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NEW LIGNANS IN *CONOCARPUS ERECTUS*

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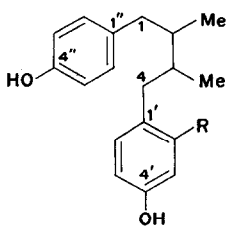
Key Word Index—*Conocarpus erectus*; Combretaceae; lignans; conocarpol; conocarpan; 1,4-diarylbutane; dehydrodi-*iso*eugenol.

Abstract—The wood of *Conocarpus erectus* contains conocarpol and 2′-methoxyconocarpol, simple 1,4-diarylbutane-type lignans, and conocarpan, a lignan of the dehydrodi-*iso*eugenol type.

Wood which is used for under-water construction in tropical seas is subject to attack by marine borers. In a recent survey [1] of a large number of woods for marine borer resistance, *Conocarpus erectus* was found to have good resistance to pholads and limnoria although more susceptible to teredo attack. It was therefore of interest to examine the extractives of this timber.



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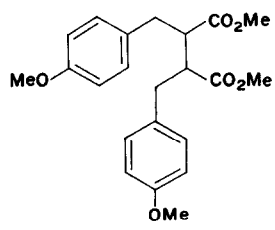

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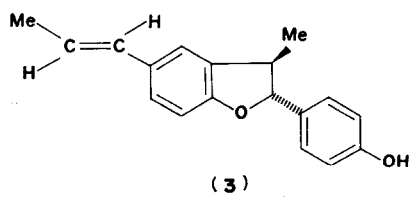

(3)

Extraction with hot chloroform ($CHCl_3$) yielded three phenols, two of which could be conveniently separated by virtue of their relative insolubility in cold $CHCl_3$. The simplest compound, conocarpol, $C_{18}H_{22}O_2$, formed a dimethyl ether, and the NMR spectrum (see Experimental) indicated a symmetrical structure each half possessing the C_6–C_3 moiety p-$HOC_6H_4CH_2CH(Me)$–. This indicates structure (**1**; R=H) for conocarpol. In agreement the MS showed a weak molecular ion at *m/e* 270, the base peak at *m/e* 107 corresponding to the *p*-hydroxybenzyl (hydroxytropylium) ion. Structure (**1**; R=H) was confirmed by synthesis of the dimethyl ether following a standard procedure [2]. Stobbe condensation of *p*-anisaldehyde and diethyl succinate, followed by hydrogenation and esterification gave (**2**). Reduction to the diol, tosylation, and further reduction with $LiAlH_4$ afforded conocarpol dimethyl ether. The mp was lower than that of the "natural" dimethyl ether although the IR (KBr) spectra were identical. The natural compound was not optically active, and presumably both natural and synthetic products are mixtures of racemic and *meso* forms. Surprisingly, this very simple lignan has not been reported previously.

The second $CHCl_3$-insoluble compound was clearly an aromatic methoxy derivative of (**1**; R=H) by spectroscopic comparison [e.g., *m/e* 300(13%)(M^+), 137(100), 107(10)], and we initially assumed, on biogenetic grounds, that it was 3′-methoxyconocarpol. This is not so. In conocarpol (**1**; R=H) deuteriation with D_2O–Et_3N–DMF [3] leads to exchange of the four protons *ortho* to the hydroxyl groups. The same procedure applied to methoxyconocarpol also leads to exchange of four protons in agreement with structure (**1**; R=OMe) (and the NMR spectrum at low field) whereas only three protons would exchange

if the compound had the isomeric 3′-methoxy structure. Under the conditions used the two protons *ortho* to hydroxyl in the more reactive ring *B* exchanged completely, and those in ring *A* exchanged ~50%. In lignans a 2′-methoxy substituent is very rare although examples are known in the flavanoid series. Methoxyconocarpol was optically active.

