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SYNTHESIS OF TWO TOXIC 4-IPOMEANOL ANALOGS

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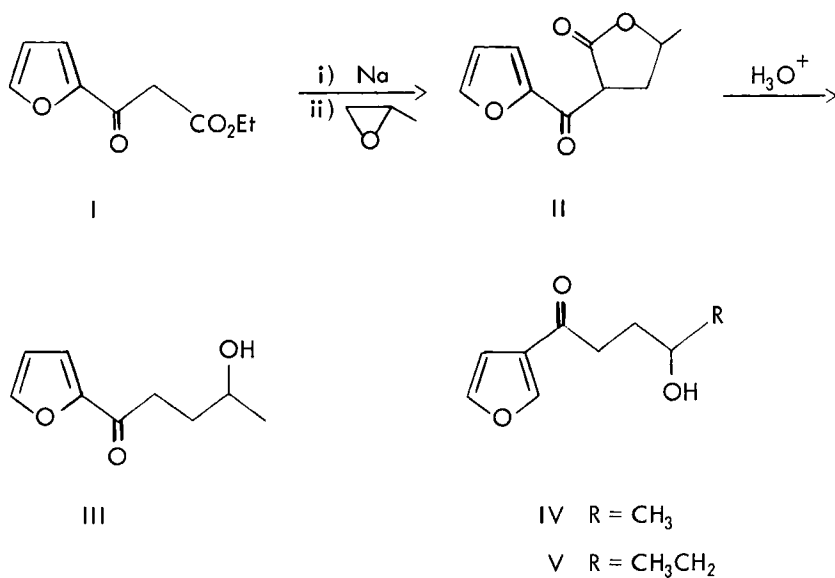
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SYNTHESIS OF TWO TOXIC 4-IPOMEANOL ANALOGS

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Mold damaged sweet potatoes, *Ipomoea batatas*, produce hepatotoxic ipomeamarone¹, ipomeamaronol² and a potent lung toxin, 4-ipomeanol (IV).^{3, 4} A report describing the outbreak of a fatal lung disease in cattle from consumption of such tubers has appeared.⁴ Adapting the method of Boyd *et al.* for the synthesis of 4-ipomeanol,⁵ we now report the synthetic details for the preparation of 1-(2-furyl)-4-hydroxy-1-pentanone (III) and 1-(3-furyl)-4-hydroxy-1-hexanone (V).



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A nucleophilic ring opening of propylene oxide with the sodio carbanion generated from ethyl 2-furoylacetate (I) afforded the lactone II, which upon mild acid hydrolysis gave the α -analog (III) of 4-ipomeanol. Substituting ethyl 3-furoylacetate for I and 1,2-epoxybutane for propylene oxide in the synthesis yielded compound V, which represents a one carbon lengthening of the side chain of 4-ipomeanol.

EXPERIMENTAL

Ethyl 2-furoylacetate (I). —¹ To 37.6 g (0.27 mole) of ethyl 2-furoate in 40 ml of dry benzene, 9 g (0.39 g. atoms) of sodium metal was added, followed by a dropwise addition of 110 ml of ethylacetate. The resulting dark red solution was vigorously stirred and heated at 95° for 15 hours. The solution was poured into ice-water and carefully neutralized with cold 6N HCl. Extraction of the organic layer with benzene, drying over sodium sulfate, evaporation of the solvent and distillation at 1.5 mm/Hg gave 25 g (51%) of ethyl 2-furoyl acetate (I).

Lactone (II). —⁶ To a solution of 2.3 g (0.1 mole) of sodium in 80 ml of absolute ethanol and 20 ml of anhydrous benzene, 18.2 g (0.1 mole) of (I) was added dropwise. Further addition of 7.0 ml of propylene oxide, previously chilled in ice, produced an orange-red mixture which was heated for two days at 45–50°. Excess alcohol was removed in vacuo and after addition of water, the mixture was neutralized with cold glacial acetic acid. Extraction with ether, drying over sodium sulfate and evaporation of the solvent afforded an oil, which was separated on 3 mm thick preparative silica gel t.l.c. to give 10.5 g (54%) of white crystals, mp. 75.5–77°. ν_{\max} (KBr) 3130, 1775, 1680, 1570, 1475, and 780 cm^{-1} .

SYNTHESIS OF TWO TOXIC 4-IPOMEANOL ANALOGS

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.85; H, 5.21.

1-(2-Furyl)-4-hydroxy-1-pentanone (III). —⁶ A solution containing 630 mg (1 m. mole) of lactone (II) in 8 ml of absolute ethanol and 4 ml of 6 N HCl was stirred and heated at 45° for 15 hours. The reaction mixture was saturated with potassium carbonate and washed with anhydrous ether. Drying the ethereal layer over anhydrous sodium sulfate after removal of K_2CO_3 , evaporation and separation on preparative silica gel t.l.c. afforded 450 mg (83%) of light yellow oil, ν_{\max} (neat) 3400, 3130, 1680, 1580, 1480, 880 cm^{-1} ; nmr. ($CDCl_3$), δ (TMS) 1.20 (3H, d, $J = 7$ Hz, 5-CH₃), 1.85 (2H, m, 3-CH₂), 3.03 (2H, t, $J = 7$ Hz, 2-CH₂), 3.83 (1H, s, OH), 3.91 (1H, m, 4-CH), 6.78 (1H, m, 4'-CH), 7.53 (1H, m, 3'-CH) and 7.91 (1H, m, 5'-CH). Mass spectroscopy (70 eV), m/e (%), 168 (2), molecular ion; 153 (7), M-CH₃; 150 (70), M-H₂O; 124 (14), M-CH₃-HCO; 110 (81), furyl-C = $\begin{matrix} OH \\ | \\ CH_2 \end{matrix}$; 95 (100), furoyl.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.29; H, 7.14. Found: C, 64.22; H, 7.16.

1-(3-Furyl)-4-hydroxy-1-hexanone (V). —⁷ This compound was prepared as an oil by the above route, substituting 3-furoylacetate for (I) and 1,2-epoxybutane for propylene oxide. ν_{\max} (neat) 3450, 3130, 2940, 1680, 1570, 1510, 1160, and 875 cm^{-1} . Nmr. ($CDCl_3$), δ (TMS) 0.95 (3H, t, $J = 7$ Hz, 6-CH₃), 1.21-2.00 (4H, m, 3-CH₂ and 5-CH₂), 2.95 (2H, t, $J = 7$ Hz, 2-CH₂), 3.12 (1H, s, OH), 3.29-3.80 (1H, m, 4-CH), 6.83 (1H, m, 4'-CH), 7.50 (1H, m, 5'-CH) and 8.18 (1H, m, 2-CH). Mass spectroscopy (70 eV), m/e (%), 182 (8), molecular ion; 164 (100), M-H₂O; 153 (12), M-Et; 135 (14), M-H₂O-Et; 124 (6), M-Et-HCO;

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110 (40), furyl-C=CH₂, 95 (98), furyl-CO.
 |
 OH

Anal. Calcd. for C₁₀H₁₄O₃: C, 65.91; H, 7.74. Found: C, 65.65;

H, 7.78.

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7. Preliminary toxicity studies indicates compound V to be just as acutely toxic to mice as naturally occurring 4-ipomeanol. Compound III, contrary to expectations, also produced similar symptoms in mice, but requires a larger lethal dosage.

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