# 576. *Taxine. Part II.*[1] *Glycol Cleavage Fragments from O-Cinnamoyltaxicin-I.*

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From the periodate cleavage of *O*-cinnamoyltaxicin-I an acidic and a neutral fragment are obtained which together account for all the carbon atoms of the molecule. Degradative experiments show the acidic fragment to have the structure (I) and the neutral fragment to have the structure (XV; R = CO·CH:CHPh).

After the functional groups of *O*-cinnamoyltaxicin-I had been provisionally defined,[1] means for its further degradation were sought, and one of the earliest found and most promising of these was the reaction with sodium metaperiodate. Preliminary studies enabled us to find conditions under which the molecule was split by the oxidant into two fragments, each of which contained one half of the original number of carbon atoms of the taxicin-I residue. The structures of these two fragments form the subject of the present paper.

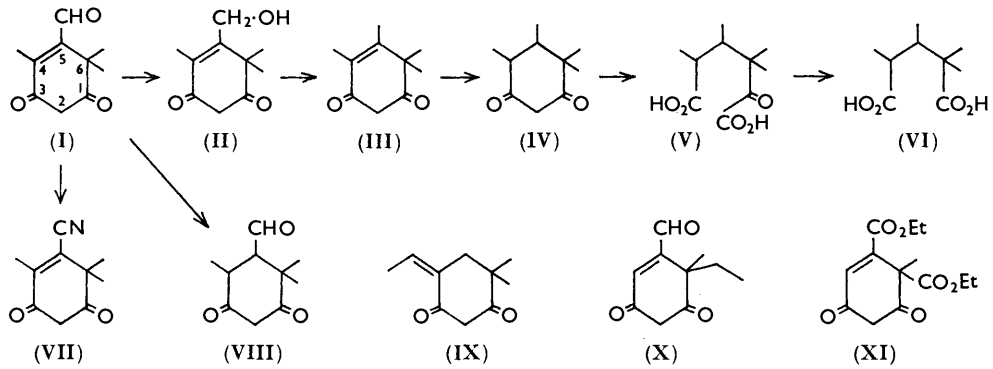
In aqueous alcohol with an excess of periodate, *O*-cinnamoyltaxicin-I reduced some 5 mol. of the oxidant, giving a mixture of acidic and neutral products none of which was readily isolated in the pure state. One experiment, in which the excess of oxidant and the reaction time were both restricted, gave an acidic fraction from which a very low yield of a pale yellow crystalline acid was obtained. This acid reduced periodate, giving non-crystalline acidic products. It seemed likely that the crystalline acid was an initial, or at any rate an early, product of the periodate oxidation, which suffered further oxidation at a rate comparable to, or faster than, that of its formation. Fortunately we found that when the reaction was carried out in the two-phase system ethyl acetate–water, under the somewhat critical conditions described in the Experimental part, the over-oxidation was suppressed, and the crystalline acid was obtained in yields of over 80%. Titration then showed that two mol. of the oxidant were consumed in its formation. No small carbonyl or acidic fragments were produced at the same time; the other product was a neutral substance which was amorphous and also unstable, so that initially it proved intractable. However, as information on the acidic substance accumulated, the reasons for the instability of the neutral substance became clearer, and this made possible its stabilisation and purification. Crystalline material was then obtained from it in yields of over 50% based on *O*-cinnamoyltaxicin-I, and we were able to undertake its degradation. The experiments on the acidic and the neutral fragment are described separately below; for clarity, the structures to which these experiments lead are used from the outset.

*The Acidic Fragment.*—The same crystalline acid was obtained in similar yields from cleavage of *O*-cinnamoyltaxicin-I, *O*-β-phenylpropionyltaxicin-I, and dihydrotaxicin-I β-phenylpropionate. It was clear from this that the arylacyloxy-group and the isolated methylene double bond were present, not in the acid, but in the neutral fragment.

The crystalline acid, $C_{10}H_{12}O_3$, was monobasic and optically inactive. Solutions in alcohol were pale yellow, but became brighter yellow when alkali was added; in 50% alcohol 0·1N in hydrochloric acid the acid had $\lambda_{max.}$ 325 mμ (ε 4100), whereas similar solutions 0·1N in potassium hydroxide had $\lambda_{max.}$ 378 mμ (ε 5100); in both spectra a less well-defined band in the region 240—250 mμ was present. The group responsible for the acidity was evidently part of a conjugated unsaturated system. The infrared spectrum of the acid (in KCl) in the 3 μ region was not typically carboxylic, whilst in the 6 μ region strong bands near 1680, 1638, and 1580 cm.$^{-1}$ were shown. The neutral monomethyl derivative, obtained by reaction of the acid with diazomethane, also showed bands near

[1] (*a*) Baxter, Lythgoe, Scales, Trippett, and Blount, *Proc. Chem. Soc.*, 1958, 9; (*b*) Part I, Baxter, Lythgoe, Scales, Scrowston, and Trippett, preceding paper.

1680, 1630, and 1570 cm.$^{-1}$, and was clearly not a methyl ester. The acid was therefore regarded as an enolised α- or β-dicarbonyl compound, and in support of this view, when solutions in aqueous sodium hydrogen carbonate were treated with iodine, they decolorised 1 mol. in a substitution reaction which was reversed when the solution was acidified.




In the formulæ, the two carbonyl groups which are responsible for the acidity of the acid (I) and its relatives are written for simplicity in the non-enolic form. In addition to them, the acid contained an aldehyde group, which was reactive towards the normal carbonyl reagents, whereas the other two carbonyl groups were more sluggish. Thus the acid (I) formed a monoxime, which hot acetic anhydride converted into a crystalline nitrile (VII), $\nu_{max.}$ (in KCl) 2250 cm.$^{-1}$. Controlled reduction of the acid (I) with sodium borohydride reduced the aldehyde group selectively, giving the primary alcohol (II). All these derivatives were acidic, showing that the enolised dicarbonyl system persisted in them unchanged. Their formation from the acid (I) was accompanied by changes in ultraviolet absorption, which showed that the original aldehyde group was conjugated; this was also apparent from its $\nu_{max.}$ 1680 cm.$^{-1}$.

Hydrogenation of the acid (I) was undertaken as a means of determining the number of ethylenic links present, but it gave unsatisfactory results. With palladium, two mol. of hydrogen were absorbed rapidly and nearly one further mol. more slowly, but the product was inhomogeneous. However, the stepwise reduction described below shows that, in its hypothetical non-enolic form, the acid (I) contains one ethylenic link and is thus monocyclic.

Zinc dust and acetic acid converted the primary alcohol (II) into the deoxy-compound (III) which was still acidic, and showed ultraviolet absorption closely similar to that of its precursor (II) [in 50% alcohol 0·1N in acid, $\lambda_{max.}$ 286 mμ (ε 5900); with 0·1N-alkali, $\lambda_{max.}$ 323 mμ (ε 12,300)]. Palladium and 1 mol. of hydrogen converted the deoxy-compound (III) into the dihydro-compound (IV); this was acidic, but showed $\lambda_{max.}$ (with 0·1N-acid) 260 mμ (ε 14,500), $\lambda_{max.}$ (with 0·1N-alkali) 285 mμ (ε 28,500). These values, and also its infrared characteristics, $\nu_{max.}$ (in KCl) 1611 and 1524 cm.$^{-1}$, closely resembled those of dimedone, which suggested that the dihydro-compound (IV) was a cyclohexane-1,3-dione. Whereas in 50% alcohol 0·1N in potassium hydroxide dimedone itself shows $\lambda_{max.}$ 283 mμ, its 2-methyl derivative shows $\lambda_{max.}$ 295 mμ, so it was likely that the 1,3-diketone (IV) was unsubstituted at position 2. In confirmation, it condensed with formaldehyde to give a methone, a reaction not given by 2-alkylcyclohexane-1,3-diones.