The third extractive was a monohydric phenol, conocarpan, $C_{18}H_{18}O_2$. Compared to conocarpol it has four hydrogens less and contains a propenyl group (NMR) and an additional ring. Detailed analysis of the NMR spectrum (see Experimental), together with biogenetic considerations indicated a structure of the dehydrodi-*iso*eugenol type, the NMR data for (**3**) being in good agreement with known [4–6] values. The *trans* stereochemistry in the dihydrofuran ring follows [7] from the chemical shifts of the proton at C-2 (δ 5·08) and the C-3 methyl protons at δ 1·38, and correlation of the C.D. curve of conocarpan acetate ($\Delta\epsilon$ positive at 260 nm) with published data [5, 8] on like compounds shows that the absolute stereochemistry must be that shown in (**3**). A synthesis of conocarpan was effected in 20% yield by oxidative dimerisation of *p*-propenylphenol with ferric chloride [9]. Conocarpan appears to be the simplest example of this small group of lignans.

EXPERIMENTAL

Spectra were run in MeOH (UV), KBr (IR), and $CDCl_3$ (NMR) unless otherwise stated. Chromatography was carried out on SiO_2, and CD measurements in MeOH.

Extraction of Conocarpus erectus. Finely ground heartwood (430 g) was extracted (Soxhlet) with petrol (bp 60–80°), and then with $CHCl_3$. Evaporation of the latter yielded a crude product (9·5 g) which was treated with a little cold $CHCl_3$. The insoluble material (550 mg) contained mainly conocarpol and 2′-methoxyconocarpol which were separated by PLC in $CHCl_3$–EtOH (20:1). The soluble portion contained in addition conocarpan which was separated by column chromatography in $CHCl_3$ followed by $CHCl_3$–EtOH, and further purified by PLC in $CHCl_3$.

Conocarpol (**1**; R=H) crystallized from EtOH in cubes, mp 174–175° (80 mg) (Found: C, 80·1; H, 8·2%. M^+ 270·1620. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·15%. M^+ 270·1619). $\Delta\epsilon$ 0·0, λ_{max} 226, 280 nm (log ϵ 4·23, 3·51), ν_{max} 3400(br), 3030, 1615, 1600, 1510 cm^{-1}, δ ($CDCl_3$–CD_3OD), 0·81 (6H, *d*, *J* 6Hz, C<u>H</u>$_3$CH), 1·74 (2H, m, CH_3C<u>H</u>), 2·24 (2H, *dd*, *J* 13 and 9Hz, $ArCH_2$), 2·72 (2H, *dd*, *J* 13 and4Hz, $ArCH_2$), 6·72 and 6·96 (each 4H, *d*, *J* 8Hz, ArH), *m/e* (%) 270(7), 107(100). The *dimethyl ether* formed leaflets, mp 90–90·5° (from EtOH) (Found: C, 80·5; H, 9·0%. M^+ 298·1932. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·7%. M^+ 298·1932), λ_{max} 227, 280, 286 nm (log ϵ 4·25, 3·50, 3·45), ν_{max} 2840, 1615, 1585 cm^{-1}.

Deuterium exchange [3] on conocarpol was effected by heating it (25 mg) in D_2O (0·2 ml) with Et_3N (0·4 ml) and dimethylformamide (3 drops) in a sealed tube at 100° for 44 hr. After evaporation to dryness, the residue was crystallized from EtOH. It had mp 170–171° and δ ($CDCl_3$–CD_3OD) 6·72 (~1·5H, d, J 9Hz) and 6·96 (4H, bs) corresponding to 62·5% exchange of H-3′,5′,3″ and 5″; *m/e* (%) 274(3·5), 273(7), 272(5·5), 109(80), 108(100).

