

## The Constitution and Stereochemistry of Culmorin

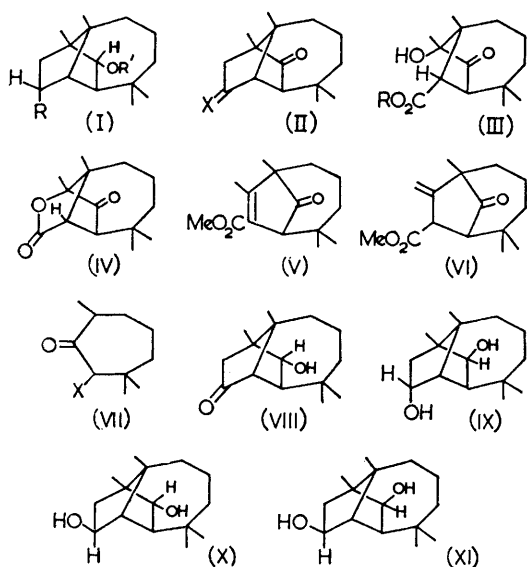
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THE mould metabolite culmorin,  $C_{15}H_{26}O_2$ , was isolated from *Fusarium culmorum* by Ashley, Hobbs, and Raistrick.<sup>1</sup> These authors prepared a diacetate and a di-*p*-bromobenzoate, thus showing the presence of two hydroxyl groups. We have proved that culmorin has the constitution and stereochemistry indicated in (I; R=OH, R'=H).

Oxidation of culmorin gave a diketone (II; X=O)

m.p. (from light petroleum) 103—104°,  $[\alpha]_D -29^\circ$  (all  $[\alpha]_D$  in  $CHCl_3$ ),  $\nu_{max}$  1755 and 1740  $cm^{-1}$ , which on alkaline autoxidation<sup>2</sup> gave a crystalline hydroxy-acid (III; R=H) (83%), m.p. (from cyclohexane) 163—164°, which with diazomethane afforded a methyl ester (III; R=Me), m.p. (from cyclohexane) 134—135°,  $[\alpha]_D +1^\circ$ . The hydroxy-acid (III; R=H) readily lactonised on treatment



with acetic anhydride to give the  $\gamma$ -lactone (IV), m.p. (from cyclohexane) 136–137°,  $[\alpha]_D -24^\circ$ ,  $\nu_{\max}$  1780 and 1750  $\text{cm}^{-1}$ . Treatment of the hydroxy-ester (III; R=Me) with thionyl chloride and pyridine at room temperature overnight gave a mixture of two olefins in equal (27%) yield. The first olefin (V) had m.p. (from light petroleum) 45–47°,  $\nu_{\max}$  1745 and 1715 (carbonyl) and 1635 ( $\text{C}=\text{C}$ )  $\text{cm}^{-1}$ ,  $\lambda_{\max}$  225 ( $\epsilon$ , 8760) and 300  $\text{m}\mu$  ( $\epsilon$ , 40) in EtOH. The second olefin (VI) had m.p. (from light petroleum) 62–63°,  $[\alpha]_D + 30^\circ$ ,  $\nu_{\max}$  1740 and 1735 (carbonyl) and 1655 ( $\text{C}=\text{C}$ )  $\text{cm}^{-1}$ ,  $\lambda_{\max}$  300  $\text{m}\mu$  ( $\epsilon$ , 40). The second olefin (VI), on treatment with sodium methoxide in methanol at room temperature for 1 hr., was smoothly isomerised (90%) to the first olefin (V).

Ozonolysis of (V) gave a stable ozonide, m.p. (from cyclohexane) 107–108°,  $[\alpha]_D + 82^\circ$ , which with methanolic potassium hydroxide at reflux temperature for 2 hr. gave tetrahydroeucarvone (VII; X=H), identified as its 2,4-dinitrophenylhydrazone.<sup>3</sup> Acidification of the basic solution and extraction afforded the keto-acid (VII; X=CO<sub>2</sub>H) (35%), m.p. (from cyclohexane-ether) 117–125°, converted into tetrahydroeucarvone (VII; X=H) on heating at 160° for 25 min. (sealed tube).