The formation of the deoxy-compound (III) is clearly the hydrogenolysis of the vinylogue of an α-ketol, and may be represented $-CO-C=C-CH_2\cdot OH \longrightarrow -CO-C=C-CH_3$. In this expression, the keto-group is one of those present in the β-diketone system; the double bond might thus be endocyclic, as in the structure (III), or semicyclic, as in the structure (IX) for the deoxy-compound. The latter kind of structure was ruled out because the deoxy-compound gave no acetaldehyde (or other volatile aldehyde) on

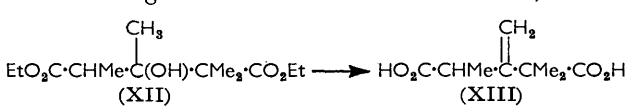
ozonolysis. It was thus clear that the acid (I) contains a double bond and two keto-groups in a six-membered ring; since it does not aromatise, two alkyl groups must be present at the remaining ring position, 6. Its structure is thereby limited to either (I) or (X). Of these, the former seemed much the more probable, on account of the observed lack of optical activity.

This type of structure found support in Woodward and Reed's [2] observation that the product of condensation of ethyl chlorofumarate and the sodio-derivative of ethyl α-acetyl-propionate, which they showed to have the structure (XI), shows at its own acid pH in alcohol $\lambda_{max.}$ 326 mμ (ε 4800) and an inflection near 250 mμ. The close similarity of the chromophores in compounds (I) and (XI) and the closeness of the observed absorption data are striking. Woodward and Reed presented reasons for the view that the carbonyl group in compound (XI) which is actually enolised is that adjacent to the saturated quaternary ring carbon atom, and no doubt this is valid for the acid (I) also.

As a further check on our structural deductions, the acid (I) was treated with zinc dust in pyridine and acetic acid, reagents which specifically reduce the double bond in ene-1,4-diones. A crystalline dihydro-compound (VIII) was obtained, which contained an unconjugated aldehyde group [$\nu_{max.}$ (in Nujol) 1724 cm.$^{-1}$], and also an enolised cyclohexane-1,3-dione system which showed the acidity and also the ultraviolet and infrared absorption characteristics of the similar system present in dimedone. This provided strong support for the type of structure (I) deduced for the acidic fragment.

Further degradation of the β-diketone(IV) was then undertaken by using, as the reagent, periodate, which first hydroxylates and then cleaves β-diketones. Wolfrom and Bobbitt [3] showed that cyclohexane-1,3-dione reduces 4 mol. of periodate, giving glutaric acid; its 2-alkyl derivatives reduced only 3 mol., giving glutaric acid and the expected aliphatic acid. They considered that the first reaction proceeded through the 2-hydroxy- and 2-keto-derivatives and, finally, 2-oxoglutaric acid as intermediates; this would explain why 2-alkylcyclohexane-1,3-diones require 1 mol. less of the oxidant. In view of this, we expected the diketone (IV) to consume 4 mol. of periodate and to give a derivative of glutaric acid. In fact, it reduced only 3 mol. and gave an α-keto-acid, possibly (V), which was characterised as the 2,4-dinitrophenylhydrazone. The difference in behaviour from the simpler models may be due to the *gem*-dimethyl group; in any case, α-keto-acids react rather sluggishly with periodate in our experience, although they are readily degraded by lead tetra-acetate. With this reagent the α-keto-acid (V?) was oxidised, giving as the isolated product a glutaric anhydride, $\nu_{max.}$ 1773 and 1812 cm.$^{-1}$. Alkaline hydrolysis gave the corresponding acid (VI), m. p. 128°, which slowly reverted to the anhydride when kept; this reaction is no doubt promoted by the *gem*-dimethyl group.

A tetramethylglutaric acid of this structure, m. p. 121°, was reported by J. W. Baker,[4] who combined ethyl α-bromopropionate in a Reformatski reaction with ethyl dimethyl-acetoacetate, which gave the hydroxy-diester (XII). Treatment with phosphorus penta-chloride and then with alkali gave an unsaturated dibasic acid, formulated as (XIV);




(XII) (XIII)

$HO_2C{\cdot}CMe{=}CMe{\cdot}CMe_2{\cdot}CO_2H$

(XIV)

hydrogenation then gave the substituted glutaric acid m. p. 121°. We repeated this work and obtained an unsaturated dibasic acid identical with Baker's; however, it showed no selective absorption in the near-ultraviolet region and gave formaldehyde on ozonolysis; clearly it is to be formulated as (XIII) and not as (XIV). It was difficult to hydrogenate

[2] Woodward and Reed, *J. Amer. Chem. Soc.*, 1943, **65**, 1569.
[3] Wolfrom and Bobbitt, *J. Amer. Chem. Soc.*, 1956, **78**, 2489.
[4] Baker, *J.*, 1931, 1546.

but, when this had been satisfactorily achieved, the product had m. p. 128°; it was identical with the acid (VI) from our degradation, and it gave the same anhydride. At first it seemed possible that Baker's acid of m. p. 121° might have differed in its stereochemistry from ours of m. p. 128°, but it now seems likely that its low m. p. was due to contamination with its unsaturated precursor.

These experiments demonstrate the structure of the β-diketone (IV), and show that the acidic fragment from the cleavage of *O*-cinnamoyltaxicin-I is 5-formyl-4,6,6-trimethylcyclohex-4-ene-1,3-dione (I).

*The Neutral Fragment.*—The crude neutral material (XV; R = CO·CH:CHPh) from cleavage of *O*-cinnamoyltaxicin-I was amorphous. Its optical rotation changed when it was kept; it was evidently unstable. Similar amorphous and unstable materials (XV; R = CO·$CH_2$·$CH_2$Ph) and (XXVI), respectively, were obtained by periodate cleavage of *O*-β-phenylpropionyltaxicin-I and of dihydrotaxicin-I β-phenylpropionate. Their instability was due to their dialdehyde nature, and, when the formyl groups were reduced to primary alcohol groups with sodium borohydride, the products were stable and could be purified by counter-current distribution. They were then acetylated to give diacetates which, although amorphous, were identifiable by their optical rotations.

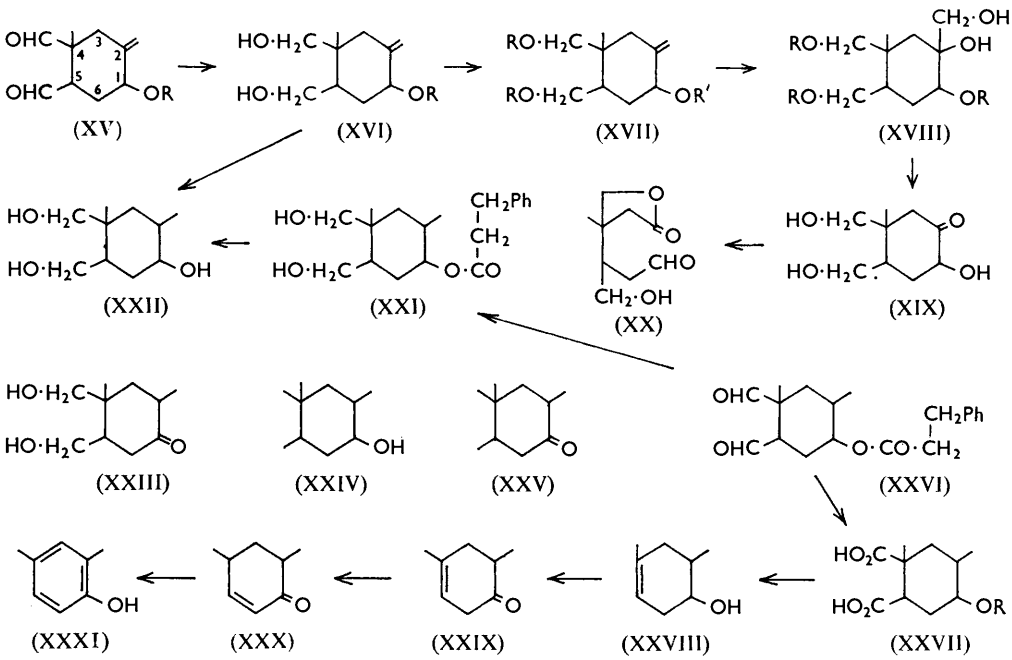
The neutral fragment from *O*-cinnamoyltaxicin-I gave in this way a cinnamate diol (XVI; R = CO·CH:CHPh) and then a cinnamate diacetate (XVII; R = Ac, R′ = CO·CH:CHPh). The presence of the cinnamate group was evident from the spectroscopic data, and was confirmed by the formation of cinnamic acid on hydrolysis. The cinnamate diacetate gave on controlled hydrogenation (1 mol. of hydrogen) a phenylpropionate diacetate (XVII; R = Ac, R′ = CO·$CH_2$·$CH_2$Ph), identical with material obtained in the expected manner from the neutral fragment from *O*-β-phenylpropionyltaxicin-I. This phenylpropionate diacetate was able to take up one further mol. of hydrogen, giving a phenylpropionate diacetate (as in XXI, with 2AcO in place of 2HO), identical with that obtained in the expected manner from the neutral fragment from dihydrotaxicin-I β-phenylpropionate. Moreover, the phenylpropionate diacetate (XVII; R = Ac, R′ = CO·$CH_2$·$CH_2$Ph) gave formaldehyde upon ozonolysis. These experiments confirmed our expectations that the neutral fragment from *O*-cinnamoyltaxicin-I would prove to contain the cinnamate group and the reactive methylene double bond.

