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HEARTWOOD CONSTITUENTS OF *SCIADOPITYS VERTICILLATA SIEB. et ZUCC.*—I

THE CONSTITUTION OF SCIADIN

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Abstract—Extensive investigations on the constitution of sciadin, a new diterpenoid bitter principle, are reported. The structure Ie is proposed for sciadin and the isolation of a new diterpenoid ester is also described.

THE wood of *Sciadopitys verticillata Sieb. et Zucc.*, endemic to the central and the western parts of Japan, has long been used for various purposes, because of its high durability. In earlier work on the essential oil of the leaf and the wood of this species, Kawamura,[1] demonstrated the presence of cedrene, cedrol, phyllocladene and diterpene-X $C_{20}H_{32}O$, m.p. 135°. Later Kondo[2] isolated from a methanolic extract of the wood a neutral compound, $C_{20}H_{24}O_4$, m.p. 160°, containing a lactonic group, and further investigations on this compound named sciadin have been carried out with Professor Kondo's kind consent. During the course of this work another new diterpenoid ester $C_{21}H_{34}O_4$, m.p. 108·5°, named methyl sciadopate, was isolated and its chemical structure will be discussed later. In the present paper, Ie is proposed for sciadin, the diterpenoid bitter principle.

Sciadin gives a positive Ehrlich test and shows the characteristic I.R. absorption bands of a furan ring (1636, 1607, 1505, 870 cm^{-1}),[3] a vinylidene group (1636, 894 cm^{-1}) and a lactonic group (1736 cm^{-1}). On hydrogenation over Adams' catalyst in acetic acid, sciadin absorbs about 3·6 moles hydrogen, but in the presence of ethanol as solvent dihydrosciadin (II) is produced after absorption of only one mole of hydrogen. The I.R. (3175, 1492, 879, 817 cm^{-1}) and U.V. spectra (λ_{max} = 210 mμ:ε 5840)[4] as well as a positive Ehrlich test also suggest the presence of the furan ring but not of the vinylidene group.

Ozonolysis of dihydrosciadin followed by methylation yields the methyl ester of a C-17 acid (III) the I.R. spectrum of which and a negative Ehrlich test indicate the absence of a furan ring. Similar treatment of sciadin with ozone yields formaldehyde, identified by its dimedone derivative and the methyl ester of a C-16 ketoacid (IV) which involves a six-membered ring ketone according to I.R. spectral data (1762, 1743,1710 cm^{-1}) and the formation of a 2,4-dinitrophenylhydrazone.

Saponification of sciadin with ethanolic potash yields sciadinic acid (V) which may

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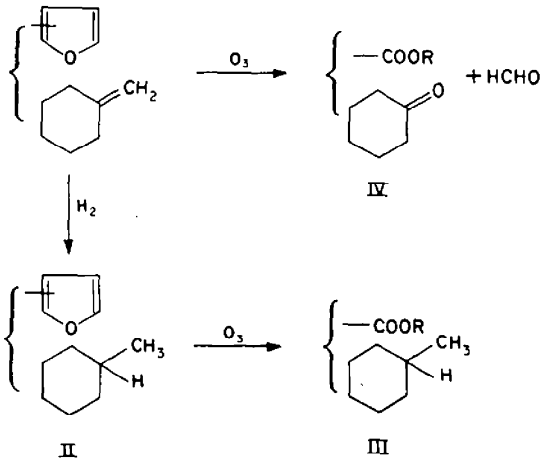
[1] J. Kawamura, *Bull. For. Exp. Sta. Meguro* **31**, 93 (1931).

[2] T. Kondo. Unpublished.

[3] T. Kubota, *Tetrahedron* **4**, 68 (1958).

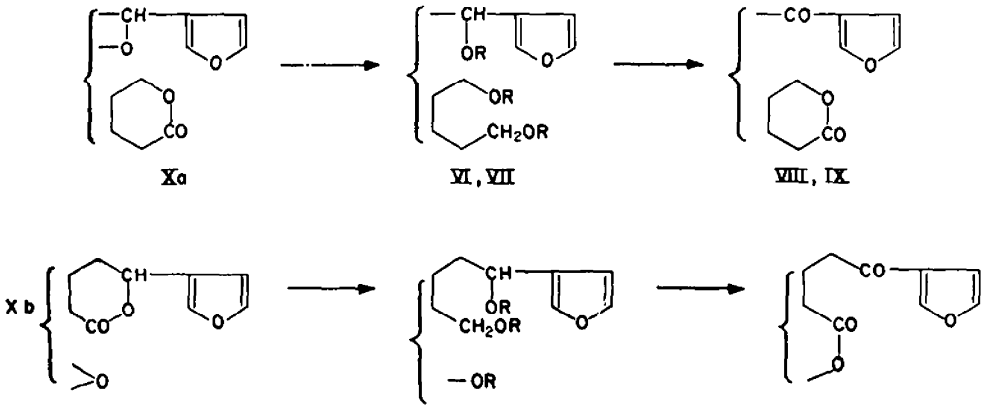
[4] T. Tokoroyama, *Nippon Kagaku Zassi* **79**, 314 (1958).



be reconverted into the original lactone not only on heating at its melting point but also during recrystallization from dilute methanol. This lactone was also reformed during an attempted methylation of the acid with ethereal diazomethane and acetylation with acetylchloride in pyridine.

On the other hand, sciadin shows no I.R. absorption band due to an hydroxyl group and does not react with any carbonyl reagents. This probably indicates that the fourth oxygen atom in the molecule of sciadin is present as an ethereal linkage. Lithium aluminum hydride erduction of sciadin and of dihydrosciadin give gelatinous products which on benzoylation furnish tribenzoates $C_{41}H_{42}O_7$ (VI) and $C_{41}H_{44}O_7$ (VII) respectively. During these reductions the three oxygen atoms (excluding one in the furan ring) appear to be reduced to triols, which when oxidized with chromic acid in pyridine, yield a ketolactone $C_{20}H_{24}O_4$ (VIII) and a dihydroketolactone $C_{20}H_{26}O_4$ (IX) respectively. The I.R. and U.V. spectra (λ_{max} = 254 mμ; ε 3,600)[5] and the negative Ehrlich test[6] suggest the presence of a δ-lactone and a β-furyl ketone system, which is proved later in this paper.

