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THE STRUCTURE OF ZEARALENONE

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Classical chemical, as well as n.m.r. and mass spectrometric, study of the substance of striking physiological activity isolated$^{(1)}$ from the mycelia of the fungus Gibberella zeae (Fusarium graminearum) has shown that it is one of the enantiomorphs of 6-(10-hydroxy-6-oxo-trans-1-undecenyl)-β-resorcylic acid lactone I. It is a member of a rare class of natural products, the β-resorcylates.$^{(2)}$ Zearalenone I (white crystals, $C_{18}H_{22}O_5$;** m.p. 164-165°; $[a]^{25}_{546} = -170.5^{\circ}$, C = 1.0 in methanol; u.v. maxima at 236 [ε 29,700], 274 [ε 13,909] and 316 mμ [ε 6,020];$^{(2e)}$ insoluble in water, but soluble in aqueous alkali, ether, benzene and alcohols) gives reactions (Figure 1) that indicate that it has one olefinic and one ketonic group, and two phenolic hydroxyls and an ester group in a β-resorcylate structure.

Five products from reduction of the olefinic and/or ketonic groups of I have been prepared. Hydrogenation of I in ethanol over platinum, or palladium on charcoal, yielded zearalanone II ($C_{18}H_{24}O_5$, m.p. 192-193°). However, its hydrogenation over Raney

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**All analyses are acceptable, and all n.m.r. spectra are in accord with the structure shown.

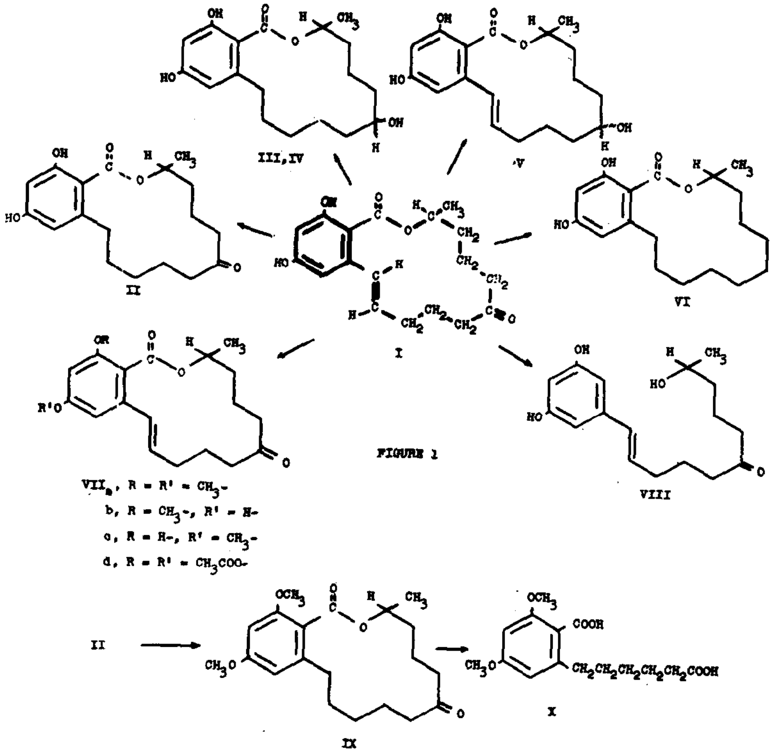
III,IV
V
II
I
VI
VII$_a$, R = R' = CH$_3$-
b, R = CH$_3$-, R' = H-
c, R = H-, R' = CH$_3$-
d, R = R' = CH$_3$COO-
VIII
II
IX
X

FIGURE 1

nickel (25°, 50 psi) gave a mixture of the two diastereomeric zearalanols III ($C_{18}H_{26}O_5$, m.p. 182-183°, 41%) and IV (m.p. 145-147°, 49%). Only IV was obtained when I in potassium hydroxide solution was hydrogenated over Raney nickel. Reduction of I with sodium borohydride in methanol gave a mixture of the two diastereomeric zearalenols V ($C_{18}H_{24}O_5$, m.p. 90-102°). Treatment of I with 1,2-ethanedithiol in benzene in the presence of p-toluenesulfonic acid gave the expected thioketal that was heated at reflux for 8 hr. in ethanol-water with an excess of Raney nickel to give zearalane VI ($C_{18}H_{26}O_4$, m.p. 154-156°). I also gave an oxime (m.p. 210-211°; quantitative oximation --- equ. wt. of I, 328), and a 2,4-dinitrophenylhydrazone (m.p. 283-285°).