2′-Methoxyconocarpol (**1**; R=OMe) separated from C_6H_6 in micro crystals, mp 129–130° (110 mg) (Found: C, 76·0; H, 8·0%. M^+, 300·1728. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0%. M^+, 300·1725), λ_{max} (EtOH) 235, 280, 285(sh) nm (log ϵ 3·53, 3·70, 3·53), ν_{max} 3420(br), 3020, 1620, 1600, 1520 cm^{-1}, $[\alpha]_D = 0°$ (EtOH), C.D., 225 ($\Delta\epsilon$ + 0·7), 237 (−0·27), 280 nm (+0·40), δ 0·83 (6H, *d*, *J* 6Hz, C<u>H</u>$_3$CH), 1·8 (2H, *m*, MeC<u>H</u>), 2·3 and 2·7 (each 2H, *m*, $ArCH_2$), 3·72 (3H, *s*, OMe), 6·36 (1H, *d*, *J* 2Hz, H-3′), 6·40 (1H, *dd*, *J* 9 and 2Hz, H-5′), 6·96 (1H, *d*,*J* 9Hz, H-6′), 6·72 (2H, *d*, *J* 9Hz, H-3″ and 5″), 7·02 (2H, *d*, *J* 9Hz, H-2″ and 6″), *m/e* (%) 300(13), 137(100), 107(10). After deuteriation, as above, the NMR spectrum at low field showed δ 6·72 (~1H, *d*, *J* 9Hz), 6·96 (1H, *s*) and 7·02 (2H, bs).

Conocarpan (**3**) could not be crystallized satisfactorily (20 mg) (Found: M^+, 266·1306. $C_{18}H_{18}O_2$ requires M^+, 266·1306), λ_{max} (EtOH) 229, 268, 305(sh) nm, ν_{max} (film) 3400(br), 3020, 1620, 1520, 1480, 970, 830 cm^{-1}, δ 1·38 (3H, *d*, *J* 7Hz, 3-Me), 1·86 (3H, *d*, *J* 6Hz, C<u>H</u>$_3$CH=CH), 3·40 (1H, *dq*, *J* 9 and 7Hz, H-3), 5·08 (1H, *d*, *J* 9Hz, H-2), 6·06 (1H, *dq*, *J* 16 and 6Hz, MeC<u>H</u>=CH), 6·38 (1H, *d*, *J* 16Hz, MeCH=C<u>H</u>), 6·72–6·85 (3H, *m*, ArH), 7·10–7·32 (4H, *m*, ArH). The *acetate* crystallized from petrol in cubes, mp 94–95° (Found: M^+, 308·1410. $C_{20}H_{20}O_3$ requires M^+, 308·1412), λ_{max} (EtOH) 221, 264, 305 nm (log ϵ 4·42, 2·64, 3·62), C.D., 226 ($\Delta\epsilon$ −0·70), 260 nm ($\Delta\epsilon$ +0·76), ν_{max} 3010, 1760, 1605, 1480, 970, 915 cm^{-1}.

Synthesis of conocarpol dimethyl ether (a) A soln of diethyl succinate (6·53 g) and anisaldehyde (10·2 g) in dry ether (150 ml) was added, with cooling, to a suspension of NaOEt in ether (50 ml). A yellow ppt soon appeared, and after stirring 3 hr further water (50 ml) was added, and the mixture was acidified with 6 N HCl. The product was extracted with ether which was dried (Na_2SO_4) and evaporated, and the residue crystallized from EtOH to give *1,4-di(4-methoxyphenyl)buta-1,3-diene-2,3-dicarboxylic acid*, mp 230–231° (2·71 g) (Found: M^+, 354·1102. $C_{20}H_{18}O_6$ requires M^+, 354·1103). λ_{max} 228, 286, 315(sh) nm, ν_{max} 3500–2400, 1690(sh), 1670, 1610, 1520 cm^{-1}, δ [CD_3OD–$(CD_3)_2CO$] 3·75 (6H, *s*, OMe), 6·84 (4H, *d*, *J* 8Hz, ArH), 7·50 (4H, *d*, *J* 8Hz, ArH), 7·80 (2H, *s*, –CH=). The *dimethyl ester* (prepared using Me_2SO_4, K_2CO_3, Me_2CO, N_2) had mp 145–146° (from EtOH) (Found: C, 68·9; H, 6·1%; M^+, 382·1415. $C_{22}H_{22}O_6$ requires C, 69·0; H, 5·8%. M^+, 382·1416), ν_{max} 1715 cm^{-1}.