These observations indicate that sciadin contains one of two combined groupings,

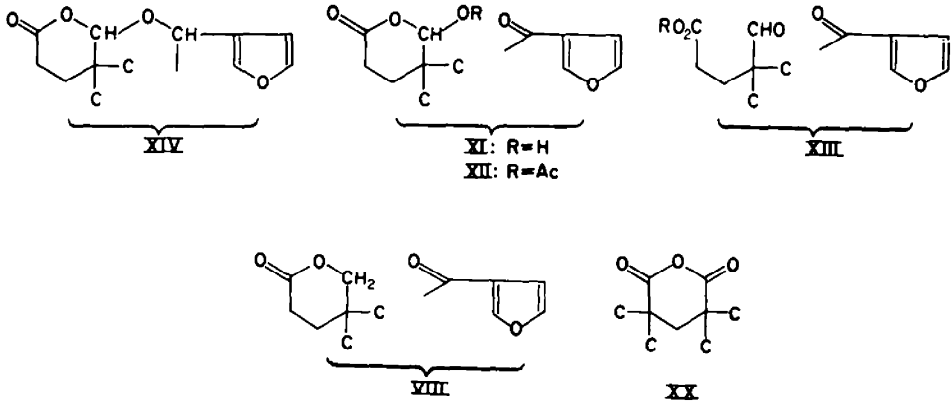


[5] T. Kubota. Private communication.

[6] T. Kubota and K. Naya, *Nippon Kagaku Zassi* 77, 86 (1956); T. Tokoroyama *loc. cit.*

Xa and Xb. The latter type is well known, readily undergoes hydrogenolysis to afford a saturated acid.[7] As sciadin does not yield even a trace of acidic compound on hydrogenation under the same conditions as described in the literature,[7] the Xb grouping is probably absent. Moreover, the following experiments give positive evidence for the presence of the Xa grouping.

Sciadinic acid, on chromic acid oxidation in pyridine, yields the ketolactol $C_{20}H_{24}O_5$ (XI) which reduces Fehling's solution and gives a positive tetrazolium chloride test. Its I.R. and U.V. spectra indicate the presence of a lactol and a β-furyl ketone group. Its monoacetate (XII) gives a negative tetrazolium chloride test and exhibits an abnormaly high frequency of lactonic carbonyl absorption band (1771 cm^{-1}) in comparison with those of sciadin (1736 cm^{-1}), dihydrosciadin (1728 cm^{-1}), the ketolactone (VIII; 1737 cm^{-1}) and the ketolactol (XI; 1696 cm^{-1}). This is apparently due to its lactol-acetate structure. On methylation with ethereal diazomethane the ketolactol affords the aldehyde-ester $C_{21}H_{28}O_5$ (XIII) the I.R. spectrum of which suggests the presence of an aldehyde grouping (2752, 1716 cm^{-1}) and an ordinary methyl ester (1730 cm^{-1}). The ester (XIII) gives a precipitate with 2,4-dinitrophenylhydrazine but none with silver oxide, and, therefore, the aldehyde group must be in a hindered position. On treatment with sodium borohydride in an alkaline medium the ketolactol (XI) affords the ketolactone (VIII). As a result of these experiments a partial structure of sciadin may be represented as XIV.



This was further confirmed by similar experiments carried out on dihyrosciadin as follows. Saponification of dihydrosciadin gives amorphous dihydrosciadinic acid, which on chromic acid oxidation in pyridine furnishes the corresponding dihydroketolactol $C_{20}H_{26}O_5$ (XV), a ketoanhydride $C_{20}H_{24}O_5$ (XVI) as well as dihydrosciadin. This ketolactol (XV) was derived from the monoacetate (XVII) and the aldehyde-ester (XVIII). The latter in its N.M.R. spectrum shows characteristic peaks of aldehyde (τ = 0·00) and ester groupings (τ = 6·35). The ketoanhydride (XVI) was also obtained after oxidation of dihydro-ketolactol (XV) with chromic acid in acetic acid and was unexpectedly fairly resistant to alkali but finally reacted with two moles to afford the viscous oil (XIX) which was reconverted into the ketoanhydride (XVI) although in

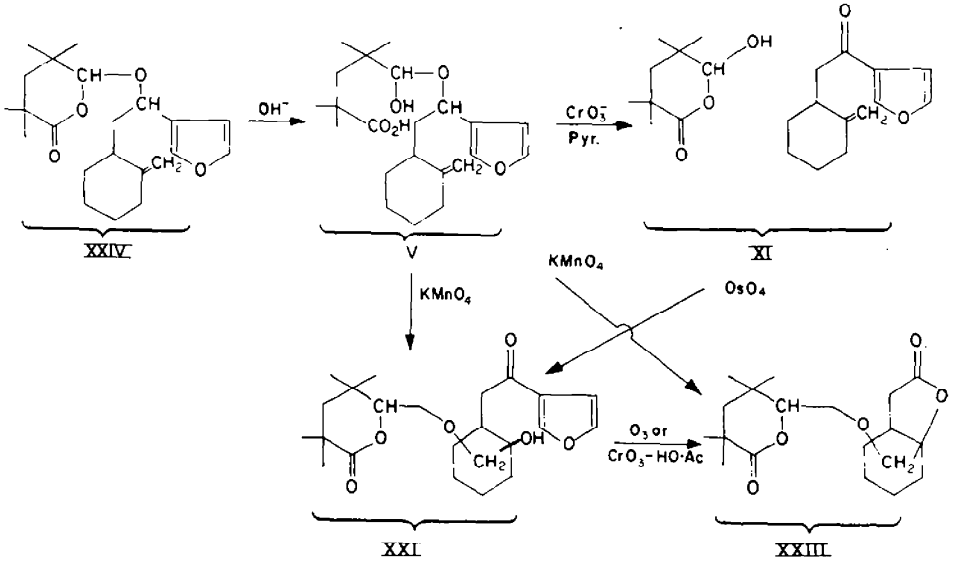
[7] A. Melera, K. Schaffner, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **40**, 1420 (1957); D. H. R. Barton and D. Elad, *J. Chem. Soc.* 2085 (1956).

very low yield. The stability in alkali may be attributed to the steric hindrance as shown in XX, since the I.R. absorption bands of this ketoanhydride (1787, 1759 cm^{-1}) are in good accord with those of glutaric anhydride.

Permanganate oxidation of sciadinic acid in bicarbonate solution affords the hydroxyketolactone $C_{20}H_{24}O_6$ (XXI), which reacts with one mole of alkali and again yields the starting material on acidification. Its I.R. and U.V. spectra and also a negative Ehrlich test substantiate the presence of β-furyl ketone. The hydroxyketolactone (XXI) is not acetylated by acetic anhydride and pyridine, but gives a low yield of monoacetate (XXII) with boiling acetic anhydride and sodium acetate. Its I.R. spectrum indicates the absence of a hydroxyl group. Furthermore, the hydroxyketolactone (XXI) is neither oxidized with chromic acid in pyridine nor dehydrated with phosphoryl chloride or thionyl chloride in pyridine. These facts are in agreement with the presence of a hydroxyl group attached to a bridge-head.

