Furoguaiaoxidin—A New Enedione Lignan of *Guaiacum officinale* L: A Novel Method of Sequential Introduction of Alkoxy Functions in the 3- and 4-Methyl Groups of 2,5-Diaryl-3,4-dimethylfurans

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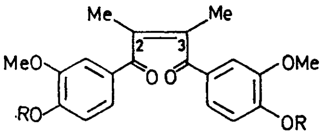
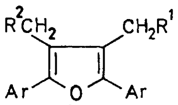
Summary The structure of furoguaiaoxidin, a new enedione lignan of *Guaiacum officinale* has been elucidated and a novel method of sequential introduction of alkoxy functions in the 3- and 4-methyl groups of 2,5-diaryl-3,4-dimethylfurans is described.

In continuation of our work[1] on the polar extractives (alcoholic extract) of Lignum Vitae, the heartwood of *Guaiacum officinale* L (*Zygophyllaceae*), we now report the isolation, as the diethyl derivative, of another new lignan which we have called furoguaiaoxidin. Structure (I) is assigned to diethylfuroguaiaoxidin (DFO) on the basis of spectral and chemical evidence. During this investigation a novel method of sequential introduction of alkoxy functions in the 3- and 4-methyl groups of 2,5-diaryl-3,4-dimethylfurans has been developed.

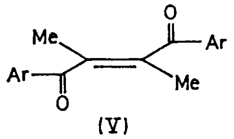
Analytical and spectroscopic data are in good agreement with the proposed structure (I): $C_{24}H_{28}O_6$, *m/e* 412 (M^+) (*cf.* 409, Rast; 429, benzene, 45 °C), other significant peaks at 179 and 151; m.p. 105 (light petroleum–EtOAc, small volume) and 120 °C (light petroleum–EtOAc, large volume); λ_{max} (EtOH) 230 (log ϵ 4·33), 280(4·17), 315 (4·13) nm (3,4-dioxygenated aroyl chromophore); ν_{max} (KBr) 1585 (Ph) and 1635 cm^{-1} (conjugated $>$C=O); δ† ($CDCl_3$), 1·46 (6H, t, *J* 7 Hz) and 4·1 (4H, q, *J* 7 Hz, $ArOCH_2Me$), 2·16 [6H, s, –(*Me*)C=C(*Me*)–], 3·80 (6H, s, ArO*Me*), 6·75 (2H, d, *J* 8 Hz), 7·00 (2H, d, *J* 2 Hz), and 7·25 (2H, dd, *J* 8 and 2 Hz). The structure of (I) was finally confirmed by a series of transformations and a partial synthesis of DFO.



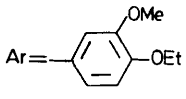
(I) R = Et
(IV) 2,3-Dihydro-(I)
(X) R = H



(II) $R^1 = R^2 = H$
(III) Tetrahydro-(II)
(VI) $R^1 = OMe, R^2 = H$
(VII) $R^1 = R^2 = OMe$
(VIII) $R^1 = OEt, R^2 = H$
(IX) $R^1 = R^2 = OEt$



(V)



Catalytic hydrogenation of DFO (I) with 10% Pd–C afforded diethylfuroguaiacin[2] (II) and its tetrahydro-derivative[2] (III), the diethyl ethers of the two congener lignans of furoguaiaoxidin. Reduction of DFO with Zn–AcOH (80%) at 45—50 °C furnished, in addition to (II), another product, m.p. 185 °C which from its various spectral data [λ_{max} (EtOH) 232 (log ϵ 4·18), 280 (4·06), 310 (4·01) nm; ν_{max} (Nujol) 3300, 1670, and 1595 cm^{-1}; δ† 1·1

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† All compounds derived from DFO exhibit usual n.m.r. signals for two 4-ethoxy-3-methoxyphenyl units and are not mentioned separately.

(6H, d), 1·66 (1H, s, disappears with D_2O); *m/e* 414 (M^+), 179, and 151] was assigned the structure (IV). DFO is also smoothly reduced to (II) by $NaBH_4$, and $Na_2S_2O_3$ or Na_2SO_3 in acidic solution at room temperature, but it fails to liberate iodine from an acidified solution of KI and is also not amenable to reduction with Na_2SO_3 in CS_2 solution. These observations, together with the results of oxygen analysis (23·02%) of DFO, rule out a peroxide or hydroperoxide structure.

