Synthesis of 6-Hydroxy-5,7-dimethoxy-2-naphthoic Acid, an Extractive of Elm Wood

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The title compound has been prepared from 4-hydroxy-3,5-dimethoxybenzaldehyde by a Stobbe tetralone carboxylic acid synthesis.

FROM the aqueous extract of the heartwood of *Ulmus thomasii* Sarg. (' rock elm '), there have been isolated [1-3] three racemic lignans (thomasic acid, thomasidioic acid, and lyoniresinol), a lignan glycoside [(+)-lyoniresinol 2-α-rhamnoside], a quinone (2,6-dimethoxybenzoquinone), and two phenolic naphthoic acid derivatives, formulated as (1) and (2). (±)-Lyoniresinol [4,5] and the quinone [6] were previously known, and the two lignan carboxylic acids have been synthesized recently.[7] The

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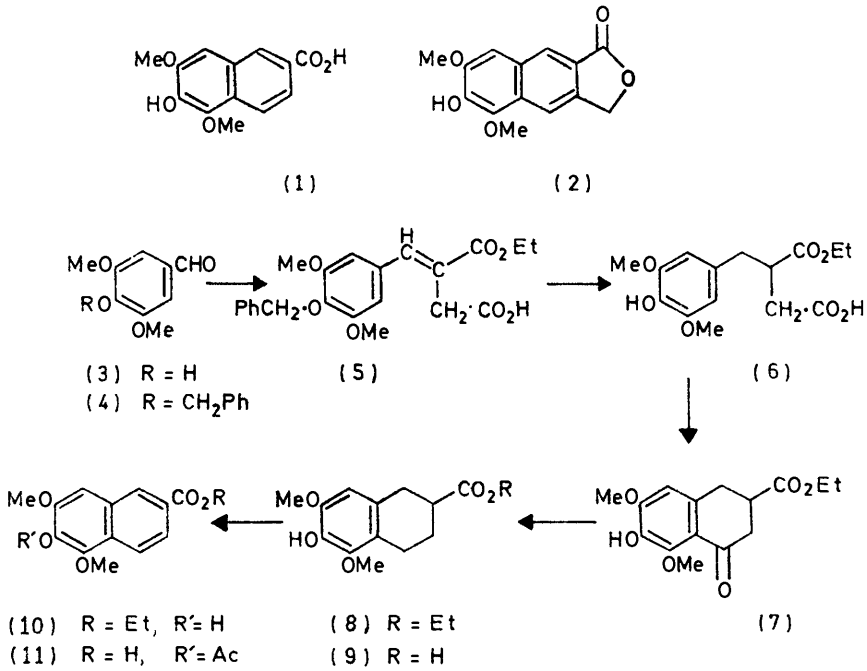
[3] C.-L. Chen and F. D. Hostettler, *Tetrahedron*, 1969, **25**, 3223.
[4] K. Freudenberg and K. Weinges, *Tetrahedron Letters*, 1959, 19.
[5] K. Weinges, *Chem. Ber.*, 1961, **94**, 2522.
[6] J. Polonsky and E. Lederer, *Bull. Soc. chim. France*, 1959, 1157.
[7] R. Ahmed, M. Lehrer, and R. Stevenson (*a*) *Tetrahedron Letters*, 1973, 747; (*b*) *Chem. and Ind.*, 1973, 1001; (*c*) *Tetrahedron*, 1973, **29**, 3753.

natural occurrence of the naphthalene derivatives, probably a result of lignan biodegradation, is of biogenetic interest, and we report here the synthesis of 6-hydroxy-5,7-dimethoxy-2-naphthoic acid (1).