All of the possible methyl ethers of I were obtained. The reaction of I in 10% sodium hydroxide solution with excess methyl sulfate gave a mixture of VIIa ($C_{20}H_{26}O_5$, m.p. 112-114°) and VIIb ($C_{19}H_{24}O_5$, m.p. 190-192°); and with excess diazomethane in ether I gave VIIc(3) ($C_{19}H_{24}O_5$, m.p. 120-122°). Further, reaction of I with acetic anhydride in pyridine gave its diacetate VIId ($C_{22}H_{26}O_7$, m.p. 123-125°).

Degradation studies elucidated the positions of the olefinic and ketonic groups in the alicyclic lactone ring of I, and gave the first indication that it was a β-resorcylate. Accordingly, a solution of II in sodium hydroxide solution was treated with methyl sulfate to give IX ($C_{20}H_{28}O_5$, m.p. 124-125.5°), and IX was converted to its oxime ($C_{20}H_{29}NO_5$, m.p. 130-132°) with hydroxylammonium chloride in pyridine. The Beckmann rearrangement of this oxime with phosphorous pentachloride in ether (0°) gave predominantly one lactam (m.p. 119-121°) that was saponified with sodium hydroxide solution in ethanol-water (5%, reflux 64 hr.). Acidification gave X ($C_{15}H_{20}O_6$, m.p. 111-112°, neut. equ. 159, molecular ion 296. H^1 n.m.r. in $DCCl_3$ with TMS: 6H multiplet envelope 1.2-2.0δ, peak at 1.52δ; 2H triplet at 2.38δ, J 7 c.p.s.; 2H triplet at 2.76δ, J 6 c.p.s.; 3H singlet at 3.76δ; 3H singlet at 3.82δ; 2H singlet at 6.43δ; and 2H singlet at 9.70δ that vanishes when D_2O added).

The ozonolysis of VIIa gave 2,4-dimethoxy-6-formylbenzoic acid (m.p. 195.5-197°(4)), identical with an authentic sample supplied(4) (i.r.,m.p. of mixture, and tlc). When this ozonolysis product was treated with methanolic hydrochloric acid, 3,5,7-trimethoxyphthalide (m.p. 117-119°) was obtained. When VIIa was heated at reflux (70 min. with nitric acid (14%), 2-nitro-3,5-dimethoxybenzoic acid was obtained and glutaric, succinic and oxalic acid (tlc) remained in the aqueous solution.

A suspension of I in sodium bicarbonate solution (10%) was held at reflux until all of it dissolved (8 hr.) and acidification gave VIII ($C_{17}H_{24}O_4$, m.p. 89-91°). VIII is apparently a product of hydrolysis of I followed by the expected decarboxylation of the resulting dihydroxybenzoic acid. In sodium hydroxide solution (10%, 8 hr. reflux), I is converted to an equilibrium mixture of VIII and 1-(3,5-dihydroxyphenyl)-6-hydroxy-1-undecen-10-one (probably via hydride shift between the 6- and 10- positions by a 6-membered ring transition state). Similar treatment of III in sodium hydroxide solution (10%, 8 hr.) gave 2,6-dihydroxy-11-(3,5-dihydroxyphenyl)-undecane.

The n.m.r. spectrum of I in deuterochloroform is shown in Figure 2 with the assignments indicated. Of principal importance

