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CHEMICAL SYNTHESIS OF THE FIRST LIGNANS TO BE FOUND IN HUMANS AND ANIMALS

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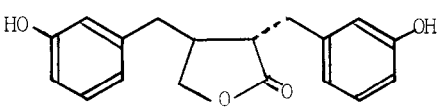
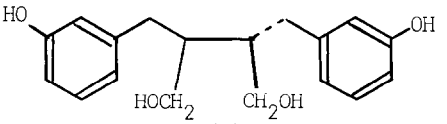
Abstract: Trans-2,3-bis-(3'-hydroxybenzyl)-butyrolactone (1) and 2,3-bis-(3'-hydroxybenzyl)-butane-1,4-diol (2), recently identified in urine, have been synthesised in racemic form.

Lignans of many types have been found in plants[1] but not hitherto in man or animals. Having recently participated in the identification[2] of two lignans of novel structures found in the urine of humans, baboons, vervet monkeys, and rats, we now describe a chemical synthesis which served to confirm the structures of these compounds. Their biological importance has yet to be assessed, but the observation of cyclical excretion in the female with a surge in the luteal phase,[3] a sharp rise in lignan excretion during early pregnancy,[3] and the known anti-cancer properties of certain plant lignans,[4] would suggest the possibility of a significant physiological rôle. The new lignans are unusual in lacking any para-oxygen substituent in the phenolic rings.



(1)



(2)

A condensation of classic Stobbe type[5] was employed to construct the C_{18} framework. Diethyl succinate in ether was condensed with 3-benzyloxybenzaldehyde (1 molar proportion) in the presence of sodium ethoxide. Alkaline hydrolysis and acidification gave 3'-benzyloxybenzylidene succinic acid, m.p. 194-196° (from acetone-hexane), λ_{max}^{EtOH} 213-217 (ε = 25,600), 261 (ε = 18,700) and ca 300 nm (sh) (ε ≈ 5500); ν_{max} (Nujol) 3400-2500 (CO_2H) and 1705-1675 cm^{-1}; δ($CDCl_3$-C_5D_5N) 3.62 (CH_2CO_2H), 5.09 ($PhCH_2$), 6.92-7.42 (9H, Ar-H), 7.95 (=CH); and 10.18 ppm (CO_2H). The methyl ester (formed by reaction with CH_3I-K_2CO_3-DMF) was condensed with a second molar proportion of 3-benzyloxybenzaldehyde under similar conditions to give bis-(3'-benzyloxybenzylidene)-succinic acid, m.p. 178-179° (from acetone), ν_{max} (Nujol) 3200-2200 and 1670 cm^{-1}; λ_{max} (EtOH) 215 (ε = 30,400), 264.5 (ε = 24,100) and ca 310 nm (sh) (ε ≈ 12,100); δ($CDCl_3$-C_5D_5N) 4.92 ($PhCH_2$), 6.8-7.35 (18H, Ar-H), 7.90 (2H, =CH), and 12.33 ppm (CO_2H).

Catalytic hydrogenation of bis-(3'-benzyloxybenzylidene)-succinic acid in ethyl acetate over palladium-charcoal gave (±)-2,3-bis-(3'-hydroxybenzyl)-succinic acid m.p. 243-244° (from acetone-hexane), ν_{max} (Nujol) 3400-2300 and 1694 (CO_2H) cm^{-1}; δ($CDCl_3$-C_5D_5N) 3.1-3.28 [m,(CH_2-CH)$_2$], 6.76-7.10 (Ar-H), and 11.08 ppm (CO_2H). The relative configuration was inferred from that of the

derived lignan (1) (see below).

This succinic acid derivative afforded its anhydride with acetic anhydride and pyridine, the phenolic groups also being acetylated. The anhydride {ν_{max} 1850 and 1760 cm^{-1}; $\delta(CDCl_3)$ 2.32 [s, $(OAc)_2$], 2.90-3.10 [m, 6H, $(CH_2\text{-}CH)_2$], 6.78-7.4 ppm (8H, ArH)} was reduced with $NaBH_4$ in DMF to give the diacetate of the lignan (1) as a gum, ν_{max} 1760-1735 cm^{-1} (lactone and OAc); $\delta(CDCl_3)$ 2.30 [6-H, $(OAc)_2$], 2.57 (4H) and 2.98 (2H) ($ArCH_2\text{-}CH\text{-}CH\text{-}CH_2Ar$), 3.85 and 4.08 (2H, two m, CH_2O), 6.65-7.06 (6H, m, Ar-H) and 7.14-7.38 ppm (2H, t of d, ArH). Careful hydrolysis ($NaHCO_3$-aqu. 80% methanol; 18 h at room temperature) gave (±)-trans-2,3-bis-(3'-hydroxybenzyl)-butyrolactone (1). Purification by hplc gave the lignan as a gum, λ_{max} (EtOH) 272.5 (ε = 2040) and 279 nm (sh, ε = 1840); ν_{max} (KBr) 3380 (OH) and 1747 (lactone) cm^{-1}; $\delta(CDCl_3)$ 2.52 (4H, m, $W_{\frac{1}{2}}$ = 7Hz) and 2.92 (2H, m, $W_{\frac{1}{2}}$ = 9Hz) ($ArCH_2\text{-}CH\text{-}CH\text{-}CH_2Ar$), 3.87 and 4.13 (dd of doublets, J = 10Hz and 6Hz, $CH\text{-}CH_2O$), 5.35 (br. s, $W_{\frac{1}{2}}$ ~50Hz, OH), 6.48-6.76 (complex, Ar-H, 6H), 7.06-7.25 (dt, Ar-H, 2H). Mass spectrum (as bis-trimethyl silyl ether), m/z 442 (M^+) and 180 (base peak).[3]

Reduction of a further sample of the succinic anhydride derivative with $LiAlH_4$ afforded (±)-2,3-bis-(3'-hydroxybenzyl)-butane-1,4-diol (2), m.p. 145-148° (from CH_2Cl_2), ν_{max} (KBr) 3410, 3150 (br. sh.) and 1588 cm^{-1}; $\delta(CDCl_3\text{-}C_5D_5N)$ 1.92 (br. s, $W_{\frac{1}{2}}$ = 18Hz, CH-CH), 2.69-2.87 [m, $(Ar\text{-}CH_2)_2$, and $(OH)_2$ removed by D_2O], 3.52 (dd, J 11.5 and 4.2Hz) and 3.83 (dd, J 11.5 and 2.0 Hz) [$(CH_2OD)_2$], 5.4 [br. s, $(ArOH)_2$], 6.63-6.76 (m, 6H, Ar-H), and 7.02-7.18 (m, 2H, Ar-H). Mass spectrum (as tetrakis-trimethylsilyl ether) m/z 590 (M^+), 500, 410, and 180 (base peak).[3]

Identity of (1) and (2) with the corresponding urinary products was confirmed by spectral comparisons, tlc, hplc, and gc-ms (as trimethylsilyl ethers). The relative configurations of compounds (1) and (2) (and thence of the intermediate succinic acid) followed from comparisons of their ^1H and ^{13}C nmr spectra with those respectively of matairesinol dimethyl ether [the 3',4'; 3",4"-tetramethoxy analogue of (1)][1] and dihydrocubebin [3',4'; 3",4"-bis-methylenedioxy analogue of (2)].[1] Spectral details will be published elsewhere.

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