Syringaldehyde (3), prepared from 2,6-dimethoxyphenol by the Duff reaction,[8] was converted into the benzyl ether (4) in excellent yield and this was subjected to the Stobbe condensation with diethyl succinate in t-butyl alcohol containing potassium t-butoxide as condensing agent to give the itaconic half ester (5) as a mixture of isomers. In accord with customary practice, this was hydrogenated (without further purification) over palladium–carbon in acetic acid to give the succinic half ester (6), cyclization of which with polyphosphoric acid gave the tetralone (7). Catalytic hydrogenolysis of the carbonyl group of (7) yielded the tetralin ester (8) or acid (9), depending on the work-up procedure. Dehydrogenation of the ester (8) with palladium–carbon in diethylene glycol yielded the ethyl naphthoate (10), which on hydrolysis gave the acid (1). Comparisons with physical and spectral data reported for the elm phenolic acid (1) and the acetate derivative (11) established the identity of the synthetic and natural products.



EXPERIMENTAL

N.m.r. spectra were determined for solutions in [^{2}H]-chloroform (unless otherwise stated) with tetramethylsilane as internal standard.

Syringaldehyde (4-hydroxy-3,5-dimethoxybenzaldehyde) (3), prepared as previously described,[8] had m.p. 113—114°; δ 3·95 (s, 3- and 5-OMe), 6·23 (s, 4-OH), 7·15 (s, 2- and 6-H), and 9·80 (s, CHO).

4-Benzyloxy-3,5-dimethoxybenzaldehyde (4).—(*a*) Sodium hydroxide (12·6 g) in water (45 ml) was added to a solution of syringaldehyde (5·0 g) in hot water (20 ml). The resultant yellow precipitate was collected, washed with ether, and dried (65°; 1 h). Freshly distilled benzyl chloride (20 ml) and xylene (15 ml) were added to this salt, and the mixture was heated under reflux for 5 h. Saturated aqueous sodium hydrogen carbonate (45 ml) was added and the excess of benzyl chloride removed by steam distillation. Potassium hydroxide solution (20%; 25 ml) was then added and the product was extracted with ether. Evaporation of the washed and dried extract gave a yellow oil, which on one crystallization from ether–light petroleum (b.p. 38—45°) yielded the benzyl ether as prismatic needles (6·8 g, 90%), m.p. 59—60° (lit.,[9] yield 62·5%, m.p. 63°) (Found: C, 70·8; H, 6·2. Calc. for $C_{16}H_{16}O_4$: C, 70·55; H, 5·9%); δ 3·87 (s, 3- and 5-OMe), 5·13 (s, PhCH_2·O), 7·17 (s, 2- and 6-H), 7·25—7·60 (m, ArH), and 9·86 (s, CHO); *m/e* 272 (M^+), 244 (M − CO), and 181 (M − $PhCH_2$).

(*b*) In a shorter procedure, a mixture of syringaldehyde (250 mg), potassium hydroxide (0·3 g), water (2 ml), and freshly distilled benzyl chloride (180 mg) was heated under reflux overnight, then extracted with chloroform. Evaporation of the washed and dried extract gave the benzyl ether as yellow oil (290 mg) of sufficient purity for further reaction.

Stobbe Condensation of the Benzyl Ether (4) *with Diethyl Succinate.*—A solution of the aldehyde (4) (3·6 g) and diethyl succinate (3·4 g) in dry t-butyl alcohol (15 ml) was added to a solution of potassium t-butoxide (2·2 g) in the same solvent (25 ml) under nitrogen and the mixture was heated at 150—160° for 90 min. It was then cooled, acidified with concentrated hydrochloric acid, and concentrated under reduced pressure to give a viscous yellow oil, which was treated with ice–water and extracted with ether. The ether layer was then repeatedly extracted with saturated sodium hydrogen carbonate solution. This base-soluble

[8] C. F. H. Allen and G. W. Leubner, *Orb. Synth.*, Coll. Vol. 4, 1963, p. 866.