Shortly afterwards, crystalline material was obtained by hydrolysis of the cinnamate diacetate (XVII; R = Ac, R′ = CO·CH:CHPh). The product (XVI; R = H) was an unsaturated triol, which on hydrogenation absorbed 1 mol. of hydrogen and gave a crystalline saturated triol (XXII); this was also obtained by hydrolysis of the diacetate of the diol (XXI). The triol (XXII) formed a triacetate, and this, together with the analytical data, showed that the triols were monocyclic $C_{10}$ compounds. Thus all the carbon atoms in the intact molecule were accounted for in terms of the acidic and neutral cleavage fragments.

The relative positions of the oxygen functions in the neutral fragments were established as follows. Oxidation of the purified diol (XXI) or of the crude dialdehyde (XXVI) with chromic acid gave a dibasic acid (XXVII; R = CO·$CH_2$·$CH_2$Ph). Although amorphous it gave satisfactory titration values. Hot acetic anhydride converted it into an amorphous anhydride, $\nu_{max.}$ 1802 and 1875 cm.$^{-1}$ (succinic anhydride), which was characterised by the formation of a crystalline mono-*p*-toluidide. Hydrolysis of the amorphous dibasic acid gave β-phenylpropionic acid and the crystalline hydroxy-acid (XXVII; R = H). When this acid was treated with acetic anhydride, part of it was converted into the anhydride, and part into a γ-lactone, $\nu_{max.}$ 1767 cm.$^{-1}$. The results show that the fragment (XXVI) contains two aldehyde groups which form part of a succindialdehyde system, and that one of them is situated γ to the phenylpropionyloxy-group.

In order to study the nature of the ring present in the saturated diol (XXI) we wished to reduce the two hydroxymethyl groups to methyl groups. To this end, the ditoluene-*p*-sulphonate of the diol was heated with potassium ethanethiol in t-butyl alcohol. The

ester group was partially removed, and the sulphonate groups were replaced by alkylthio-groups. Desulphurisation by Raney nickel then gave the crystalline alcohol (XXIV). This showed bands near 1379 and 1370 cm.$^{-1}$ which suggested the presence of a *gem*-dimethyl group; this feature was not present in the triols (XVI; R = H) or (XXII), although they showed absorption compatible with the presence of a *C*-methyl group. Oxidation of the alcohol (XXIV) afforded a ketone (XXV), $\nu_{max.}$ 1712 cm.$^{-1}$, which was characterised as the semicarbazone. The ketone reacted with benzaldehyde to give a monobenzylidene derivative, but not a dibenzylidene derivative. These results showed that the hydroxyl group which carried the arylacyl residue is secondary, and suggested that it is present in a cyclohexane ring which, in the fragment (XV; R = H), bears also two




formyl groups in adjacent positions, with one methyl group attached at the same position as one of the two formyl groups, and one exocyclic methylene group. Moreover, it appeared that one, and only one, of the two positions adjacent to the hydroxyl group in the ring was unsubstituted.

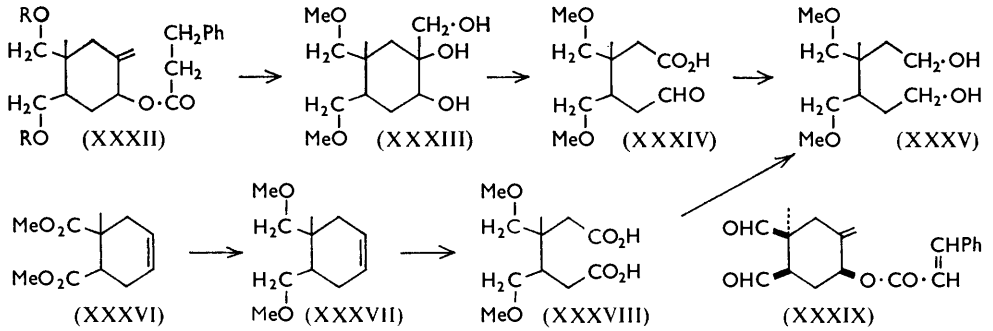
Although the infrared evidence for the presence of the exocyclic methylene group was not convincing, the following chemical evidence placed the matter beyond doubt. The triacetate (XVII; R = R′ = Ac) was converted into the tribenzyl ether (XVII; R = R′ = $CH_2Ph$), and thence, by reaction with osmium tetroxide and then with lithium aluminium hydride, into the crude α-glycol (XVIII; R = $CH_2Ph$). Periodate cleavage gave formaldehyde and a crude keto-compound, catalytic debenzylation of which provided a crystalline keto-triol (XIX), which showed $\nu_{max.}$ 1715 cm.$^{-1}$ (cyclohexanone). The keto-triol reacted with 1 mol. of periodate without loss of carbon, owing to the presence of a cyclic α-ketol system. However, instead of the aldehydo-acid which is the usual product from such a fission, a crystalline neutral product was obtained, containing two hydrogen and one oxygen atoms less than expected. It was formulated as a γ-lactonic hydroxy-aldehyde (XX) on the following grounds. It showed $\nu_{max.}$ (in $CHCl_3$) 3448 (OH), 1786 (γ-lactone), and 2755 and 1736 (CHO) cm.$^{-1}$. Titration with warm alkali confirmed the lactone system; the hydroxyl group was confirmed by the preparation of a crystalline

*p*-nitrobenzoate, and the aldehyde group by the formation of a dimedone derivative. A simpler route to the lactone (XX) was found in the reaction of the triacetate (XVII; R = R′ = Ac) with performic acid, followed by hydrolysis to the crude pentaol (XVIII; R = H). This reduced 2 mol. of periodate, giving the crystalline lactone (XX) and formaldehyde.

These results establish, first, that the triol (XVI; R = H) is a 2-methylenecyclohexanol. The same feature was, in fact, demonstrated in several other ways, of which only the simplest need be mentioned here. Treatment of the triol with dilute hydrochloric acid isomerised it to the 2-methylcyclohexanone (XXIII), which was characterised as the 2,4-dinitrophenylhydrazone. Similar changes,[5] which are due to prototropic shift of the semicyclic methylene double bond, are well known among 2-methylenecyclohexanols and 2-methylenecyclopentanols. Secondly, the results of the previous paragraph show that one of the two formyl groups in the dialdehydes (XV) is situated $\gamma$ to the ring-terminus of the semicyclic methylene double bond. In this way the natures of the ring positions 1, 2, and 6 were defined, and one of the formyl groups was placed at position 4. The remaining formyl group must lie at either 3 or 5; its site, and that of the methyl group, remained to be determined.

