; H, 6·65. $C_{36}H_{44}O_{10}$ requires C, 67·8; H, 6·9%). The n.m.r. spectrum showed *inter alia* the following features: characteristic cinnamate signals τ 2—3 and near 3·67; the usual quartet ($J$ = 10 c./sec.) signal of the (9)- and (10)-protons near 4·05; the usual signals near 4·4 due to one (16)-proton and near 4·7 due to the other (16)-proton and the (5)-proton; two doublets ($J$ = 5 c./sec.) near 5·45 and 5·62, of combined intensity 1 proton, assigned to position 2; singlet methoxyl signals at 6·65 and 6·72 of combined intensity 3 protons; singlet signals at 7·25 and 7·14 of combined intensity 2 protons, assigned to position 14 (the part-signals mentioned above showed the same intensity ratio in the three different cases); the 18-methyl singlet signal at 7·72; two singlet acetate signals at 7·92 and 7·96; $\geqslant$C–Me signals at 8·35, 8·46, 8·73, and 9·03. For comparison, it may be noted that the two β-D-mannose 1,2-methyl orthoacetate 3,4,6-triacetates, stereoisomeric at the orthoacetate centre, show signals due to the position 2 proton at 5·37 and 5·60.[25]

The mixed orthoacetates (200 mg.) dissolved in chloroform (2 c.c.) were kept at 18° for 15 min. with ethanol (8 c.c.) containing 2N-hydrochloric acid (0·2 c.c.). The mixture was then diluted with chloroform, washed with water, dried, and evaporated. Chromatography of the residue on Grade II neutral alumina (12 g.) and elution with 0·1% ethanol in benzene gave *O*-cinnamoyltaxicin-I triacetate (142 mg.), identified by comparison with authentic material.

*Optical Rotatory Dispersion Data*.—*O*-β-Phenylpropionyltaxicin-I triacetate showed (in methanol) a trough [φ] −71,000 at 233 mμ, a peak [φ] +61,000 at 294 mμ, a trough [φ] −2430 at 373 mμ. *O*-β-Phenylpropionyltaxicin-II triacetate showed (in methanol) a trough [φ] −85,400 at 228 mμ, a peak [φ] +72,100 at 284 mμ, an inflection [φ] +31,000 at 326 mμ, and a trough [φ] −6500 at 377 mμ.

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[25] A. S. Perlin, *Canad. J. Chem.*, 1963, **41**, 399.