Total Synthesis of the Macrolide, Zearalenone

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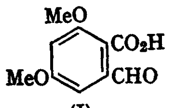
THE factor isolated from *Gibberella zeae* and found to possess anabolic and uterotrophic activity[1] was reported recently by Urry *et al.*,[2] to have structure (V) and designated zearalenone. We now report the total synthesis of (±)-zearalenone (V).

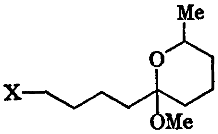
The aromatic component (I) (m.p. 193—196°) was prepared from 3,5-dimethoxyphthalic anhydride[3] by reduction and found to be identical with material prepared by Urry *et al.*, [2,4] from zearalenone.

The aliphatic component (II) was synthesized from 5-hydroxy-δ-hexanolactone[5] and pent-4-enylmagnesium bromide followed by treatment with 1% methanolic hydrogen chloride (b.p. 57—59°/0·65 mm.) [n.m.r. ($CDCl_3$) δ 1·13 (d, J = 6·5 c./sec., H·C·Me) and 3·17 (s, OMe)].

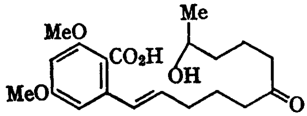
Ozonolysis of (II) in methanol at −60° followed by reduction of the ozonide with sodium borohydride produced the unstable carbinol (IIa)* [n.m.r. ($CDCl_3$) δ 1·15 (d, J = 6·5 c./sec., H·C·Me): 2·45 (s, OH; exchanged with D_2O) and 3·46 (s, OMe)].



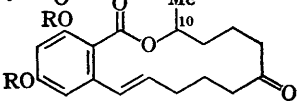
(I)



(II; $X = CH_2$:)
(IIa; X = HO)
(IIb; $X = C_7H_7SO_3$)
(IIc; X = Br)
(IId; $X = Ph_3P^+Br^-$)



(III)



(IV; R = Me)
(V; R = H)

The carbinol (IIa) was converted successively with *p*-toluenesolphonyl chloride in pyridine into the tosylate derivative (IIb), which was refluxed with sodium bromide in methanol to form the bromide (IIc) and thence by treatment with triphenylphosphine in hot methanol to yield the noncrystalline phosphonium salt (IId) [n.m.r. ($CDCl_3$) δ 1·04 (d, J = 6·5 c./sec., H·C·Me), 3·09 (s, OMe) and ~7·75 (centre of multiplet due to aromatic protons)].

Conversion of the salt (IId) into its ylid with methylsulphinyl carbanion in dimethyl sulphoxide[6] followed by coupling with the sodium salt of (I) and final acidification yielded a noncrystalline mixture of geometrical isomers containing predominantly the *trans*-acid (III); the latter was cyclized directly with trifluoracetic anhydride[7] in benzene to give crystalline (±)-zearalenone dimethyl ether (IV) (m.p. 124—126°). Ether cleavage of (IV) with boron tribromide[8] in methylene chloride at 0° afforded (±)-zearalenone (V) (m.p. 187—189°). This material was identical with the natural product in its infrared and n.m.r. spectra as well as with a sample of (±)-zearalenone prepared from the natural product *via*: (1) lactone ring opening with accompanying racemization at C–**10** (NaOH–DMSO) followed by (2) recyclization [$(CF_3{\cdot}CO)_2O$] and (3) ether cleavage (BBr_3).

The authors acknowledge samples of natural zearalenone from Commercial Solvents Corp. (Terre Haute, Ind.) as well as discussions with members of its staff and with Professor W. H. Urry of the University of Chicago.

(*Received, January 23rd,* **1967**; *Com.* 071.)

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* On contact with wet chloroform (IIa) is transformed into 2-methyl-1,7-dioxaspiro[5,5]undecane identical with a sample derived from degradation of zearalenone.

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