This was done by transforming the dialdehyde (XXVI) into a known aromatic compound, a method chosen because it promised to avoid the stereochemical difficulties which might otherwise result from the multiplicity of asymmetric centres. As the first step the dibasic acid (XXVII; R = CO·$CH_2$·$CH_2$Ph) reacted with lead tetra-acetate in pyridine,[6] hydrolysis then giving the dimethylcyclohexenol (XXVIII), characterised as the 3,5-dinitrobenzoate. Oxidation of the free alcohol with chromic oxide in pyridine gave an unconjugated ketone (XXIX) contaminated by small amounts of a conjugated ketone (XXX); the former was isomerised to the latter by treatment with acid, the crude product then showing $\lambda_{max.}$ 226 mμ (ε 8000).

By applying Woodward's rule,[7] the double bond in the conjugated ketone (XXX) is seen to be of the type –CH=CH–, and therefore situated at the 5,6- and not at the 2,3-position. This locates the formyl groups in the dialdehyde (XXVI) at positions 4 and 5, and the remaining methyl group must be at either position 3 or 4. Dehydrogenation of the cyclohexenone (XXX) with palladised charcoal gave 2,4-dimethylphenol (XXXI), isolated as the 3,5-dinitrobenzoate. This establishes position 4 as the site of the unplaced methyl group, and completes the determination of structure.



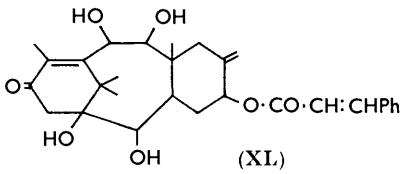

In order to verify the above conclusions, the phenylpropionate-diol (XXXII; R = H) was methylated to the dimethyl ether (XXXII; R = Me). Hydroxylation of the methylene double bond with osmium tetroxide and removal of the ester residue gave the

[5] See, *e.g.*, Mosettig and Nes, *J. Org. Chem.*, 1955, **20**, 884; Djerassi, Smith, Lippman, Figdor, and Herran, *J. Amer. Chem. Soc.*, 1955, **77**, 4800; Dreiding and Hartman, *ibid.*, 1956, **78**, 1216.
[6] Grob, Ohta, Renk, and Weiss, *Helv. Chim. Acta*, 1958, **41**, 1191.
[7] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 72, 76.

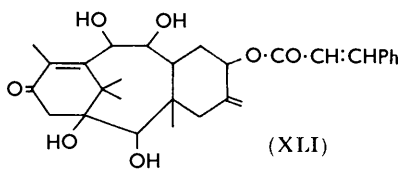
triol (XXXIII), which periodate oxidation converted into the aldehydo-acid (XXXIV). The corresponding diol (XXXV) was obtained crystalline as the di-*p*-nitrobenzoate. A racemic sample of this substance was then prepared synthetically.

Nazarov and Kucherov [8] obtained from the diene addition of butadiene and citraconic anhydride an adduct from which was prepared the diester (XXXVI), the ester groups being *cis*-related. We reduced the diester with lithium aluminium hydride, and prepared from the product the *cis*-di(methoxymethyl) compound (XXXVII). Ozonolysis gave the adipic acid (XXXVIII), the dimethyl ester of which was then reduced to give the racemate of (XXXV). The di-*p*-nitrobenzoate had the same m. p. as the material from the degradation and, more significantly, the infrared solution spectra of the two samples were identical.

The structures of the neutral fragments (XV) and (XXVI) are thus confirmed. The experiments also show that it is probable, although admittedly not certain, that the two formyl groups in them are related *cis* to each other and also to the arylacyloxy-group. This probable relative stereochemistry is embodied in the structure (XXXIX) for the neutral fragment obtained from the cleavage of *O*-cinnamoyltaxicin-I.




(XL)




(XLI)

Two matters arising from the above results require brief mention. First, it was with a knowledge of the main features of the structures of the two cleavage fragments that the suggestion was first [1a] made that taxicin-I is diterpenoid. Secondly, *O*-cinnamoyltaxicin-I has three secondary and one tertiary hydroxyl groups; its fission with two mol. of periodate should generate three formyl and one new keto-group. These, together with the other pre-existing functions, are in fact found in the two cleavage fragments. Few abnormalities or rearrangements have been recorded for periodate cleavages in general, and the present example appears to be normal. The somewhat remarkable structures (XL) and (XLI) must therefore be regarded as serious possible representations of *O*-cinnamoyltaxicin-I. Experiments designed to test their validity are in progress.

## Experimental

Optical rotations were determined for solutions in chloroform except where otherwise stated.

*Periodate Oxidation of* O-*Cinnamoyltaxicin-I and Isolation of the Acid Fragment.*—Solutions of *O*-cinnamoyltaxicin-I (2·0 g.) in ethyl acetate (100 c.c.) and of sodium metaperiodate (4 g.) in water (100 c.c.) were emulsified by continued shaking at room temperature. After 85 min. the ethyl acetate layer was separated, washed with water (5 c.c.), and then extracted with aqueous sodium hydrogen carbonate until free from acidic material (*i.e.*, extracts were no longer coloured yellow). The ethyl acetate solution was kept for the isolation of the neutral fragment as described below. The sodium hydrogen carbonate extracts were combined and acidified with concentrated hydrochloric acid, and the product was isolated with ether. The pale yellow solid (0·64 g.) so obtained was dissolved in the minimum of hot alcohol, and the solution was treated with ether and allowed to crystallise. Recrystallisation from 50% alcohol gave the acid fragment (*5-formyl-4,6,6-trimethylcyclohex-4-ene-1,3-dione*) (I) (0·54 g.) as plates, m. p. 201—202·5° (decomp.) (Found: C, 66·5; H, 6·65%; equiv., 182. $C_{10}H_{12}O_3$ requires C, 66·65; H, 6·7%; equiv., 180).

The neutral *monomethyl ether*, obtained by treating a suspension of this product in ether and tetrahydrofuran with diazomethane, separated from cyclohexane as colourless crystals,

[8] Nazarov and Kucherov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1952, 289.

m. p. 118°, $\lambda_{max.}$ (in EtOH) 324 mμ (ε 6800) (Found: C, 68·0; H, 7·2. $C_{11}H_{14}O_3$ requires C, 68·05; H, 7·3%).

*Conversion of the Acid* (I) *into the Nitrile* (VII).—A solution of the acid (360 mg.) and hydroxylamine hydrochloride (1·05 equiv.) in alcohol (6 c.c.) and pyridine (12 c.c.) was kept at 70° for 18 hr. The cooled solution was diluted with benzene (50 c.c.) and washed with dilute hydrochloric acid and then with water. The benzene solution was then extracted with aqueous sodium hydrogen carbonate; the extract gave a solid when acidified; this was isolated with ether and crystallised from aqueous alcohol. The *oxime* (320 mg.) had m. p. 214·5° (decomp.) (Found: C, 61·55; H, 6·6. $C_{10}H_{13}NO_3$ requires C, 61·55; H, 6·65%). Solutions in 50% alcohol 0·1N in hydrochloric acid had $\lambda_{max.}$ 305 mμ (ε 6200) and those 0·1N in potassium hydroxide had $\lambda_{max.}$ 340 mμ (ε 8900).

The oxime (150 mg.) and acetic anhydride (10 c.c.) were heated together at 100° for 16 hr., and the solvent then removed under reduced pressure. The non-acidic residue was hydrolysed by shaking it for 5 min. with ether (20 c.c.) and 5% aqueous sodium carbonate (20 c.c.). The alkaline layer was then separated and acidified, and the product isolated with ether. The *nitrile* (100 mg.) separated from dilute alcohol as plates, m. p. 223° (Found: C, 67·75; H, 6·2. $C_{10}H_{11}NO_2$ requires C, 67·8; H, 6·3%). In aqueous-ethanolic 0·1N-hydrochloric acid it had $\lambda_{max.}$ 310 mμ (ε 5100); in aqueous-ethanolic 0·1N-potassium hydroxide, $\lambda_{max.}$ 355 mμ (ε 7000).