Thus the hydroxyketolactone (XXI) has β-furyl ketonic, δ-lactonic and tertiary alcoholic groupings. A remaining oxygen atom, as yet without characterization, may be present in the molecule as a ketone because of the occurrence of three carbonyl absorption bands (1760, 1728, 1673 cm^{-1}), although it does not react with any carbonyl reagents.

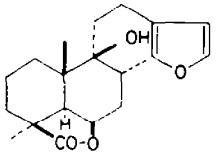
On the other hand, ozonolysis or, better, chromic acid oxidation in acetic acid of the hydroxyketolactone (XXI) gives a fully saturated dilactone $C_{16}H_{20}O_5$ (XXIII), the I.R. and U.V. spectra of which demonstrate the presence of a δ- and γ-lactone (1772–8 cm^{-1}, superimposed) but not of an hydroxyl and a β-furyl ketone. Reaction with two moles of alkali on hydrolysis and the reformation on subsequent acidification prove the presence of two lactonic groups. The newly formed lactonic group should therefore be five-membered. The dilactone (XXIII) is also produced by direct permanganate oxidation of sciadinic acid (V). Since this dilactone (XXIII) does not react with carbonyl reagents and shows no characteristic absorption in the U.V. region, it is concluded that the oxygen atom in question in the molecule of the dilactone (XXIII)



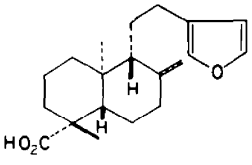
as well as the hydroxyketolactone (XXI) must be present as an ether linkage in spite of the occurrence of three carbonyl absorption bands (1760, 1728, 1673 cm^{-1}) in the I.R. spectra of the hydroxyketolactone and of two bands (1772–8, 1737 cm^{-1}) in that of the dilactone. Consequently, it was assumed that, on permanganate oxidation of sciadinic acid, the vinylidene group is first attacked to afford the glycol, the primary alcoholic group of which could form a new lactol ether. This was confirmed by treatment of the ketolactol (XI) with osmum tetroxide to afford a neutral product identical with the hydroxyketolactone (XXI). These results are incorporated in the partial structure (XXIV) for sciadin.

It is interesting to note that the frequencies of the lactonic carbonyl absorption bands of the lactol-ethers in sciadin (1736 cm^{-1}) and dihydrosciadin (1728 cm^{-1}) are too low for the compounds to be regarded as δ-lactol-ethers, although the bands in the hydroxyketolactone (XXI) (1760 cm^{-1}), the acetoxyketolactone (XXII; 1759 cm^{-1}), the dilactone (XXIII; 1772-8 cm^{-1}) and the methyl esters of C-17 acid (III) (1750 cm^{-1}) and C-16 ketoacid (IV; 1762 cm^{-1}) show reasonable values.

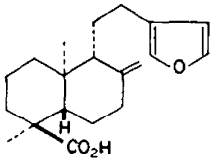
Based on the analytical results and the determination of the functional groups mentioned above, it is concluded that sciadin contains a bicarbocyclic ring in the molecule. In order to confirm this, sciadin was first reduced with lithium aluminum hydride to a gelatinous triol, which was hydrogenated in acetic acid over Adams' catalyst. Subsequent oxidation of the hydrogenation product with chromic acid in pyridine furnished an oil, which was reduced by the Clemensen procedure and the



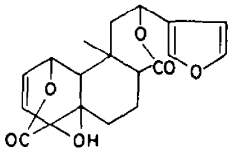
XXV



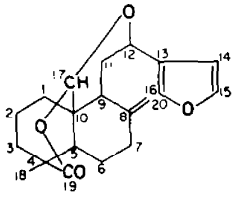
XXVI



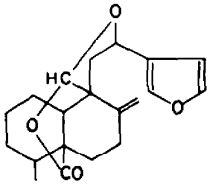
XXVII



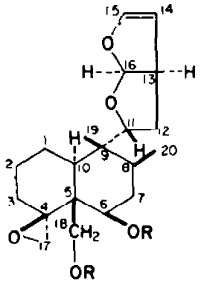
XXVIII



Ia



Ib



XXIX

product dehydrogenated with selenium to afford a small amount of an oil, which was identical with 1,2,5-trimethylnaphthalene. This suggests that sciadin has the manool type skeletone, and therefore the structure is probably very similar to the known furanoid diterpenes such as marrubiin (XXV),[8] danielic acid (XXVI),[9] polyalthic acid (XXVII)[10] and columbin (XXVIII).[11]

There are therefore, only two plausible structures (Ia and Ib) for sciadin, the former of which is favoured for the following reasons. The N.M.R. spectrum of sciadin exhibits a sharp singlet (τ = 8·77) indicating the presence of only one tertiary methyl group attached to the carbon atom adjacent to a carbon which carries an oxygen such as the C-4 methyl group in many resin acids, aldehydes or alcohols.[12] The spectrum also provides proof of the presence of a β-substituted furan (τ = 2·60, 3·53)[13] and of a proton (τ = 4·50) attached to a carbon carrying two oxygen atoms such as the C-16 proton of clerodin derivatives (XXIX).[14] Sharp singlets (τ = 8·76, 8·78) due to the tertiary methyl group were also demonstrated in the spectra of dihydrosciadin and the dihydro-aldehyde ester. Fine peaks (τ = 5·17–4·99) due to the vinylidene group in sciadin are absent in the spectrum of dihydrosciadin. This information clearly shows that the formula Ia is preferable to Ib as the possible structure of sciadin.

This is further supported by the fact that sciadin, on treatment with hydrogen chloride gas, is converted into anhydrosciadin $C_{20}H_{22}O_3$ (XXX). Anhydrosciadin gives a less positive Ehrlich test than either sciadin or dihydrosciadin. Its I.R. spectrum indicates the presence of an aromatic nucleus and of a γ-lactone but not a β-substituted furan. Further, its U.V. spectrum is similar to that of benzofuran.[15] It is well known that on ozonolysis a benzofuran derivative gives a salicylaldehyde derivative.[16] Anhydrosciadin (XXX) was ozonized to a norphenol $C_{19}H_{22}O_4$ (XXXI), which gives a yellow colour with alkali, purple with ferric chloride and an orange precipitate with 2,4-dinitrophenylhydrazine similar to salicylaldehyde. Its I.R. spectrum confirms the presence of a chelated hydroxyl (3 μ region, weak and very broad) and a carbonyl group conjugated to an aromatic nucleus (1674 cm^{-1}). Its U.V. spectrum in neutral as well as in alkaline solution is in keeping with that of salicylaldehyde[17] but not with that of *o*-hydroxyacetophenone. Thus the accumulated evidence supports the presence of a salicylaldehyde type structure in the norphenol (XXXI) and accordingly the presence of a benzofuran nucleus in anhydrosciadin (XXX). Hydrolysis of anhydrosciadin with potassium hydroxide in diethylene glycol, is accompanied by simultaneous

[8] W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward and T. F. Holley, *J. Chem. Soc.* 2540 (1953); *Chem. & Ind.* 772 (1955).