Pyrolysis of DFO at 180 °C gave (V), m.p. 167 °C; λ_{max} (EtOH) 235 (log ϵ 4·53), 286 (4·32), 308 (4·34) nm; ν_{max} (KBr) 1660 (conjugated $\rangle$C=O) and 1580 cm^{-1}; δ† 1·8 [6H, s, (*Me*)C=C(*Me*)]; *m/e* 412 (M^+). These observations clearly suggest that DFO and (V) are geometrical isomers and the latter has the *trans* configuration. This is supported by the observation that irradiation[3,4] of (V) in THF for 4 h with u.v. light at 253 nm gave DFO in about 50% yield. DFO undergoes base-catalysed isomerisation[5] to (V) upon treatment with methanolic alkali. Reduction of (V) with Zn–AcOH readily converts it into (II). This reaction thus provides a new method for a one-step conversion of enediones into the corresponding furans. Unlike DFO, (V), however, does not give (II) upon reduction with $NaBH_4$, and Na_2SO_3 or $Na_2S_2O_3$ in acidic solution. This may be ascribed to the fact that such reductions presumably involve a cyclic transition state which is only possible if DFO has the *cis*-configuration. The *cis*-enedione structure (I) of DFO also accounts[6] for the lower i.r. carbonyl frequency and is finally confirmed by its partial synthesis from (II).

Although diethylfuroguaicin (II) is stable to molecular oxygen, it is converted into DFO when air is bubbled through an ethanolic solution in the presence of a photosensitizer (eosin) at room temperature.

DFO is readily converted into diethylfuroguaiacidin[1] (VI) upon heating with methanolic H_2SO_4 which confirms its structure proposed[1] earlier mainly on the basis of spectral data.‡ The compound (VI) was converted into (VII) [m.p. 125 °C; λ_{max} (EtOH) 260 (log ϵ 4·17), 322 (4·44) nm; δ† 3·50 (6H, s) and 4·50 (4H, s) (each furan-CH_2O*Me*); *m/e* 456 (M^+)] by bubbling air through an ethanolic solution in the presence of eosin followed by treatment of the product with methanolic H_2SO_4.

Analogously, treatment of DFO with ethanolic H_2SO_4 gave (VIII), m.p. 110 °C; λ_{max} (EtOH) 255 (log ϵ 3·84), 322 (4·16) nm; δ† 1·28 (3H, t, *J* 7 Hz), 3·63 (2H, q, *J* 7 Hz), and 4·45 (2H, s) (furan-CH_2OCH_2*Me*), 2·28 (3H, s, furan-*Me*); *m/e* 440 (M^+). The second ethoxy function was introduced in the 4-methyl group of (VIII) by photosensitised air-oxidation followed by treatment of the resultant product with ethanolic H_2SO_4 to give (IX), m.p. 125 °C; λ_{max} (EtOH) 260 (log ϵ 4·17), 321 (4·43) nm. The ^1H n.m.r. spectrum of (IX) does not show furan-methyl signals but shows signals for two furan-CH_2OEt groups, δ† 1·27 (6H, t, *J* 7 Hz), 3·65 (4H, q, *J* 7 Hz), and 4·55 (4H, s).

The overall yields in the conversions (II) → (I) → (VI) →(VII) and (II) → (I) → (VIII) → (IX) were about 90%. These transformations involving DFO thus offer a convenient general method for step-wise introduction of alkoxy functions in the 3- and 4-methyl groups of 2,5-diaryl-3,4-dimethylfurans.

Furoguaiaoxidin should, therefore, have the structure (X) and is the first member of an enedione lignan family. The possibility of its being a non-enzymic conversion product of (II) seems to be unlikely in view of the stability of (II) towards molecular oxygen in absence of a photosensitiser.

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‡ Professor R. Stevenson, Brandeis University, and Professor G. W. Griffin, University of New Orleans, have also synthesised (VI) by different routes.

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