*Reduction of the Acid* (I) *to the Primary Alcohol* (II).—To a solution of the acid (540 mg.) in water containing sodium hydroxide (2 equiv.) sodium borohydride (70 mg.) was added. Immediately after the solution was decolorised it was acidified and the product was isolated with ether. Crystallisation from ethyl acetate gave the *alcohol* (210 mg.), m. p. 170° (Found: C, 65·7; H, 7·8%; equiv., 182. $C_{10}H_{14}O_3$ requires C, 66·0; H, 7·75%; equiv., 182).

*Reduction of the Alcohol* (II) *to the Deoxy-compound* (III).—Zinc powder (16 g.) was added in portions to a solution of the alcohol (0·68 g.) in acetic acid (70 c.c.), chloroform (35 c.c.), and water (0·5 c.c.). When the zinc had dissolved, water (170 c.c.) was added, and the chloroform phase was separated, washed, and evaporated under reduced pressure. The solid residue crystallised from benzene–methanol, giving crude *4,5,6,6-tetramethylcyclohex-4-ene-1,3-dione* (0·5 g.). After sublimation at 130°/12 mm., it had m. p. 208·5° (Found: C, 72·3; H, 8·4%; equiv., 166. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%; equiv., 166).

*Reduction of the Deoxy-compound* (III) *to the Dihydro-compound* (IV).—The deoxy-compound (600 mg.), in ethyl acetate (80 c.c.) and methanol (20 c.c.) containing 5% palladised charcoal, was shaken with hydrogen until 1·1 mol. had been absorbed (5 hr.). Filtration, evaporation, and crystallisation from ether–light petroleum (b. p. 40—60°) gave the *dihydro-compound* (IV) (400 mg.), m. p. 120·5° (Found: C, 71·45; H, 9·5. $C_{10}H_{16}O_2$ requires C, 71·45; H, 9·6%).

When a solution in aqueous methanol containing formaldehyde was kept overnight, the *methone* separated, having m. p. 142—142·5° (from aqueous methanol) (Found: C, 72·1; H, 9·15. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·25%).

*Reduction of the Acid* (I) *to the Dihydro-compound* (VIII).—To a solution of the acid (500 mg.) in dry pyridine (5 c.c.), zinc dust (500 mg.) was added in one portion, followed by glacial acetic acid (1 c.c.), and the mixture was shaken for 30 min. The solution was then filtered and diluted with benzene (25 c.c.), and acidic material was extracted from it by aqueous sodium hydrogen carbonate, and recovered by acidification and continuous ether-extraction. Crystallisation from acetone–light petroleum (b. p. 60—80°) gave *5-formyl-4,4,6-trimethylcyclohexane-1,3-dione* (350 mg.) as rosettes of needles, m. p. 109—110° (Found: C, 65·9; H, 7·6. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%). In aqueous-ethanolic 0·1N-hydrochloric acid it had $\lambda_{max.}$ 260 mμ (ε 13,200); in aqueous-ethanolic 0·1N-sodium hydroxide, $\lambda_{max.}$ 285 mμ (ε 24,800).

*Degradation of the Compound* (IV) *to an ααα'β-Tetramethylglutaric Anhydride.*—The dihydro-compound (170 mg.), dissolved in water (10 c.c.) containing sodium hydrogen carbonate (170 mg.) was kept for 16 hr. with 0·25M-sodium metaperiodate (25 c.c.). Acidification and extraction with ether provided an oily α-keto-acid (200 mg.), which solidified but could not be crystallised from solvents. The *2,4-dinitrophenylhydrazone* formed needles (from methanol–benzene), m. p. 215—216·5° (Found: C, 48·5; H, 5·1; N, 14·55. $C_{16}H_{20}N_4O_8$ requires C, 48·5; H, 5·1; N, 14·15%).

A portion of the oily keto-acid (350 mg.) in pure chloroform (22 c.c.) was kept overnight with 0·25M-chloroformic lead tetra-acetate (8 c.c.). The mixture was washed with dilute hydrochloric acid and then with water, dried, and evaporated. The residue crystallised from

ether–light petroleum (b. p. 60—80°), giving the *anhydride* (150 mg.), m. p. 71—71·5° (Found: C, 63·25; H, 8·2. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%).

The anhydride (50 mg.) and 2N-sodium hydroxide (2 c.c.) were heated together, and the diluted solution passed through a column of cation-exchange resin (Dowex 50). Evaporation of the filtrate to small volume gave *ααα'β-tetramethylglutaric acid* (VI) (40 mg.), m. p. 127·5—128° (Found: C, 57·7; H, 8·35. $C_9H_{16}O_4$ requires C, 57·4; H, 8·6%).

*Synthesis of ααα'β-Tetramethylglutaric Acid.*—β-Methylene-ααα'-trimethylglutaric acid (Baker's " αβγ-tetramethylglutaconic acid "), prepared by his method,[4] had m. p. 127—128° (lit., 128°), and showed no specific ultraviolet absorption above 205 mμ. A portion (176 mg.), dissolved in ethyl acetate (5 c.c.) and acetic acid (10 c.c.), was ozonised at 0° for 1 hr.; zinc dust (500 mg.) and water (8 c.c.) were then added to the solution, and it was distilled. The distillate contained 54% of the expected amount (1 mol.) of formaldehyde, determined as the dimedone derivative, m. p. 189°.

When the acid (785 mg.), dissolved in acetic acid (10 c.c.) containing Adams platinum catalyst (200 mg.), was shaken with hydrogen, 1·0 mol. was taken up in 2 hr. The product (580 mg.), isolated in the usual manner and crystallised from ether–light petroleum (b. p. 40—60°), had m. p. 124—125° and was contaminated with the corresponding anhydride. A portion (210 mg.) was heated under reflux with acetic anhydride (6 c.c.) for 2 hr.; removal of the solvent and crystallisation from ether–light petroleum gave ααα'β-tetramethylglutaric anhydride as needles (170 mg.), m. p. 72° (Found: C, 63·7; H, 8·25. Calc. for $C_9H_{14}O_3$: C, 63·5; H, 8·3%). It gave no depression of m. p. in admixture with the anhydride from the degradation, and the infrared spectra of the two samples were identical. Reconversion into the acid, m. p. and mixed m. p. 127—129°, was carried out as described above.

*The Crude Neutral Fragment* (XV; R = CO·CH:CHPh).—The ethyl acetate solution of this material, obtained from the fission of *O*-cinnamoyltaxicin-I as described above, was evaporated under reduced pressure, yielding the crude fragment as an unstable oil, which showed $\nu_{max.}$ (in $CHCl_3$) 1710 (formyl and cinnamate C=O) and 1677 (cinnamate C=C) cm.$^{-1}$ and $\lambda_{max.}$ 282 mμ (ε 26,500). Hydrolysis of a portion with cold 2N-potassium hydroxide in aqueous alcohol provided cinnamic acid.

*Preparation of the Diols* (XVI) *and* (XXI).—The freshly prepared ethyl acetate solution containing the crude neutral fragment (XV; R = CO·CH:CHPh) (100 c.c.; from 2 g. of *O*-cinnamoyltaxicin-I) was diluted with alcohol (20 c.c.), and, after the addition of sodium borohydride (200 mg.), it was kept for 15 min. and then acidified with acetic acid and diluted with water (50 c.c.). The water layer was extracted with ether (2 × 50 c.c.), and the ether and the ethyl acetate phase were then combined, washed with dilute hydrochloric acid and with water, and evaporated. The colourless oily residue (1·2 g.), $[\alpha]_D$ +29°, was subjected to counter-current distribution in the system methanol–water–benzene–light petroleum (b. p. 60—80°)–ether (250 : 250 : 75 : 325 : 100), with control measurements of total weight and optical density at 280 mμ. Three peaks were obtained; the material in the second peak formed an oil (700 mg.), $[\alpha]_D^{19}$ +53°. This diol (XVI; R = CO·CH:CHPh) formed a diacetate which after chromatography on neutral, grade II alumina had $[\alpha]_D^{18}$ +70°. It was subjected to reversed-phase chromatography on Whatman No. 3 paper dipped three times in ether containing 3% of paraffin, and with 60% aqueous methanol saturated with paraffin as the mobile phase; with aqueous permanganate as the detecting spray, it gave one spot, of $R_F$ 0·7.