[9] J. Haeuser, R. Lombard, F. Lederer and G. Ourisson, *Tetrahedron* **12,** 205 (1961).

[10] K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy and N. Viswanathan, *Helv. Chim. Acta* **44,** 1040 (1961).

[11] D. H. R. Barton and D. Elad, *J. Chem. Soc.* 2085, 2090 (1956).

[12] J. C. W. Chien, *J. Amer. Chem. Soc.* **82,** 4762 (1960); C. Enzel, *Acta Chem. Scand.* **15,** 1303 (1961); and Refs 9 and 10.

[13] E. J. Corey, G. Slomp, Sukh Dev, S. Tobinaga and R. Glazier, *J. Amer. Chem. Soc.* **80,** 1204 (1958).

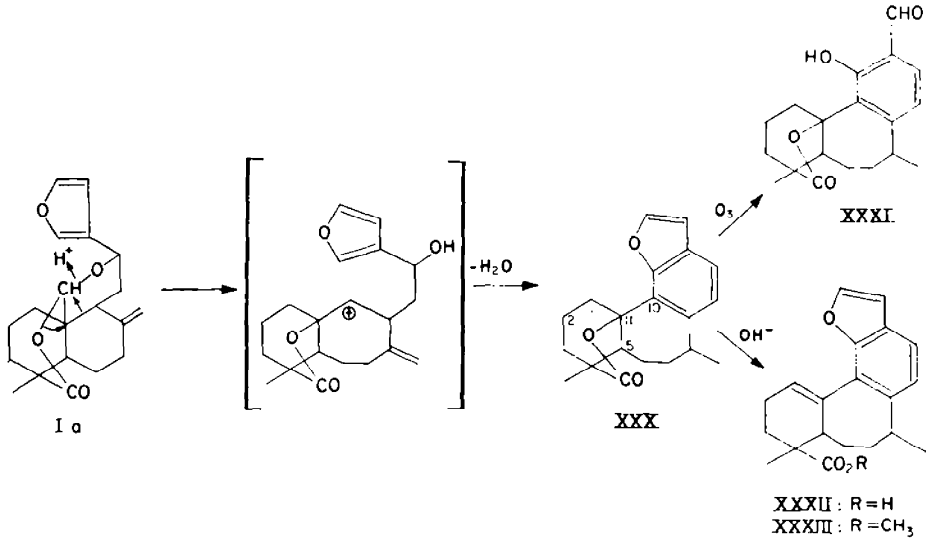
[14] D. H. R. Barton, H. T. Cheung, A. D. Cross, L. M. Jackman and M. Martin-Smith, *J. Chem. Soc.* 5061 (1961).

[15] R. A. Friedel and M. Orchin, *Ultraviolet spectra of aromatic compound*, Fig. 191. Wiley, New York (1951).

[16] A. Wacek, H. O. Eppinger and A. Bezard, *Ber. Dtsch. Chem. Ges.* **73,** 521 (1940).

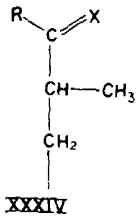
[17] J. M. Vandenbelt, J. Forsyth and A. Garrett, *Indust. Engng. Chem.* (Anal.) **17,** 235 (1940).

dehydration of the lactonic hydroxyl to bisanhydrosciadinic acid $C_{20}H_{22}O_3$ (XXXII). The I.R. spectrum of its methyl ester (XXXIII) shows the absence of an hydroxyl group. Since dehydration takes place with ease under conditions of saponification, the lactonic hydroxyl group must be tertiary and attached to a carbon atom adjacent to the aromatic nucleus. In the U.V. spectrum of the bisanhydro-compound, all maximum absorptions show increased intensities, in comparison with those of anhydrosciadin, but only slight shifts, on the whole, to the longer wavelengths. This may be attributed to the double bond between C-11 and C-1 which owing to steric hindrance cannot conjugate with the aromatic nucleus on the same plane. Based on these facts, the formation of anhydrosciadin (XXX) from sciadin (Ia) may be formulated as follows:

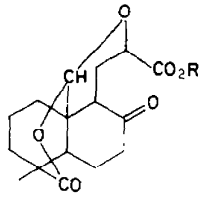


The mechanism of the first step of the reaction is similar to that of hexahydrolimonilic acid to isohexahydrolimonilic acid.[18] It is not yet certain whether the newly formed double bond in bisanhydrosciadinic acid (XXXII) is present at C(11-1) or C(11-5), but the former may be more likely because of the difficulty of decarboxylation of the acid and because of the I.R. absorption band (827 cm^{-1}) of the methyl ester (XXXIII). The N.M.R. spectrum of anhydrosciadin provides positive proof for the proposed structure (XXX). It shows the presence of two C-methyl groups, one of which is tertiary at C-4 (sharp singlet: τ = 8·77) and the other secondary (doublet: τ = 8·63; 8·52) corresponding to the grouping in XXXIV.[19] Furthermore, the spectrum shows sharp well-defined peaks (τ = 3·32; 2·35) due to α- and β-protons on the furan moiety. The adjacent two aromatic protons are characterized by a number of sharp bands (τ = 2·68). The complex bands (τ = 6·93) indicate methylene protons of the system (XXXIV).

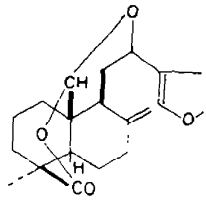
[18] D. H. R. Barton, S. K. Pradhn, S. Sternhell and J. F. Templeton, *J. Chem. Soc.* 255 (1961).
[19] V. P. Arya and A. Melera. Private communication.