(b) The above ester (929 mg) in EtOH (150 ml) and EtOAc (10 ml) was hydrogenated over Pd–C (10%, 600 mg) overnight to give the tetrahydro derivative [δ 2·80 and 2·92 (6H, $ArCH_2CH$)]. This (475 mg) in dry ether (120 ml) was added slowly to a suspension of $LiAlH_4$ (50 mg) in ether (50 ml). After refluxing a further 1·5 hr, EtOAc (3 ml) and 3N HCl (100 ml) were added, and the product was extracted with ether. Crystallization from EtOH gave the *diol*, mp 123–124° (650 mg) (Found: C, 72·8; H, 8·2%. M^+, 330·1832. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·9%. M^+, 330·1830). λ_{max} 229, 277, 284 nm (log ϵ 4·04, 3·50, 3·44), ν_{max} 3300(br), 1615, 1510 cm^{-1}, δ 1·9 (2H, *m*, CH_2C<u>H</u>C<u>H</u>$_2$OH), 2·7 (4H, *m*, $ArCH_2$), 3·78 (6H, *s*, OMe), 3·4–3·85 (4H, *m*, C<u>H</u>$_2$OH), 6·80 and 7·08 (each 4H, *d*, *J* 9Hz, ArH).

(c) The above diol (370 mg) was added to *p*-tosyl chloride (640 mg) in dry pyridine (5 ml), left overnight at room temp, and poured onto ice. The ppt was washed, dried, and without

further purification the ditosyl derivative (300 mg), in dry THF (30 ml), was added slowly to a stirred suspension of $LiAlH_4$ (100 mg) in THF (6 ml). The mixture was stirred 30 min more, refluxed for 3 hr, and worked up. After PLC and crystallization from EtOH the *dimethyl ether* had mp 69–70° (60 mg), identical (MMP, TLC, UV, IR) with conocarpol dimethyl ether (Found: C, 80·3; H, 8·9%. M^+, 298·1932. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·7%. M^+, 298·1932).

Synthesis of (±)-*conocarpan. p*-Propenylphenol was prepared [10] from *p*-hydroxybenzaldehyde and EtMgI (3 mol) in ether-THF. This phenol (300 mg) in EtOH (3 ml) and H_2O (3 ml) was stirred with $FeCl_3$ (400 mg) for 3 hr, and left overnight. The dimer was extracted with ether and passed down a short column of SiO_2 in $CHCl_3$ to give a crystalline solid, mp 108–110° (60 mg) identical (TLC, UV, IR) with conocarpan. (Found: M^+, 266·1306. $C_{18}H_{18}O_2$ requires M^+, 266·1306). *Acetate*, mp 94–94·5° (from petrol) (Found: C, 78·2; H, 6·7%. M^+, 308·1410. $C_{20}H_{20}O_3$ requires C, 78·0; H, 6·5%. M^+, 308·1412) identical (MMP, UV, IR, NMR, MS) with conocarpan acetate, δ 1·40 (3H, *d*, *J* 7Hz, 3-Me), 1·86 (3H, *d*, *J* 6Hz, C<u>H</u>$_3$—CH=CH), 3·40 (1H, *m*, H-2), 5·16 (1H, *d*, *J* 9Hz, H-2), 6·06 (1H, *dq*, *J* 16 and 6Hz, Me–C<u>H</u>=CH), 6·38 (1H, *d*, *J* 16Hz, Me–CH=C<u>H</u>), 6·78 (1H, *d*, *J* 8Hz, ArH), 7·1 (4H, *m*, ArH), 7·42 (2H, *d*, *J* 8Hz, ArH).

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