The Resolution of (±)-Zearalenone. Determination of the Absolute Configuration of the Natural Enantiomorph

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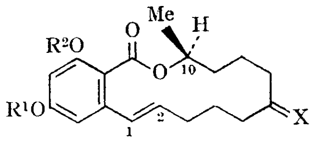
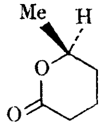
(±)-ZEARALENONE DIMETHYL ETHER (Ia)[1] on treatment with boron trichloride in methylene chloride at 0° was converted to its 4-monomethyl ether (Ib) (m.p. 108—111°; Found: C, 68·84; H, 7·12). The latter was resolved as its l-menthoxyacetate (Ic) (m.p. 123—125°, $[\alpha]_{\mathrm{D}}^{\mathrm{CHCl_3}}$ −39°; Found: C, 69·92; H, 8·29). Alkaline hydrolysis of (Ic) at room temperature to known optically active (Ib) $[\alpha]_{\mathrm{D}}^{\mathrm{CHCl_3}}$ −177°[2] followed by ether cleavage with boron tribromide in methylene chloride gave (−)-zearalenone (I), $[\alpha]_{\mathrm{D}}^{\mathrm{CHCl_3}}$ −190°, identical with the natural product.

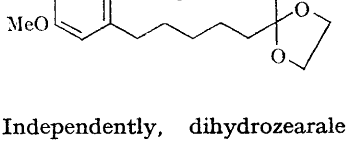
Zearalenone dimethyl ether[2] derived from natural (−)-zearalenone was converted to its 6-ethylene ketal derivative (Id) (m.p. 101—103°; Found: C, 67·51; H, 7·75) and the latter hydrogenated to its dihydro-derivative (m.p. 91—93°)[†] followed by saponification to the seco-acid ketal (II) (m.p. 63—67°; $[\alpha]_{\mathrm{D}}^{\mathrm{CHCl_3}}$ +7·4°; Found: C, 64·33; H, 8·56). The methyl ester (IIa) $[\alpha]_{\mathrm{D}}^{\mathrm{CHCl_3}}$ +3·0° derived from (II) with diazomethane, was allowed to react with (±)-α-phenylbutyric anhydride in pyridine according to the method of Horeau.[3] The recovered α-phenylbutyric acid exhibited a negative rotation ($[\alpha]_{\mathrm{D}}^{\mathrm{C_6H_6}}$ −4·5°, $[\alpha]_{365}^{\mathrm{C_6H_6}}$ −17°) thereby denoting an *S*-configuration at the optically active C(10)-centre of zearalenone.



(I) R^1=R^2=H, X=O
(Ia) R^1=R^2=Me, X=O
(Ib) R^1=Me, R^2=H, X=O
(Ic) R^1=Me, R^2=l-$C_{10}H_{19}O{\cdot}CH_2{\cdot}CO$−
(Id) R^1=R^2=Me, X= −$OCH_2{\cdot}CH_2{\cdot}O$−



(III)



(II) R=H
(IIa) R=Me

Independently, dihydrozearalenone dimethyl ether [1,2-dihydro-(Ia)] was exhaustively oxidized

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[†] First prepared by T. B. Windholz and R. D. Brown at the Merck Laboratories.

in the Baeyer–Villiger reaction with *m*-chloroperbenzoic acid in refluxing methylene chloride for 30 hr. Among the products isolated from the oxidation after saponification was 5-hydroxyhexanoic acid lactone (III), b.p. 80—83°/3 mm.; $[\alpha]_D^{CHCl_3}$ $-45°$ essentially identical in the n.m.r. with an authentic sample of (±)-(III). The absolute *S*-configuration of pure (−)-(III) $[\alpha]_D^{ethanol}$ $-51°$ has already been determined.[4]

Zearalenone becomes the first of the naturally occurring β-resorcyclic acid lactones (curvularin,[5] radicicol,[6] diaporthin,[7] *etc*.), whose absolute configuration is hereby established.

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