The diol (XVI; R = CO·$CH_2$·$CH_2$Ph) was obtained from *O*-β-phenylpropionyltaxicin-I by similar methods. Acetylation gave the diacetate which had $[\alpha]_D^{19}$ +25°. On reversed-phase chromatography, with the system described above, it showed one spot, of $R_F$ 0·65. Material with the same constants was obtained by hydrogenation of the diacetate of the diol (XVI; R = CO·CH:CHPh) with 5% palladised charcoal in ethyl acetate, the reaction being terminated when 0·98 mol. had been absorbed (75 min.). When this hydrogenation was continued for 18 hr., a total of 1·95 mol. of hydrogen were taken up. The product had $[\alpha]_D^{19}$ +14°. It was the diacetate of the diol (XXI).

The diol (XXI) was obtained from fission of dihydrotaxicin-I β-phenylpropionate by methods similar to those used for the preparation of its two relatives. On acetylation with acetic anhydride in pyridine it gave a diacetate which had $[\alpha]_D^{19}$ +14°.

*The Unsaturated Triol* (XVI; R = H).—The oily diacetate (0·55 g.) of the diol (XVI; R = CO·$CH_2$·$CH_2$Ph), prepared as described above, was kept overnight at room temperature with a solution of sodium hydroxide (0·28 g.) in methanol (10 c.c.). The solution was

neutralised with acetic acid, then evaporated to dryness, and the residue, dissolved in water (4 c.c.), was de-ionised by passage through columns of Dowex 50 and Dowex 2 ion-exchange resins. Evaporation of the eluate and crystallisation from benzene–methanol gave the unsaturated triol (overall yield from *O*-β-phenylpropionyltaxicin-I, 50%), m. p. 111·5—112°, $[\alpha]_D^{19}$ +44° (in alcohol) (Found: C, 64·15; H, 9·6. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·7%), $\nu_{max.}$ (in KCl) 3160, 1849, 1651, 990, and 908 cm.$^{-1}$.

The triol was similarly obtained from the diacetate of the diol (XVI; R = CO·CH:CHPh).

*The Saturated Triol* (XXII).—Similar hydrolysis of the diacetate of the diol (XXI) (0·52 g.) and crystallisation of the product from benzene–methanol gave 4,5-*di*(*hydroxymethyl*)-2,4-*dimethylcyclohexanol* (XXII) (198 mg.), m. p. 130—131°, $[\alpha]_D^{20}$ +25° (in alcohol) (Found: C, 63·7; H, 10·6. $C_{10}H_{20}O_3$ requires C, 63·8; H, 10·7%).

The same triol was obtained by hydrogenation of the above unsaturated triol with Adams platinum catalyst in acetic acid, 1 mol. being absorbed.

The *triacetate*, obtained by acetylation with pyridine and acetic anhydride, followed by chromatographic purification and distillation at 95°/$10^{-3}$ mm., had $[\alpha]_D^{20}$ +23·3° (in alcohol) (Found: C, 61·0; H, 8·35. $C_{16}H_{26}O_6$ requires C, 61·2; H, 8·3%).

*The Dibasic Acid* (XXVII) *and its Derivatives*.—Freshly prepared neutral material (550 mg.) obtained from the periodate oxidation of dihydrotaxicin-I β-phenylpropionate (1 g.) was dissolved in acetone (30 c.c.), and a solution of chromic oxide (365 mg.) in water (19 c.c.) and concentrated sulphuric acid (43 c.c.) was added with shaking. After 15 min. water was added, the solution was extracted with ether, and the acidic fraction of the extract was isolated in the usual manner. *1,5-dimethyl-4-β-phenylpropionyloxycyclohexane-1,2-dicarboxylic acid* (XXVII; R = CO·$CH_2$·$CH_2$Ph) (475 mg.) formed a colourless oil (Found: equiv., 170. $C_{19}H_{24}O_6$ requires equiv., 174).

This acid (390 mg.) and acetic anhydride (8 c.c.) were heated together under reflux for 10 min. The solution was evaporated under reduced pressure, the residue dissolved in ether, and the ether extract washed with sodium hydrogen carbonate solution and with water, dried, and evaporated. The residual oil (315 mg.) showed $\nu_{max.}$ (in $CHCl_3$) 1875 and 1802 cm.$^{-1}$. A portion of this anhydride (50 mg.) was heated under reflux for 30 min. with *p*-toluidine (40 mg.) in benzene (8 c.c.). More benzene was added, and the solution washed with dilute hydrochloric acid and with water, then dried and evaporated. Crystallisation of the residue from aqueous alcohol gave the *mono*-p-*toluidide* (40 mg.) as plates, m. p. 239—240° (decomp.) (Found: C, 71·3; H, 7·0; N, 3·45. $C_{26}H_{31}NO_5$ requires C, 71·35; H, 7·15; N, 3·2%).

A further portion (278 mg.) of the oily dibasic acid was kept at 50° overnight with methanol (10 c.c.) containing 2N-aqueous potassium hydroxide (7 c.c.). The methanol was removed under reduced pressure, and the solution acidified with hydrochloric acid and continuously extracted with ether. Evaporation of the ether and crystallisation from chloroform–acetone gave the 4-*hydroxy-dicarboxylic acid* (90 mg.) as rosettes of needles, m. p. 196—197° (decomp.), $[\alpha]_D^{22}$ −23° (in alcohol) (Found: C, 55·2; H, 7·2; equiv., 109. $C_{10}H_{16}O_5$ requires C, 55·55; H, 7·45%; equiv., 108).

When heated with acetic anhydride it formed an oily product which showed $\nu_{max.}$ 1800 and 1866 (succinic anhydride) and 1767 cm.$^{-1}$ (γ-lactone).

2,4,4,5-*Tetramethylcyclohexanol* (XXIV).—The diol (XXI) (228 mg.), toluene-*p*-sulphonyl chloride (500 mg.), and pyridine (2 c.c.) were kept together at 18° for 3 days. Excess of reagent was decomposed with water, and the solution was diluted with benzene and washed with dilute sulphuric acid and then water. Evaporation of the solvent gave the *ditoluene*-p-*sulphonate* which, after chromatography on alumina, formed an oil (360 mg.) showing no hydroxylic absorption near 3500 cm.$^{-1}$ (Found: S, 9·35. $C_{33}H_{40}O_8S_2$ requires S, 10·2%).

This material (745 mg.), dissolved in benzene (25 c.c.), was treated with a solution of ethanethiol (2·3 c.c.) in t-butyl alcohol (20 c.c.) in which potassium (1·05 g.) had been dissolved. The mixture was kept under reflux for 12 hr. and then at room temperature for 24 hr. Powdered ice was added and the clear solution was extracted with ether. The ether was washed, dried, and evaporated, giving the crude diethylthio-derivative as a yellow oil (276 mg.). It was heated under reflux in a nitrogen atmosphere for 5 hr. with Raney nickel (5 g.) in alcohol (30 c.c.). The filtered solution was evaporated under reduced pressure at room temperature, and the residual oil was chromatographed from benzene on neutral alumina (15 g.). After a small initial fraction (75 mg.), benzene eluted the crystalline alcohol (60 mg.), which was distilled at 55° (bath)/20 mm. The *tetramethylcyclohexanol* (50 mg.) formed long needles, m. p.

49·5°, $[\alpha]_D^{22}$ +30° (Found: C, 76·8; H, 12·8. $C_{10}H_{20}O$ requires C, 76·85; H, 12·9%), $\nu_{max.}$ (in $CHCl_3$) 1379 and 1370 cm.$^{-1}$ (*gem*-dimethyl).