XXXIV



IV



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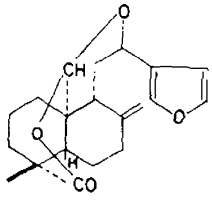
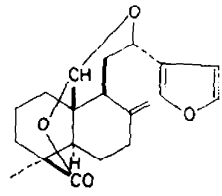


I d



I e

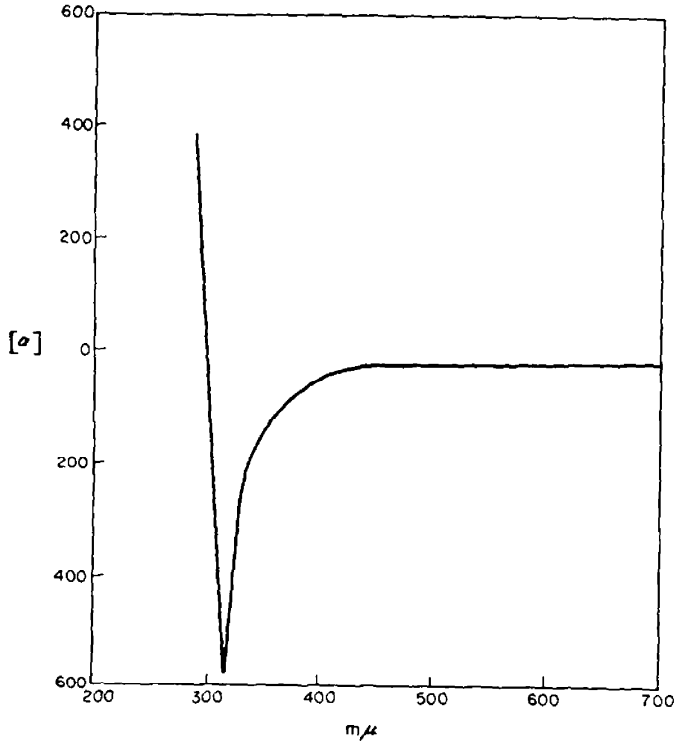


FIG. 1. The O.R.D. curve of the compound IV.

The conformation of sciadin may be represented as Ic or Id, the former of which is favoured as a result of the O.R.D. measurement of the methyl ester of the C-16 ketoacid (IV). The negative Cotten effect of the curve probably suggests that the lactol-ether grouping in the molecule of the ketoacid as well as in sciadin is situated on the β-side and not on the α-side,[20] The conformation at C-12 may be better represented in Ie when considering the mechanism for the formation of anhydrosciadin. Further confirmation of the stereochemistry of sciadin and anhydrosciadin will be reported later.

EXPERIMENTAL

M.ps are uncorrected; rotations were determined in chloroform unless otherwise stated; U.V. spectra were made in ethanol solutions; the N.M.R. spectra in deuterochloroform solutions with tetramethylsilane as internal reference using Varian-A spectrometer (60 M.C.).* The O.R.D. curve was measured in dioxane solution using Rodolf high-precision photoelectric spectropolarimeter.

Isolation of sciadin and methyl sciadopate

Powdered heartwood (1 kg) of *Sciadopitys verticillata Sieb. et Zucc.* was extracted with warm methanol. The viscous extract (110 g) was macerated with pet ether (500 cc) with vigorous stirring, and the solution allowed to stand in a refrigerator for 2 days. Crystallization of the deposited material from ethanol gave sciadin (0·9 g), m.p. 160°, $[\alpha]_D = +10{\cdot}3°$, $\lambda_{max} = 206\ m\mu$ (ε 9,100), $\nu_{max}^{Nujol} = 1736, 1636, 1606, 1505, 894, 807\ cm^{-1}$ (Found: C, 72·9; H, 7·4. $C_{20}H_{34}O_4$ requires: C, 73·14; H, 7·37%). The pet ether-insoluble fraction (49 g) was again macerated with ether (300 cc) under stirring. The ether extract (20 g) was washed with aqueous sodium carbonate, sodium hydroxide solution and water successively. The neutral ethereal solution was concentrated to 40 cc and allowed to stand in a refrigerator. Crystallization of the deposit from ethanol again afforded sciadin (1·6 g), identified by m.p., mixed m.p. and I.R. spectrum. The ethereal filtrate, almost free from sciadin, was saponified, and the unsaponified fraction steam distilled for 16 hr, and the residue dissolved in benzene to which pet ether was added until the solution became slightly turbid. After standing for 2 days in a refrigerator, the deposited cryst's were chromatographed on alumina. Crystallization of the product, obtained by evaporation of both fractions, from dil acetone afforded methyl sciadopate, m.p. 108·5°, $[\alpha]_D = -0{\cdot}7°$. (Found: C, 72·0; H, 9·8. $C_{21}H_{34}O_4$ requires: C, 71·96; H, 9·78%).

Catalytic hydrogenation of sciadin

(a) Sciadin (0·3 g) in acetic acid (20 cc) was hydrogenated over palladized charcoal (0·1 g). After absorption of 3·4 moles hydrogen, the reaction ceased yielding only an oily neutral product and no trace of acidic substances.

(b) Sciadin (0·3 g) in ethanol (50 cc) was also hydrogenated over Adams' catalyst (30 mg). The reaction was stopped after absorption of 1 mole hydrogen. Crystallization of the product from ethanol containing a small amount of acetic acid furnished dihydrosciadin (II), m.p. 206°, $[\alpha]_D = +44{\cdot}8°$, $\lambda_{max} = 210\ m\mu$ (ε 5,840), $\nu_{max}^{Nujol} = 3175, 1728, 1492, 879, 817\ cm^{-1}$. (Found: C, 72·5; H, 8·0. $C_{20}H_{36}O_4$ requires: C, 72·70; H, 7·93%).

Ozonolysis of dihydrosciadin to C-17 *acid* (III)

Dihydrosciadin (0·5 g) in chloroform (40 cc) was treated with ozone at $-13°$ and then heated with water (5 cc) under reflux for 20 min. Crystallization of the acidic product from dil. methanol afforded the C-17 acid (Y, 85 mg), m.p. 135–175°. (Found: C, 64·5; H, 7·7. $C_{17}H_{34}O_5 \cdot \frac{1}{2}H_2O$ requires: C, 64·35; H, 7·85%). Ethereal diazomethane formed the methyl ester, m.p. 191°, $[\alpha]_D +4{\cdot}1°$, ν_{max}^{KBr} 1750 cm^{-1}. (Found: C, 67·2; H, 8·1. $C_{18}H_{36}O_5$ requires: C, 67·06; H, 8·13%).

Ozonolysis of sciadin to C-16 *ketoacid* IV

(a) The solution of sciadin (132 mg) in chloroform (20 cc) was saturated with ozone and the solvent evaporated *in vacuo* without heating. The residue was steam distilled and dimedone (150 mg)

[20] C. Djerassi and D. Marshall, *Tetrahedron* **1**, 238 (1957); and Ref. 9.

was added to the distillate (pH adjusted at ca. 7). Crystallization of the product afforded formaldehyde-dimedone compound (65 mg), identified by m.p. and mixed m.p. with an authentic sample.

