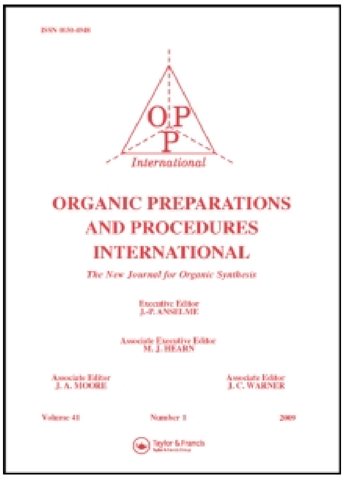

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SYNTHESIS OF α-GUAIACONIC ACID (FUROGUAIACIN)

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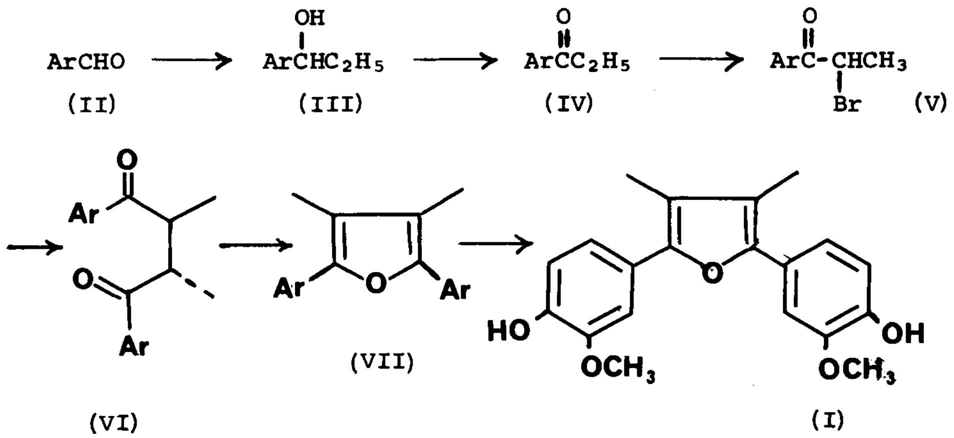
The hardwood, Guaiacum officinale, known commercially as "lignum vitae" and renowned for durability and high density, yields a resin extractive called gum guaiac on boiling with seawater. Both the resin and wood have had pharmacological application and were formerly included in the U.S. Pharmacopoeia. An ethanolic extract of the resin gives a blue colour on exposure to air and has been used as a sensitive test for oxidizing agents including oxidative enzymes.



$$\underset{\text{(II)}}{\mathrm{ArCHO}} \longrightarrow \underset{\text{(III)}}{\mathrm{Ar}\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}\mathrm{HC_2H_5}} \longrightarrow \underset{\text{(IV)}}{\mathrm{Ar}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{C_2H_5}} \longrightarrow \mathrm{Ar}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\text{-}\underset{\mathrm{Br}}{\underset{|}{\mathrm{C}}}\mathrm{HCH_3}\ \text{(V)}$$

Ar = 4-Benzyloxy-3-methoxyphenyl

The active constituent, known since 1906 as α-guaiaconic acid[1] escaped isolation and adequate characterization[2] until the recent report indicating the structure 2,5-di-(4-hydroxy-3-methoxyphenyl)-3,4-dimethylfuran (1) for this product and the derived bis-methylenequinone for guaiacum blue.[3] In earlier work, the constituent phenolic lignans were isolated as their methyl and/or ethyl ethers; thus, furoguaiacin, the natural precursor of the isolated dimethyl- and diethylfuroguaiacins, would be identical to α-guaiaconic acid. We now report a short efficient synthesis of this phenol furan lignan.

Benzylvanillin (II) was converted to the ethyl ketone (IV) by treatment with ethyl magnesium bromide followed by Jones' oxidation of the intermediate alcohol (III). Alkylation of (IV) with the derived α-bromoketone (V), conducted in liquid ammonia by the procedure of Perry and coworkers,[4] yielded the diketone (VI) in excellent yield. Cyclization of (VI) to the furan (VII) and debenzylation completed the synthesis of (I) with empirical constants in excellent agreement with those reported.

EXPERIMENTAL

P.m.r. spectra are reported for $CDCl_3$ solutions.

