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4-HYDROXYMYOPORONE, A KEY INTERMEDIATE IN THE BIOSYNTHESIS OF PULMONARY TOXINS PRODUCED BY FUSARIUM SOLANI INFECTED SWEET POTATOES

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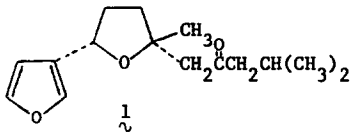
Under stress conditions, particularly fungus infection, the sweet potato (Ipomoea batatas) elaborates ipomeamarone (1) and a number of other furanoid metabolites.[1] We have been especially



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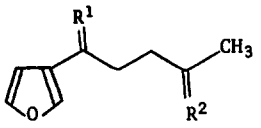
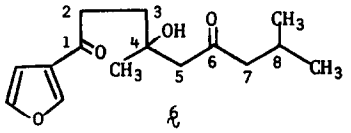
interested in the C_9 group of furans (2-5) produced in sweet potatoes infected with Fusarium solani. These compounds have been shown to be potent pulmonary toxins in laboratory animals and appear to be the causative agents in the atypical interstitial pneumonia occurring in cattle that have ingested mold-damaged sweet potatoes.[2] Whereas ipomeamarone is obviously a sesquiterpene, the biosynthetic origin of compounds 2-5 is less certain. They might arise by degradation of either a sesquiterpene or a monoterpene or, less probably, by some other route altogether. We have now obtained evidence that 2-5 are degraded sesquiterpenes.

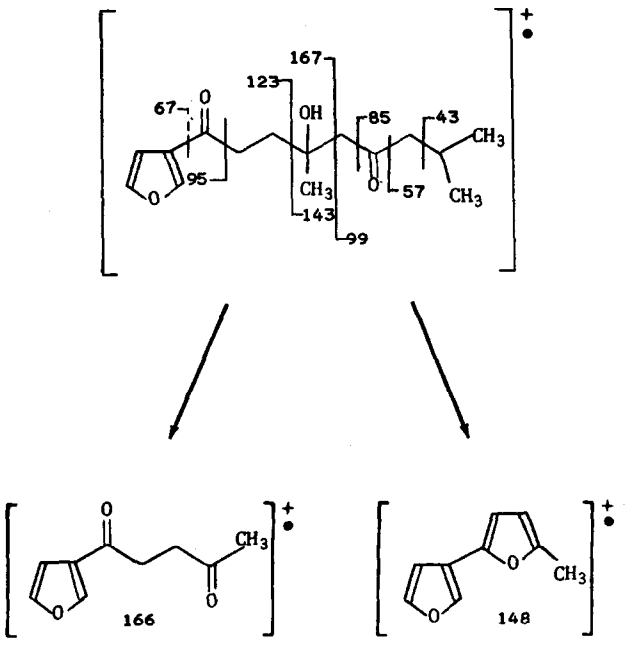


2 R^1 = O R^2 = O
3 R^1 = H,OH R^2 = O
4 R^1 = O R^2 = H,OH
5 R^1 = H,OH R^2 = H,OH

A further investigation of the metabolites of damaged sweet potatoes has lead to the isolation and identification of a new sesquiterpene, 4-hydroxymyoporone (6).[3] The compound is produced by sweet potatoes treated with mercuric chloride, infected by F. solani, and particularly



infected by Ceratocystis fimbriata, the fungus causing black-rot disease in sweet potatoes. The sesquiterpene was isolated by column chromatography on silica gel followed by high pressure liquid chromatography (HPLC) on Corasil II. The empirical formula ($C_{15}H_{22}O_4$) was deduced from the parent ion at m/e 266 in the mass spectrum and from the elemental analysis. The 3-furylalkanone functionality was suggested by the characteristic pmr signals at δ 6.77, 7.17, and 8.08,[2] by the stretching frequency of the conjugated carbonyl group (1680 cm^{-1}) and the furyl absorptions[4] (3180, 1560, 1510, and 875 cm^{-1}) in the infrared and a maximum at 251 nm (ε 3100) in the ultraviolet spectrum,[5] and by the intense ion at m/e 95 in the mass spectrum. A second, unconjugated carbonyl group was suggested by the infrared spectrum (1700 cm^{-1}); a broad absorption at 3480 cm^{-1} indicated the presence of a hydroxyl group. The hydroxyl group was assigned as a tertiary alcohol since the pmr spectrum showed no evidence for protons bound to a carbon bearing a hydroxyl group; this assignment was supported by an absorption at 1155 cm^{-1} in the infrared spectrum. Additional pmr signals were observed at δ 0.92 (d, J = 6 Hz, $CH(CH_3)_2$), 1.22 (s, 4-CH_3), 2.55 (s, 5-CH_2), and 2.90 (m, 2-CH_2). Signals from the protons on carbons 3, 7, and 8 were contained in a multiplet at δ 1.50-2.40. Finally, the major fragment ions in the mass spectrum can be explained by structure 6 as shown below.



The occurrence of 6 is noteworthy because a retro-aldol reaction should convert the β-hydroxyketone to 2 and methyl isobutyl ketone. This reaction was, in fact, observed when 6 was treated with dilute, aqueous sodium hydroxide. Similarly, the biosynthesis of the lung toxins appears to proceed by retro-aldol reaction of 6 to give 2 and reduction of one or both carbonyl groups in 2 to give 3-5. Radiolabelled 6, prepared by growing C. fimbriata on sweet potato slices in the presence of 2-^{14}C-acetate, was transformed by F. solani into 2-5. The most prominent metabolites (2 and 4) were isolated by HPLC. After addition of unlabelled carrier, the 2,4-dinitrophenylhydrazone of 2 and the semicarbazone of 4 were prepared and recrystallized to constant specific activity. The radioactivity from 6 was incorporated into 2 and 4 to the extent of 10 and 5%, respectively. 4-Hydroxymyoporone was stable to the incubation conditions in the absence of F. solani and no conversion to 2-5 was noted when 6 was incubated with C. fimbriata. These data indicate that 6 is the precursor of 2 and 4 (and presumably 3 and 5, as well). It is interesting that the pulmonary toxins 2-5 are not produced by the sweet potato or F. solani directly but result from fungal metabolism of a stress metabolite of the host.

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