(b) Sciadin (1·0 g) in chloroform (40 cc) was saturated with ozone as described for dihydrosciadin. The acidic product (85 mg) was methylated with ethereal diazomethane and chromatographed on a short column of alumina. Crystallization of the product from acetone–ligroin and dil. methanol followed by sublimation furnished the methyl ester of C-16 ketoacid (11 mg), m.p. 210°, $[\alpha]_D^{EtOH}$ −9·5°, $[\alpha]_{789}^{Dioxane}$ −17·8°, $[\alpha]_{589}^{Dioxane}$ −22·3°, $[\alpha]_{317}^{Dioxane}$ −565°, $[\alpha]_{290}^{Dioxane}$ +393°, ν_{max}^{KBr} 1762, 1743, 1710 cm^{-1}. (Found: C, 63·4; H, 6·9. $C_{17}H_{22}O_6$ requires: C, 63·34; H, 6·88%). The 2,4-Dinitrophenylhydrazone was crystallized from dil. methanol m.p. 249°. (Found: C, 55·3; H. 5·2; N, 10·2. $C_{23}H_{26}O_9N_2$ requires: C, 54·97; H, 5·22; N, 11·15%).

Lithium aluminum hydride reduction of sciadin and dihydrosciadin

To a solution of sciadin (0·2 g) in tetrahydrofuran, the ethereal solution of lithium aluminum hydride (0·2 g) was added and the mixture heated under reflux for 6 hr. Wet ether (10 cc) and then dil. sulphuric acid (20%, 15 cc) were added to the mixture with cooling. The solution was extracted several times with ether and the combined extracts washed with aqueous sodium carbonate, water, dil. hydrochloric acid and water successively, and then dried and evaporated. The gelatinous product was dissolved in pyridine (1·5 cc), to which benzoyl chloride (0·5 cc) was added dropwise with cooling. After standing overnight the mixture was poured into water (30 cc) and extracted with ether. The resulting neutral oil was chromatographed on alumina. Crystallization of the product from methanol gave tribenzoate (VI), m.p. 114°, $[\alpha]_D$ −11·9°, (Found: C, 76·1; H, 6·4. $C_{41}H_{42}O_7$ requires: C, 76·11; H, 6·55%).

In a similar manner dihydrosciadin was converted to the corresponding tribenzoate (VIII) and recrystallized from methanol, m.p. 142°, $[\alpha]_D$ −29·7°. (Found: C, 75·9; H, 6·8. $C_{41}H_{44}O_7$ requires: C, 75·90; H, 6·84%).

Hydrolysis of sciadin to sciadinic acid (V)

Sciadin (1·0 g) was heated under reflux with ethanolic potash (10%, 15 cc) for 40 min. An equal volume of water was added and the solution condensed to about half volume *in vacuo* and the procedure repeated to remove all traces of ethanol. The aqueous solution was allowed to stand 24 hr and acidified with dil. hydrochloric acid with cooling. Crystallization of the deposit from dil. methanol furnished sciadinic acid (1·1 g), m.p. 112°. (Found: C, 65·7; H, 7·8. $C_{20}H_{28}O_6$ requires: C, 65·91; H, 7·74%). The water of crystallization was determined with Carl-Fisher reagent yielding 0·95 mole of water as $C_{20}H_{26}O_5 \cdot H_2O$. The titrated value of the mol. w. was 358; while $C_{20}H_{26}O_5 \cdot H_2O$ requires 364. The acid is soluble in sodium bicarbonate solution and easily lactonized with effervescence at its m.p. 112°.

Chromic acid oxidation of the gelatinous triol to the ketolactone (VIII)

The gelatinous triol (0·1 g) in pyridine (1 cc) was treated with chromic acid (0·2 g) in pyridine (2 cc). After standing overnight methanol (2 cc) was added with stirring for 1 hr. The solution was poured into water, extracted with ether, and the extract washed with dil. hydrochloric acid, aqueous sodium carbonate solution and water, dried and evaporated. Crystallization of the neutral product from dil. methanol furnished the ketolactone (VIII), m.p. 137–140°, $[\alpha]_D$ −52·8°, λ_{max} = 254 mμ (ε 3,600), ν_{max}^{KBr} 3145, 1735, 1673, 1572, 1519, 887, 871 cm^{-1}. (Found: C, 73·2; H, 7·6. $C_{20}H_{24}O_4$ requires: C, 73·14; H, 7·37%).

In a similar manner the gelatinous triol obtained from dihydrosciadin was converted to the corresponding ketolactone (IX), and recrystallized from dil. methanol m.p. 154°, $[\alpha]_D$ +41·9°, λ_{max} = 253 mμ (ε 3,450), ν_{max}^{KBr} 3170, 1735, 1680, 1572, 1518, 870 cm^{-1}. (Found: C, 72·5; H, 7·7. $C_{20}H_{26}O_4$ requires: C, 72·70; 7·93%).

Chromic acid oxidation of sciadinic acid to the ketolactol (XI)

Sciadinic acid (1·0 g) in pyridine (10 cc) was treated overnight with chromic acid (2·0 g) in pyridine (20 cc) as described for the oxidation of the gelatinous triol to the ketolactone (VIII). Crystallization of the acidic product from dil. methanol afforded the ketolactol (0·41 g), m.p. 178°, $[\alpha]_D^{EtOH}$ −52·8°, λ_{max} = 253 mμ (ε 3,550), ν_{max}^{Nujol} 3356, 3145, 1696, 1645, 1578, 1513, 908, 873 cm^{-1}. (Found: C, 69·7;

H, 6·9. $C_{20}H_{24}O_5$ requires: C, 69·75; H. 7·02%). The ketolactol was acetylated in the usual way with acetic anhydride and pyridine. Crystallization of the resulting product from dil. methanol gave the monoacetate (XII), m.p. 123°, $[\alpha]_D^{EtOH}$ −29·1°, ν_{max}^{Nujol} 1771, 1742, 1676 cm^{-1} as well as the usual furan bands. (Found: C, 68·3; H, 6·7. $C_{22}H_{26}O_6$ requires: C, 68·38; H, 6·78%). Methylation of the ketolactol with ethereal diazomethane furnished the aldehyde-ester (XIII) which crystallized from dil. methanol, m.p. 106°, $[\alpha]_D^{EtOH}$ −18·0°, ν_{max}^{KBr} 2752, 1730, 1716, 1677 cm^{-1} as well as the usual furan bands. (Found: C, 70·4; H, 7·5. $C_{21}H_{26}O_6$ requires: C, 70·37; H, 7·31%).