The initial fraction from the above chromatogram was the β-phenylpropionate of the above alcohol, and furnished on hydrolysis a further 30 mg. of material, m. p. 49·5°.

2,4,4,5-*Tetramethylcyclohexanone* (XXV).—The above alcohol (116 mg.) in acetone (2 c.c.) was added to a solution of chromic oxide (55 mg.) in water (3·2 c.c.) and concentrated sulphuric acid (0·75 c.c.). After 5 min. the acetone was removed under reduced pressure, and the solution was extracted with ether. The ethereal extract was washed with sodium hydrogen carbonate solution and with water, then dried and evaporated. Distillation of the residual oil at 80—85° (bath)/14 mm. gave the *tetramethylcyclohexanone* (50 mg.) as an oil, $[\alpha]_D^{21}$ +38° (Found: C, 78·0; H, 11·8. $C_{10}H_{18}O$ requires C, 77·85; H, 11·75%). The *semicarbazone*, prepared in pyridine, separated from aqueous alcohol as needles, m. p. 152—152·5° (Found: C, 62·75; H, 9·9; N, 19·55. $C_{11}H_{21}N_3O$ requires C, 62·5; H, 10·0; N, 19·9%). The oxime (amorphous) was prepared and heated with acetic anhydride; it failed to give a nitrile.

The above ketone (80 mg.), ethanol (0·5 c.c.), 8% aqueous sodium hydroxide (0·3 c.c.), water (0·25 c.c.), and benzaldehyde (0·065 c.c.) were shaken together overnight, and finally heated to 100° for 10 min. The cooled mixture was diluted with water and ether, and the ether phase was washed with saturated aqueous sodium hydrogen sulphite and then with water, dried, and evaporated. Chromatography on alumina from benzene gave the crude yellow monobenzylidene derivative, $\lambda_{max.}$ 291 mμ (ε 12,000), $\nu_{max.}$ 1675 cm.$^{-1}$.

*Degradation of the Triol* (XVI; R = H) *to the Lactonic Aldehyde* (XX).—(*a*) The triol (277 mg.) was acetylated with pyridine (20 c.c.) containing acetic anhydride (3 c.c.) for 16 hr. at 60°, and the cooled solution kept for ½ hr. with alcohol (10 c.c.) in order to decompose the excess of reagent. After isolation in the usual way, the product was purified by chromatography on neutral alumina (grade II) from benzene and then distilled at 150°/0·06 mm. The *triacetate* (380 mg.) formed a colourless oil (Found: C, 61·45; H, 7·55. $C_{16}H_{24}O_6$ requires C, 61·5; H, 7·75%).

The triacetate (800 mg.), dissolved in dry sulphur-free toluene (100 c.c.), was stirred vigorously and heated under reflux for 18 hr. with benzyl chloride (3·6 c.c.) and powdered potassium hydroxide (11·5 g.). The cooled mixture was then stirred and diluted slowly with water, after which the toluene phase was separated, washed with water, and concentrated to 20 c.c., and impurities were removed by passage of a current of steam. The cooled solution was extracted with ether, evaporation of which gave the crude tribenzyl ether (XVII; R = R′ = $CH_2Ph$) (760 mg.). After chromatographic purification it showed no hydroxylic or ester absorption in the infrared spectrum. A portion (700 mg.) was dissolved in ether (50 c.c.) containing osmium tetroxide (500 mg.) and kept under reflux for 3 days. The ether was then evaporated, and to a stirred solution of the residue in tetrahydrofuran (50 c.c.) lithium aluminium hydride (100 mg.) was added, and the mixture was stirred and heated under reflux for 3 hr. It was then cooled and ethyl acetate (3 c.c.) was added cautiously with stirring. Solvents were then removed under reduced pressure and the residue was distributed between 2N-sulphuric acid (20 c.c.) and benzene (20 c.c.). The benzene extract was washed with water, dried, and chromatographed on neutral alumina (grade II; 200 g.), from which benzene eluted unchanged tribenzyl ether (200 mg.). Elution with benzene containing 0·2% of alcohol gave the crude oily diol (XVIII; R = $CH_2Ph$) (200 mg.).

A solution of the diol (400 mg.) in ethyl acetate (10 c.c.) was shaken for 18 hr. with 0·25M-sodium metaperiodate (10 c.c.). The mixture was then warmed to 40° whilst a current of nitrogen was passed through it and into a solution of 2,4-dinitrophenylhydrazine in dilute hydrochloric acid. After 30 min. the formaldehyde 2,4-dinitrophenylhydrazone which had precipitated was collected and recrystallised to give material (10 mg.), m. p. and mixed m. p. 166°. The ethyl acetate layer was then separated from the original reaction mixture and the product isolated by evaporation and purified by chromatography. It formed an oil (150 mg.) which showed no hydroxyl band near 3500 cm.$^{-1}$, but a strong band near 1724 cm.$^{-1}$. Hydrogenation (uptake 2·8 mol.) in ethyl acetate (5 c.c.) over 5% palladised charcoal (50 mg.), and isolation in the usual way, gave an oil (50 mg.). Crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave 2-*hydroxy*-4,5-*di*(*hydroxymethyl*)-5-*methylcyclohexanone* (XIX) (35 mg.), m. p. 74—75°, $[\alpha]_D^{18}$ +35° (Found: C, 57·95; H, 8·5. $C_9H_{16}O_4$ requires C, 57·4; H, 8·6%).

This α-ketol (20 mg.) was kept with 0·25M-sodium metaperiodate (1 c.c.) and water (4 c.c.)

for 18 hr.; the solution was then evaporated to dryness under reduced pressure, and the residue extracted thoroughly with chloroform. Evaporation of the extract and crystallisation of the residue from chloroform–light petroleum (b. p. 40—60°) gave the lactonic aldehyde (XX) (10 mg.), m. p. 109—109·5°, identical with material prepared as in (*b*) below.

(*b*) The triacetate (XVII; R = R′ = Ac) (400 mg.) was kept at room temperature for 2 days with 98% formic acid (5 c.c.) and 40% hydrogen peroxide (0·6 c.c.). After cautious addition of sodium metabisulphite (0·4 g.), the formic acid was removed under reduced pressure, and the residue was distributed between water (8 c.c.) and ether (30 c.c.). The ether-soluble material was hydrolysed with sodium hydroxide (1 g.) in methanol (10 c.c.) and water (2 c.c.) at room temperature for 18 hr. The methanol was then removed under reduced pressure, and the residual solution was diluted with water and passed through a cation-exchange column (Dowex-50; 10 g.). Evaporation of the aqueous eluate gave the crude pentaol (XVIII; R = H) (300 mg.).

Its solution in water (35 c.c.) and 0·25M-sodium metaperiodate (15 c.c.) was kept for 16 hr., after which 1·9 mol. of the oxidant had been reduced. The presence of formaldehyde in the solution was shown by its removal in a current of nitrogen and formation of the 2,4-dinitrophenylhydrazone (60 mg.), m. p. 166°. The solution from which the formaldehyde had been removed was evaporated to dryness under reduced pressure; extraction of the residue with chloroform gave an oil, which crystallised from chloroform–light petroleum (b. p. 40—60°), giving the *lactonic aldehyde* (XX) (50 mg.), m. p. 109—109·5°, $[\alpha]_D^{18}$ +20° (Found: C, 58·05; H, 7·4. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%). The lactone (7·5 mg.) and 0·05N-sodium hydroxide (2·2 c.c.) were kept at 100° for 2 hr. and the excess of alkali determined by titration (alkali consumed by the lactone: 1·0 equiv.).

The *dimedone derivative* of the lactonic aldehyde separated from aqueous alcohol and had m. p. 178—179° (Found: C, 66·35; H, 8·0. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·1%). The p-*nitrobenzoate* of the lactonic aldehyde, crystallised from ethyl acetate–light petroleum (b. p. 60—80°), had m. p. 190° (Found: C, 57·2; H, 5·2; N, 4·3. $C_{16}H_{17}NO_7$ requires C, 57·3; H, 5·1; N, 4·2%).