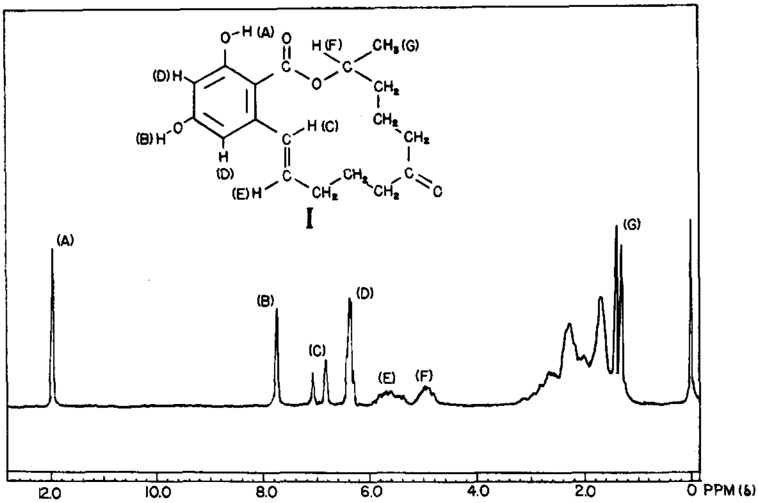

FIGURE 2

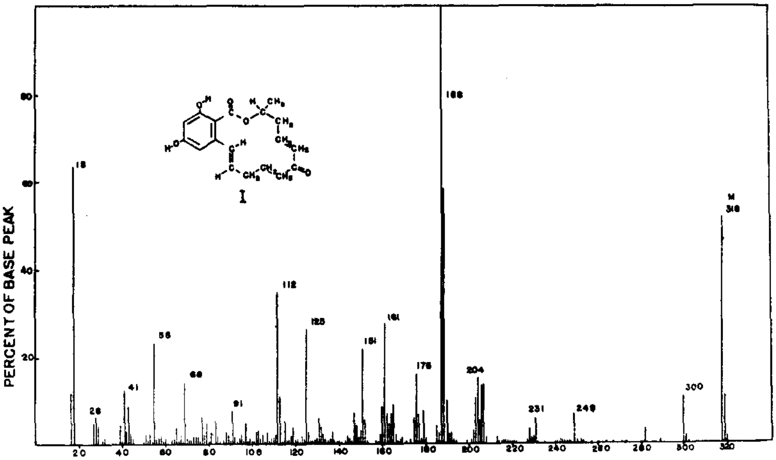

FIGURE 3

are singlets A and B due to hydroxyl hydrogen atoms with A that of the one hydrogen-bonded to the ester function (does not shift with concentration as B does); and the low field doublet C (6.98δ) due to the olefinic hydrogen atom alpha to the aromatic ring with its splitting constant (J 16 c.p.s.) indicating the trans configuration.

These structures were confirmed by the mass spectrometry (AEI, MS9) of I (Figure 3) and its derivatives II-X. As expected, these substances give stable molecular ions, whose m/e and peak intensity ratios verify the molecular formulae. The mass spectra of I, VIIa and VIIc have the same prominent peaks (41, 55, 69, 112, 125 and 151) due to the aliphatic ions, and the peaks of aromatic ions from I (161 to 318) are indicated since the mass spectra of VIIa and VIIc have corresponding ones 28 and 14 units higher, respectively. Detailed description of the spectrometric structural evidence will be included in future publications.

REFERENCES

1. M. Stob, R. S. Baldwin, J. Tuite, F. N. Andrews and K. G. Gillette, Nature, 196, 1318 (1962).
2. (a) E. Sondheimer, J. Am. Chem. Soc., 79, 5036 (1957); (b) A. J. Birch, O. C. Musgrave, R. W. Rickards and H. Smith, J. Chem. Soc., 3146 (1959); (c) A. Kamal, M. Ali Kahn and A. Ali Qureschi, Tetrahedron, 19, 111 (1963); (d) R. N. Mirrington, E. Ritchie, C. W. Shoppee, W. C. Taylor and S. Sternhell, Tetrahedron Letters, 364 (1964); and (e) F. McCapra, A. I. Scott, P. Delmotte, J. Delmotte-Plaquee and N. S.Bhacca, ibid., 869 (1964).
3. R. H. Thomson, "Biochemistry of Phenolic Compounds," J. B. Harborne, Editor, Academic Press, New York, N. Y., 1964, p.8. Discussion of resistance to such methylation of phenolic groups hydrogen-bonded to ortho-carbonyl functions.
4. E. Sondheimer, J. Am. Chem. Soc., 79, 5036 (1957).
5. E. S. Hand and R. M. Horowitz, J. Am. Chem. Soc., 86, 2084 (1964).