The conversion of dihydrosciadin to dihydro-ketolactol (XV) *and the ketoanhydride* (XVI)

Dihydrosciadin (1·0 g) was hydrolysed with ethanolic potash (10%, 15 cc) and the resulting amorphous acid oxidized with chromic acid in pyridine following the conditions used for hydrolysis of sciadin and the oxidation of sciadinic acid. Crystallization of the acidic product from dil. methanol furnished the corresponding ketolactol (0·64 g), m.p. 176°, $[\alpha]_D^{EtOH}$ +29·7°, λ_{max} = 254 mμ (ε 3,400), ν_{max}^{Nujol} 3436, 3195, 1721, 1640 cm^{-1} as well as the usual furan bands. (Found: C, 69·4; H, 7·5. $C_{20}H_{26}O_5$ requires: C, 69·34; H, 7·57%). The acid showed positive Fehlings' and tetrazolium chloride tests and was acetylated in the usual way giving a crystalline product from dil. methanol, m.p. 138°. (Found: C, 68·1; H, 7·2. $C_{22}H_{28}O_6$ requires: C, 68·02; H, 7·27%). The acetate gave a negative tetrazolium chloride test. The derived methyl ester (XVIII), prepared with ethereal diazomethane crystallized from dil. methanol, m.p. 105°, $[\alpha]_D^{EtOH}$ −11·0°, ν_{max}^{KBr} 2722, 1722, 1657 cm^{-1} as well as the usual furan bands. (Found: C, 69·7; H, 7·7. $C_{21}H_{28}O_5$ requires: C, 69·97; H, 7·83%). The ester showed a negative Fehlings' test but a positive tetrazolium chloride test. Crystallization from ethanol of the neutral product (0·32 g), obtained in the above oxidation, gave dihydrosciadin, identified by m.p. and mixed m.p. The mother liquor from the crystallization was concentrated to afford a precipitate (35 mg), which was crystallized from dil. acetone and sublimed to the ketoanhydride, m.p. 199°, $[\alpha]_D$ − 16·3°, λ_{max} 254 mμ (ε 3,470), ν_{max}^{KBr} 1787, 1759, 1656 cm^{-1} as well as the usual furan bands. (Found: C, 69·6; H, 7·0. $C_{20}H_{24}O_5$ requires: C, 69·75; H, 7·02%).

Chromic acid oxidation of dihydro-ketolactol (XV) *to the ketoanhydride* (XVI)

To a solution of dihydro-ketolactol (0·57 g) in acetic acid (20 cc) chromic acid (0·8 g) in water (1·5 cc) and acetic acid (10 cc) was added dropwise at 15° and stirred for 5 hr. Methanol was added and the mixture stirred for 1 hr more and then diluted with water. Crystallization of the precipitate (0·31 g) from dil. acetone followed by sublimation furnished the ketoanhydride, identified by m.p. and mixed m.p.

Sodiumborohydride reduction of the ketolactol (XI) to the ketolactone (VIII)

Sodium borohydride (60 mg) was added to the solution of the ketolactol (0·1 g), methanol (4 cc) and aqueous 1N sodium hydroxide (1 cc). After standing 4 hr., water was added and the solution concentrated *in vacuo*. The resulting mixture was then acidified and extracted with ether and the extract separated into the acidic and the neutral fractions. Crystallization of the acidic product (56 mg) from dil. methanol regenerated the starting material, identified by m.p. and mixed m.p. Crystallization of the neutral product (43 mg) from dil. methanol furnished the ketolactone, also identified by m.p. and mixed m.p.

Hydrolysis of the ketoanhydride (XVI)

The ketoanhydride (0·1 g) was hydrolysed with boiling 0·2N ethanolic potash (10 cc); 1·6 moles of potassium hydroxide being consumed after 2 hr and 1·92 moles after 3 hr. After adding an equal volume of water to the solution, ethanol was removed *in vacuo*, the alkaline solution washed with ether and acidified with dil. hydrochloric acid. The resulting viscous oil (XIX), which was soluble in aqueous sodium bicarbonate, was heated with acetic anhydride for 2 hr, poured into water and extracted with ether, the extract washed with sodium carbonate solution and water, dried and evaporated. Crystallization of the product from dil. acetone followed by sublimation afforded the ketoanhydride (5 mg) identified by m.p. and mixed m.p.

Permanganate oxidation of sciadinic acid to the hydroxyketolactone (XXI)

An aqueous permanganate solution (3·4%, 50 cc) was added dropwise with vigorous stirring to the solution of sciadinic acid (2·64 g) in 0·1N sodium bicarbonate solution (250 cc) at 4°. After

3·5 hr, the mixture was heated on the water-bath for 10 min, MnO_2 filtered off, washed with hot water and the combined filtrates acidified. Crystallization of the product, from ethanol–benzene furnished the hydroxyketolactone (1·06 g), m.p. 262°, $[\alpha]_D$ +40·0°, λ_{max} = 253·3 mμ (ε 3,400), ν_{max}^{Nujol} 3480, 1760, 1728, 1673 cm^{-1} as well as the usual furan bands. (Found: C, 67·0; H, 6·8. $C_{20}H_{24}O_6$ requires: C, 66·65; H, 6·71%). The compound gave a negative Ehrlich test and no colouration with conc. sulphuric acid. Attempted acetylation with acetic anhydride–pyridine, oxidation with chromic acid–pyridine and dehydration with phosphoryl chloride–pyridine or with thionyl chloride–pyridine according to the usual methods were all unsuccessful and resulted in recovery of starting material.

Acetylation of the hydroxyketolactone

The mixture of the hydroxyketolactone (0·5 g), acetic anhydride (15 cc), and sodium acetate (1·5 g) was heated under reflux for 2 hr and poured into water. Crystallization of the product from ethanol furnished acetoxyketolactone (XXII, 0·21 g), m.p. 272°, $[\alpha]_D$ +0·9°, λ_{max} = 253 mμ (ε 3,500), ν_{max}^{Nujol} 1759, 1746, 1666 cm^{-1} as well as the usual furan bands. (Found: C, 65·66; H, 6·5. $C_{22}H_{26}O_7$ requires: C, 65·66; H, 6·51%).