*Isomerisation of the Methylenecyclohexanol* (XVI; R = H) *to* 4,5-*Di*(*hydroxymethyl*)-2,4-*dimethylcyclohexanone* (XXIII).—The triol (XVI; R = H) (100 mg.) and a saturated solution of 2,4-dinitrophenylhydrazine in 0·5N-hydrochloric acid (10 c.c.) were kept together for 20 hr. The 2,4-*dinitrophenylhydrazone* (10 mg.) was collected and recrystallised from aqueous methanol; it had m. p. 128° (Found: C, 52·6; H, 5·55. $C_{16}H_{22}N_4O_6$ requires C, 52·5; H, 6·05%).

*The Dimethylcyclohexenol* (XXVIII).—A solution of the dibasic acid (XXVII; R = $CO{\cdot}CH_2{\cdot}CH_2Ph$) (350 mg.) in dry benzene (10 c.c.) containing pyridine (0·16 c.c.) was heated with lead tetra-acetate (470 mg.) under reflux in a nitrogen atmosphere for 4½ hr. It was then cooled and diluted with benzene, filtered, and washed successively with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, then dried and evaporated. The neutral oil (219 mg.) remaining contained *ca.* 55% of the required unsaturated ester, as shown by titration with perbenzoic acid. Hydrolysis of this material (283 mg.) with aqueous-methanolic potassium hydroxide gave an oil which was kept overnight in pyridine (2 c.c.) with 3,5-dinitrobenzoyl chloride. The product, isolated in the usual manner, was chromatographed on neutral alumina (grade II; 20 g.) from benzene; elution with benzene, evaporation, and crystallisation from light petroleum (b. p. 60—80°) gave the 3,5-*dinitrobenzoate* (140 mg.) of 4,6-dimethylcyclohex-3-enol as clusters of needles, m. p. 164·5—166°, $[\alpha]_D^{20}$ +44° (Found: C, 56·1; H, 5·0. $C_{15}H_{16}N_2O_6$ requires C, 56·25; H, 5·05%).

*Preparation and Dehydrogenation of the Dimethylcyclohexenone* (XXX).—The above dimethylcyclohexenol (190 mg.; obtained by hydrolysis of the pure 3,5-dinitrobenzoate) was kept in pyridine (5 c.c.) with chromic oxide (315 mg.) for 12 hr. After dilution with water, isolation with ether gave the crude cyclohexenone (XXIX) (140 mg.), $\nu_{max.}$ (in $CHCl_3$) 1712 cm.$^{-1}$; it was contaminated by a little of the conjugated isomer, since it showed a weak band at 226 mμ (ε 1000). When heated under reflux for 10 min. in 95% alcohol (5 c.c.) containing one drop of dilute hydrochloric acid, it was isomerised, and removal of the solvents under reduced pressure gave the conjugated cyclohexenone (XXX) (130 mg.) as an oil, $\lambda_{max.}$ 226 mμ (ε 8000), $\nu_{max.}$ (in $CHCl_3$) 1672 cm.$^{-1}$. This was heated under reflux in *p*-cymene (10 c.c.) with 5% palladised charcoal (60 mg.) in a current of nitrogen for 4 hr. The filtered solution was diluted with light petroleum (b. p. 60—80°) and extracted with 2N-aqueous sodium hydroxide (3 × 5 c.c.). The alkaline phases were combined and acidified, and the product was isolated with ether. Evaporation of the ether gave 2,4-dimethylphenol as an oil (40 mg.). Its infrared

spectrum (film) was identical with that of authentic material. The 3,5-dinitrobenzoate, prepared in the usual manner, separated from alcohol as needles, m. p. and mixed m. p. 167° (Found: C, 57·1; H, 3·8; N, 8·8. Calc. for $C_{15}H_{12}N_2O_6$: C, 56·95; H, 3·8; N, 8·85%).

*Degradation of the Diol* (XXXII; R = H) *to the Diol* (XXXV).—The diol (XXXII; R = H) (840 mg.) and freshly prepared silver oxide (10 g.) were kept together in boiling methyl iodide; further amounts of methyl iodide (2 × 5 c.c.) and silver oxide (2 × 2 g.) were added after 10 and 20 hr. After a total of 30 hr. the cooled mixture was diluted with ether (100 c.c.) and filtered. Evaporation and chromatography of the product on grade 11 alumina separated the monomethyl ether from the dimethyl ether; the former was remethylated to give the latter (total, 350 mg.). Its infrared spectrum showed no hydroxylic absorption.

The dimethyl ether (400 mg.) was kept with osmium tetroxide (500 mg.) in boiling ether (50 c.c.) for 3 days. The ether was then removed and the product was stirred under reflux in tetrahydrofuran (150 c.c.) to which lithium aluminium hydride (100 mg.) had been added. After 3 hr. the excess of the latter reagent was decomposed by ethyl acetate (3 c.c.), the solvents were removed, and the product was distributed between ether (20 c.c.) and 2N-sulphuric acid (20 c.c.). The ethereal layer was washed with water, dried, and evaporated to give the crude triol (XXXIII) as an oil (100 mg.). Its solution in ethyl acetate (5 c.c.) was shaken overnight with 0·25M-sodium metaperiodate (5 c.c.). The presence of formaldehyde was then shown in the usual manner. Evaporation of the ethyl acetate layer gave an oil (90 mg.) which was kept for 30 min. in acetone (5 c.c.) with chromic oxide (1 equiv.). The acetone was evaporated, and ether was added; extraction with sodium hydrogen carbonate removed the acidic product which was recovered by acidification and continuous extraction with ether. Since the crude acid did not crystallise, it was converted into the crude methyl ester (30 mg.) with diazomethane, and reduced in the normal manner with lithium aluminium hydride in ether. The crude 3,4-di(methoxymethyl)-3-methylhexane-1,6-diol (XXXV) so obtained reacted with *p*-nitrobenzoyl chloride (100 mg.) in pyridine (3 c.c.), giving the *di*-p-*nitrobenzoate* (30 mg.) (from alcohol), m. p. 122°, $[\alpha]_D^{18}$ +15° (Found: C, 57·85; H, 5·9; N, 5·3. $C_{25}H_{30}N_2O_{10}$ requires C, 57·9; H, 5·8; N, 5·4%).

*Synthesis of the Racemic Diol* (XXXV).—*cis*-1-Methylcyclohex-4-ene-1,2-dicarboxylic acid (9 g.) was treated with ethereal diazomethane, and the neutral product (9·2 g.) was isolated in the usual manner and purified by distillation at 100°/2 mm. The dimethyl ester (9 g.) was reduced with lithium aluminium hydride (2 g.) in ether (100 c.c.) under reflux for 3 hr., and the product, isolated in the usual way, crystallised from alcohol, giving 4-*methyl*-cis-4,5-*di*(*hydroxymethyl*)*cyclohexene* (2·6 g.), m. p. 68° (Found: C, 69·35; H, 10·05. $C_9H_{16}O_2$ requires C, 69·2; H, 10·1%). Methylation with methyl iodide and silver oxide in the usual manner gave the *dimethyl ether* (XXXVII) as an oil (Found: C, 72·4; H, 10·65. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·9%). It showed no hydroxylic absorption.

The dimethyl ether (1 g.), in ethyl acetate (50 c.c.), was ozonised at 0°, and the ozonide, obtained by removal of the solvent under reduced pressure, was decomposed by dissolution in acetic acid (20 c.c.) containing 30% hydrogen peroxide (1 c.c.). After the solution had been kept for 18 hr. it was worked up in the usual manner, and the acidic product (800 mg.) was separated from neutral material. This crude dibasic acid did not crystallise, so it was esterfied and reduced in a manner similar to that used for the optically active material described above. The di-*p*-nitrobenzoate of the racemic diol (XXXV) had m. p. 120—121° (Found: C, 58·0; H, 5·75; N, 5·4%). Its infrared spectrum (5% in chloroform) was identical with that of the optically active material (5% in chloroform).

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