[9] K. Kratzl, T. Horejschi, and G. Billek, *Monatsh.*, 1954, **85**, 1154.

fraction was then acidified and re-extracted with ether, and the washed and dried extract was evaporated to give a residual brown oil (5·0 g), regarded as crude 3-ethoxycarbonyl-4-(4-benzyloxy-3,5-dimethoxyphenyl)but-3-enoic acid (5) (mixture of geometric isomers), δ 1·22 (t) and 1·32 (t) (total 3H, $CH_3 \cdot CH_2 \cdot O_2C$), 3·60 (s) and 3·70 (s) ($CH_2 \cdot CO_2H$), 3·78 (s, OCH_3), 4·13 (q) and 4·27 (q) (total 2H, $CH_3 \cdot CH_2 \cdot O_2C$), 5·03 (s, CH_2Ph), 6·62 (s, aromatic H-2 and -6), 7·2—7·6 (m, ArH), 7·83 (s) and 7·95 (s) (vinyl H), and 10·12br (s, CO_2H). This was used without further purification.

Ethyl 1,2,3,4-*Tetrahydro*-6-*hydroxy*-5,7-*dimethoxy*-4-*oxo*-2-*naphthoate* (7).—A solution of the half ester (5) (7·4 g) in acetic acid (30 ml) was stirred with 10% palladium–carbon (150 mg) under hydrogen for 6 h with further catalyst addition (50 mg) at 2 h intervals. The catalyst was then removed and the filtrate was diluted with water and extracted with chloroform. This extract was then repeatedly extracted with saturated sodium hydrogen carbonate solution; the combined basic extract was acidified with hydrochloric acid (6N) and worked up with ether to yield 3-ethoxycarbonyl-4-(4-hydroxy-3,5-dimethoxyphenyl)butanoic acid (6) as a pale yellow oil; δ 1·18 (t, $CO_2 \cdot CH_2 \cdot CH_3$), 2·4—3·3br (m, $CH_2 \cdot CH \cdot CH_2$), 3·83 (s, OMe), 4·13 (q, $CO_2 \cdot CH_2 \cdot CH_3$), 6·40 (s, ArH), and 8·30br (s, OH and CO_2H).

A mixture of the oily half ester (6) (1·0 g) and polyphosphoric acid (2 g) was heated for 10 min with stirring on a steam-bath, cooled, diluted with ice–water and extracted with ethyl acetate. The washed and dried extract was chromatographed on neutral alumina, elution with benzene–ether (3 : 1) giving *ethyl* 1,2,3,4-*tetrahydro*-6-*hydroxy*-5,7-*dimethoxy*-4-*oxo*-2-*naphthoate* (7), as needles (300 mg), m.p. 105—106° (from diethyl ether), $\lambda_{max.}$ (KBr) 5·77 (ester C=O) and 6·01 μm (tetralone C=O) (Found: C, 60·95; H, 6·25. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·15%); δ 1·22 (t, $CO_2 \cdot CH_2 \cdot CH_3$), 2·6—3·2 (m, $CH_2 \cdot CH \cdot CH_2$), 3·83 (s) and 3·88 (s) (OMe), 4·13 (q, $CO_2 \cdot CH_2 \cdot CH_3$), 5·93br (s, OH), and 6·50 (s, H-8).

1,2,3,4-*Tetrahydro*-6-*hydroxy*-5,7-*dimethoxy*-2-*naphthoic Acid* (9).—A solution of the tetralone (7) (350 mg) in glacial acetic acid (30 ml) was stirred with 10% palladium–carbon (50 mg) for 20 min under hydrogen (uptake complete), filtered, diluted with water, and extracted with chloroform. The extract was washed with 10% sodium hydroxide solution and the combined washings were acidified with 6N-hydrochloric acid and extracted with chloroform. Crystallization of the residue obtained by evaporation of the dried extract from chloroform–octane gave the *acid* (9) as needles (300 mg), m.p. 155—156°, $\lambda_{max.}$ 3·1—3·6 and 5·84 μm (CO_2H) (Found: C, 61·7; H, 6·45. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%); δ 1·6—3·2 (m, $[CH_2]_2 \cdot CH \cdot CH_2$), 3·84 (s, 5- and 7-OMe), and 6·41 (s, H-8).