4-Benzyloxy-3-methoxypropiophenone (IV). — A solution of O-benzylvanillin[5] (20 g.) in benzene was added over 15 min. to ethylmagnesium bromide, prepared from magnesium (2.2 g.), Vitride[6] (0.5 ml), ethyl bromide (7.4 ml) and ether (100 ml), the mixture stirred for an additional 15 min. and worked up in the usual way. Removal of solvent gave the alcohol (III) as a solid [δ 0.87 (t, 3H, CH_3), 1.50-1.98 (m, 2H, CH_2), 2.33 (s, 1H, OH), 3.82 (s, 3H, OMe), 4.45 (t, 1H, Ar$C\underline{H}$-), 5.08 (s, 2H, $PhCH_2$), 6.80-7.50 (m, 8H, aryl H)] which was dissolved in acetone (150 ml) and oxidized with excess Jones' reagent (1.4 M, 60 ml) at 0-10°. Work up gave the crude product as a solid (21.5 g.) which crystallized from methylene chloride-isopropyl ether as prisms (18.0 g.), m.p. 99-101° (lit.[7] m.p. 98-101°), δ 1.20 (t, 3H, CH_3), 2.93 (q, 2H, CH_2), 3.92 (s, 3H, OCH_3), 5.22 (s, 2H, $PhCH_2$), 6.83-7.65 (m, 8H, aryl H).

α-Bromo-4-benzyloxy-3-methoxypropiophenone (V), prepared in quantitative yield in chloroform solution,[8] crystallized from methanol as clusters of needles, m.p. 89-91° (lit. m.p. 86-87°,[8] 87-90°[7]), δ 1.69 (d, 3H, CH_3), 3.90 (s, 3H, OMe), 5.20 (s, 2H, $PhCH_2$), 5.24 (q, 1H, CHBr), 6.83-7.70 (m, 8H, aryl H).

(±)-2,3-Bis(4-Benzyloxy-3-methoxybenzoyl)butane (VI). — To liquid ammonia (ca. 125 ml), ferric chloride (a few mg) was added, followed by sodium (150 mg) and the mixture stirred until disappearance of the blue colour. A solution of the ketone (IV) (1.57 g.) in tetrahydrofuran (30 ml) was then added and stirred for 10 min., followed by the bromoketone (V) (2.04 g.) in the same solvent (10 ml). Stirring was continued for 1 hr, solid ammonium chloride (2 g.) then added and the ammonia allowed to evaporate. The mixture was filtered, washed with chloroform and solvents evaporated to yield a gum (3.1 g.) which crystallized from methylene chloride-methanol to give the diketone (VI) as short fine needles, m.p. 144-145°, v (KBr) 1663 cm^{-1}, δ 1.26 (d, 6H, CH_3), 3.90 (s, 6H, OMe), *ca*. 3.90 (m. partly hidden, 2H, CH), 5.22 (s, 4H, $PhCH_2$), 6.85-7.77 (m, 16H, aryl H).

Anal. Calcd. for $C_{34}H_{34}O_6$: C, 75.81; H, 6.36

Found: C, 75.80; H, 6.41

3,4-Dimethyl-2,5-bis(4'-benzyloxy-3'-methoxyphenyl)furan (VII). — A solution of hydrogen chloride in methanol (3%, 50 ml) was added to a solution of the diketone (VI) (1.5 g.) in chloroform (25 ml), and the mixture heated under reflux for 1 hr. The product (dibenzyl α-guaiaconic acid) which separated on cooling, was collected by filtration as needles (1.43 g.) of analytical purity after washing with cold methanol, and had m.p. 161-162°, δ 2.15 (s, 6H, CH_3), 3.88 (s, 6H, OMe), 5.12 (s, 4H, $PhCH_2$), 6.83-7.57 (m, 16H, aryl H).

Anal. Calcd. for $C_{34}H_{32}O_5$: C, 78.44; H, 6.20

Found: C, 78.56; H, 6.12

α-Guaiaconic Acid (Furoguaiacin) (I). — A solution of the furan (VII) (500 mg) and *p*-toluenesulphonic acid (50 mg) in tetrahydrofuran (35 ml) and acetic acid (15 ml) was stirred with palladium-carbon (10%, 500 mg) under a hydrogen atmosphere for 25 min., the catalyst and solvent removed, and the residual oil (360 ml) crystallized from aqueous methanol containing a drop of acetic acid to give 3,4-dimethyl-2,5-bis (4′-hydroxy-3′-methoxyphenyl) furan as needles, m.p. 149-150° (lit.[3] m.p. 149°) with concordant n.m.r. spectrum.

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