Chromic acid oxidation of the hydroxyketolactone to the dilactone (XXIII)

To a solution of the hydroxyketolactone (0·5 g) in acetic acid (85 cc), chromic acid (0·55 g), in water (2 cc) and acetic acid (8 cc) was added dropwise at 18° and the mixture stirred for 3·5 hr. Methanol was added and stirring continued for 1 hr. The solvent was evaporated and the residue extracted with chloroform, washed with aqueous sodium hydroxide and water, dried and evaporated. Crystallization of the product from ethanol afforded the dilactone (0·19 g), m.p. 278°, $[\alpha]_D$ +69·8°, ν_{max}^{Nujol} 1776–1782, 1738 cm^{-1}. (Found: C, 65·6; H, 6·9. $C_{16}H_{20}O_5$ requires: C 65·74; H, 6·90%).

Ozonolysis of the hydroxyketolactone (XXI) *to the dilactone* (XXIII)

A solution of the hydroxyketolactone (0·1 g) in chloroform (60 cc) was saturated with ozone. The ozonide was decomposed with boiling water for 30 min and the chloroform layer washed with aqueous sodium hydroxide and water, dried and evaporated. Crystallization of the residue form ethanol furnished the dilactone (15 mg), identified by m.p. and mixed m.p.

Direct conversion of sciadinic acid (V) *to the dilactone* (XXIII)

An aqueous permanganate solution (5%, 106 cc) was added dropwise to a solution of sciadinic acid (2·07 g) and sodium bicarbonate (1·8 g) in water (100 cc) and stirred for 5 hr. The reaction temp was kept under 40° and the mixture treated in the same way as described in the oxidation of sciadinic acid to the hydroxyketolactone. Crystallization of the product from ethanol furnished the dilactone (0·18 g), identified by m.p. and mixed m.p.

Oxidation of the ketolactol (XI) *with osmium tetroxide to the hydroxyketolactone* (XXI)

An ethereal solution of osmium tetroxide (57 mg) was added to an ethereal solution of ketolactol (73 mg) and the mixture allowed to stand in darkness for a week. A potassium hydroxide solution (1%, 10 cc) containing mannit (1·2 g) and chloroform were added and the mixture stirred for 6 hr. After removing the chloroform layer, the aqueous phase was acidified. Crystallization of the product from ethanol–benzene followed by sublimation afforded the hydroxyketolactone (60 mg), identified by m.p., mixed m.p. and I.R. spectrum.

Selenium dehydrogenation of sciadin

Sciadin was first reduced with lithium aluminum hydride to the gelatinous triol (see above), which was then hydrogenated in acetic acid solution (100 cc) over Adams' catalyst (125 mg). The hydrogenated product (7·0 g) in pyridine (50 cc) was oxidized with chromic acid (10·0 g) in pyridine (50 cc) in the same way as described above. The resulting neutral product (6·1 g) in ethanol–benzene (120 cc; 1:1) was heated under reflux with amalgamated zinc (50 g) and conc hydrochloric acid (60 cc) for 3 hr. A second portion of hydrochloric acid (60 cc) was then added and the mixture allowed to stand overnight. Water was added and the solution extracted with ether. The ethereal

solution was washed with aqueous sodium carbonate and water, dried and evaporated. The colourless product (5·4 g) was gradually heated with selenium (6·0 g) to 320° within 6 hr and the reaction temp (320°) maintained for a further 20 hr. The product was extracted with pet ether and the solution washed with aqueous alkali and water, dried and evaporated. The residue was again dissolved in pet ether and chromatographed on alumina. Crystallization of the picrate (17 mg) of the resulting oil furnished the picrate of 1,2,5-trimethylnaphthalene, identified by m.p., mixed m.p. 129·5–132° and U.V. spectrum of the regenerated oil from the picrate, λ_{max} = 231, 287, 323 mμ.

The formation of anhydrosciadin (XXX) from sciadin

Hydrogen chloride gas was bubbled through the solution of sciadin (1·5 g) in benzene (300 cc) at 4° for 2 hr. The reaction mixture was allowed to stand in a refrigerator for 24 hr and then washed with water, dried and evaporated *in vacuo*. Crystallization of the product from ethanol–benzene gave anhydrosciadin (110 mg). m.p. 260°, $[\alpha]_D$ −33·3°, λ_{max} = 250, 257, 279, 288 mμ (ε 13,200; 11,750; 3,850; 4,000), ν_{max}^{Nujol} 1759, 1605, 1575, 1540 cm^{-1}. (Found: C, 77·5; H, 7·0. $C_{20}H_{22}O_3$ requires: C, 77·39; H, 7·14%).

Ozonolysis of anhydrosciadin to the nor-phenol (XXXI)

A solution of anhydrosciadin (0·1 g) in chloroform (20 cc) was saturated with ozone and refluxed with water (5 cc). The chloroform layer was washed with aqueous sodium carbonate and water, dried and evaporated. The residue was chromatographed on a short column of alumina. Crystallization of the product from ethanol–benzene furnished the norphenol (28 mg), m.p. 235°, $\lambda_{max}^{neutral}$ = 268, 332 mμ (ε 13,000; 4,000), $\lambda_{max}^{Alkaline}$ = 321, 278, 400 mμ (ε 15,100; 7,500; 7,800), ν_{max}^{KBr} 1758, 1674, 1612, 1572, 1500 cm^{-1}. (Found: C, 72·6; H, 7·0. $C_{19}H_{22}O_4$ requires: C, 72·59; H, 7·05%). The compound gave a yellow colouration with alkali, purple with ferric chloride and an orange precipitate with 2,4-dinitrophenylhydrazine.

Hydrolysis of anhydrosciadin to bisanhydrosciadinic acid (XXXII)

A mixture of anhydrosciadin (0·27 g), potassium hydroxide (0·3 g) and diethylene glycol (5 cc) was heated under reflux at 240° (bath temp) for 2 hr and then poured into water. The solution was washed with pet ether, acidified with dil. hydrochloric acid and extracted with ether, the extract washed with water, dried and evaporated. Crystallization of the product from dil. methanol afforded bisanhydrosciadinic acid (0·21 g), m.p. 198°, $[\alpha]_D$ −78·8°, λ_{max} = 256, 260 (sh), 278 (sh), 288 mμ (ε 15,200; 14,400; 4,000; 3,200), ν_{max}^{Nujol} = 1694 cm^{-1}. (Found: C, 77·1; H, 7·2. $C_{20}H_{22}O_3$ requires: C, 77·39; H, 7·14%). The methyl ester (XXXIII) was prepared with ethereal diazomethane in the usual way. This had, after crystallization from dil. methanol, m.p. 128°, $[\alpha]_D$ −78·8°, λ_{max} = 256, 261 (sh), 277 (sh), 288 mμ (ε 15,000; 14,500; 4,000; 3,200), ν_{max}^{Nujol} 1730, 827 cm^{-1}. (Found: C, 77·4; H, 7·6. $C_{21}H_{24}O_3$ requires: C, 77·65; H, 7·46%).

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