Ethyl 1,2,3,4-*Tetrahydro*-6-*hydroxy*-5,7-*dimethoxy*-2-*naphthoate* (8).—(*a*) The tetralone (7) was hydrogenolysed as in the previous experiment except that the sodium hydroxide extractive treatment was omitted. Evaporation of the chloroform extract gave the ethyl ester (8) as a pale yellow oil, $\lambda_{max.}$ ($CHCl_3$) 5·82 μm (ester), δ 1·27 (t, $CO_2 \cdot CH_2 \cdot CH_3$), 2·0—3·1 (m, $[CH_2]_2 \cdot CH \cdot CH_2$), 3·83 (s, 5- and 7-OMe), 4·18 (q, $CO_2 \cdot CH_2 \cdot CH_3$), 5·5br (s, OH), and 6·42 (s, H-8).

(*b*) Esterification of the tetralin acid (9) with ethanol and concentrated hydrochloric acid yielded the same ester (8) (i.r. and n.m.r. comparison), which was used without further purification.

Ethyl 6-*Hydroxy*-5,7-*dimethoxy*-2-*naphthoate* (10).—Palladium–carbon (10%; 150 mg) was added to a solution of the tetralin ester (8) (590 mg) in diethyleneglycol (5 ml) and the mixture was heated at 260—280° for 12 h under nitrogen. The filtered product was diluted with water and extracted with chloroform, and the washed and dried extract was evaporated to give a dark oil. This was purified by t.l.c. on silica gel (1 mm) with benzene–ether (1 : 3) yielding a red oil, which crystallized from chloroform–light petroleum (b.p. 60—110°) to give the *ester* (10) as dark red prisms (300 mg), m.p. 122—123° (Found: C, 65·1; H, 5·85. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·85%); δ 1·43 (t, $CO_2 \cdot CH_2 \cdot CH_3$), 3·97 (s) and 4·03 (s) (5- and 7-OMe), 4·42 (q, $CO_2 \cdot CH_2 \cdot CH_3$), 6·08 (s, OH), 7·02 (s, H-8), 7·98 (m, H-3 and -4), and 8·43 (m, H-1).

6-*Hydroxy*-5,7-*dimethoxy*-2-*naphthoic Acid* (1).—To a solution of the ester (10) (220 mg) in ethanol (3 ml), aqueous potassium hydroxide (5%; 10 ml) was added. The mixture was heated under reflux for 2 h, cooled, acidified with N-hydrochloric acid, and worked up in the usual way by ether extraction. Crystallization of the product from chloroform–methanol gave the *acid* as tan-coloured fine needles, m.p. 224—227° (lit.,[2] 215—217°; 226—228° before recrystallization); δ [$(CD_3)_2CO$] 4·02 (s, 5- and 7-OMe), 4·3br (s, OH and CO_2H), 7·30 (s, H-8), 7·95 (m, H-3 and -4), and 8·50 (m, H-1) (Found: C, 63·2; H, 4·95%. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·85%).

6-*Acetoxy*-5,7-*dimethoxy*-2-*naphthoic Acid* (11).—The phenolic acid (1) (75 mg) in acetic anhydride (20 ml) and pyridine (1 ml) was heated under reflux for 1 h, then the mixture was diluted with water and extracted with ether. The residue from evaporation of the extract was dissolved in dioxan–water (1 : 1; 8 ml) and heated on a steam-bath for 6 h. The solution was then evaporated under reduced pressure. Crystallization of the residue from aqueous methanol gave the acetate (11) as pale yellow needles (65 mg), m.p. 228—230° (lit.,[3] 219—220°), δ [$(CD_3)_2CO$] 2·36 (s, OAc), 3·96 (s) and 3·99 (s) (5- and 7-OMe), 7·39 (s, H-8), 8·05 (m, H-3 and -4), and 8·55 (m, H-1).

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