<sup>1</sup> J. N. Ashley, B. C. Hobbs, and H. Raistrick, *Biochem. J.*, 1937, **31**, 385. We thank Prof. H. Raistrick, F.R.S., for a generous supply of culmorin.

<sup>2</sup> E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1962, 1578; R. Hanna and G. Ourisson, *Bull. Soc. chim. France*, 1961, 1945; D. Lavie, E. Glotter and Y. Shvo, *Tetrahedron*, 1963, **19**, 1377; R. E. Corbett and H. Young, *J. Chem. Soc. (C)*, 1966, 1556.

<sup>3</sup> J. R. B. Campbell, A. M. Islam, and R. A. Raphael, *J. Chem. Soc.*, 1956, 4096. We thank Prof. R. A. Raphael, F.R.S., for an authentic specimen.

<sup>4</sup> L. F. Fieser and R. Stevenson, *J. Amer. Chem. Soc.*, 1954, **76**, 1728.

<sup>5</sup> P. Naffa and G. Ourisson, *Chem. and Ind.*, 1953, 917. We thank Prof. G. Ourisson for an authentic specimen.

<sup>6</sup> G. Ourisson, *Bull. Soc. chim. France*, 1955, 895; G. Jacob, G. Ourisson and A. Rassat, *ibid.*, 1959, 1374.

The diketone (II; X=O) with ethanedithiol-boron trifluoride etherate at room temperature overnight<sup>4</sup> gave a monothioketal [II; X=(CH<sub>2</sub>S<sub>2</sub>)] (83%), m.p. (from ethanol) 75–76°,  $[\alpha]_D -104^\circ$ ,  $\nu_{\max}$  1735  $\text{cm}^{-1}$ , which on desulphurisation furnished a liquid ketone (II; X=H<sub>2</sub>),  $[\alpha]_D -6^\circ$ ,  $\nu_{\max}$  1738  $\text{cm}^{-1}$  in high yield. Reduction of this ketone with sodium in ethanol gave an alcohol (I; R=R'=H), m.p. (from light petroleum) 110–111°,  $[\alpha]_D -16^\circ$ , characterised as the acetate, m.p. (from light petroleum) 44–47°,  $[\alpha]_D -18^\circ$  and as the 3,5-dinitrobenzoate, m.p. (from cyclohexane-ether) 156–157°. This alcohol was shown by direct comparison to be the enantiomer of the known longiborneol.<sup>5</sup> Since the latter has been proved<sup>6</sup> to have the absolute configuration opposite to that in (I; R=R'=H) the absolute configuration of culmorin must be as already indicated in all the formulæ already given.

Oxidation of culmorin with half the theoretical amount of chromic acid gave two ketols. The first had m.p. (from cyclohexane-light petroleum) 106–108°,  $\nu_{\max}$  (in Nujol) 3400 (hydroxyl) and 1720 (carbonyl)  $\text{cm}^{-1}$  and the second m.p. (from the same solvent mixture) 120–121°,  $[\alpha]_D -18^\circ$ ,  $\nu_{\max}$  (in Nujol) 3400 (hydroxyl) and 1735 (carbonyl)  $\text{cm}^{-1}$ . The latter ketol could not be autoxidised under basic conditions and must, therefore, be (II; X=H, OH). The first ketol must, therefore, be (VIII). Reduction of the ketol (II; X=H, OH) with sodium and ethanol afforded culmorin, whereas reduction with lithium aluminium hydride gave, as expected on steric grounds, an epimeric diol (IX), m.p. (from cyclohexane-methanol) 158–159°,  $[\alpha]_D + 6^\circ$ . Reduction of the ketol (VIII) with lithium aluminium hydride gave a further diol (X), m.p. (from ether-light petroleum) 115–116°,  $[\alpha]_D -25^\circ$ , whilst reduction of the diketone (II; X=O) with the same reagent gave yet another diol (XI), m.p. (from cyclohexane-light petroleum) 140–141°,  $[\alpha]_D -28^\circ$ . Accepting that the culmorin molecule is strongly hindered on one side and relatively unhindered on the other side (opposite to the bridge), then the direction of hydride on delivery is clear in every case and the configurations assigned then follow.

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