Phytochemistry, 1975, Vol. 14, pp. 253–255. Pergamon Press. Printed in England.

SYNTHESIS OF (±)-LICARIN-B*

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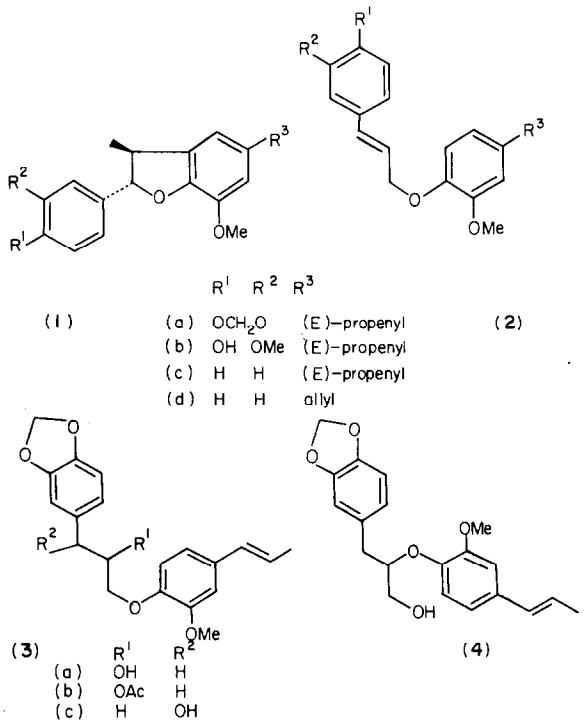
(*Received* 21 *April* 1974)

Key Word Index—Neolignans; (±)-7-methoxy-3-methyl-*trans*-2-phenyl-5-(E)-propenylcoumaran; (±)-7-methoxy-3-methyl-*trans*-2-phenyl-5-allylcoumaran; (±)-7-methoxy-3-methyl-*trans*-2-piperonyl-5-(E)-propenylcoumaran; (±)-licarin-B; pyrolysis of aryl cinnamyl ethers.

Abstract—The synthesis of (±)-licarin-B, a neolignan of *Licaria aritu* Ducke (Lauraceae), was achieved by pyrolysis of 3-hydroxy-3-piperonyl-1-propyl-2-methoxy-4-(E)-propenylphenyl ether.

Eupomatia laurina R. Br., an Australian Eupomatiaceae species, contains (+)-eupomatenoid-8, isolated as a gum, for which structure and relative stereochemistry **1**a were established [2]. The family belongs to the order Magnoliales which includes also the Lauraceae. *Licaria aritu* Ducke, a Brazilian Lauraceae species, contains not only licarin-A (**1**b), but also licarin-B, isolated as colourless crystals, m.p. 91–92°, whose structure and absolute stereochemistry are again represented by **1**a [3].



In view of the contrasting descriptions offered for eupomatenoid-8 and licarin-B, a synthesis of **1**a seemed to be required. This was achieved, even before either product was isolated from plants [4], starting from dihydrodiisoeugenol (**1**b). As this is readily obtained by $FeCl_3$ oxidation of (E)-isoeugenol, the guaiacyl unit was then selectively demethylated by periodate oxidation. SO_2 reduction of the intermediate *ortho*-quinone and methylenation of the resulting catechol led to a gum with the spectral properties of eupomatenoid-8 in 11% overall yield [2]. It was deemed desirable, nevertheless, to undertake an alternative synthesis of (±)-**1**a, in order to confirm its identity. Furthermore, since in the above process both aromatic rings of the final product stem from the same phenol which, by necessity, contains a propenyl side chain, it is useful only for the synthesis of 2-aryl-5-*propenyl*-coumarans with a limited number of oxygenation patterns. Work on neolignans is in progress [5], and additional representatives of the coumaran type may well be isolated from plant sources. For this reason a more generally applicable synthetic approach to these structures was developed.

It was shown recently that 2-(1′-arylallyl)-phenols are transformed on heating in *N*,*N*-diethylaniline at 225° into *trans*-2-aryl-3-methylcoumarans [6]. The high yields and the stereospecificity of this reaction made it an excellent general route to licarin-type compounds. It was anticipated that it would not be necessary to isolate the

* Part 28 in the series "The Chemistry of Brazilian Lauraceae". For Part 27 see Ref. 1. Sponsored by Fundação de Amparo à Pesquisa do Estado de São Paulo.

2-(1′-arylallyl)-phenols. Aryl cinnamyl ethers (**2**) are more directly available and yield initially the desired phenols through a "normal" Claisen rearrangement. If, as in the present case, the *para* position of the aryloxy-group is occupied and the reaction is allowed to continue, it proceeds in an "abnormal" way [7] leading to the coumarans.

The feasibility of this process for the synthesis of 7-propenyl- as well as of 7-allylcoumarans was tested with the cinnamyl ethers of (E)-isoeugenol (**2c**) and of eugenol (**2d**). Their pyrolysis gave, respectively, 7-methoxy-3-methyl-*trans*-2-phenyl-5-(E)-propenyl (**1c**) and 5-allylcoumaran (**1d**) in good yields. While in these cases the required ethers were prepared with ease by interaction of cinnamyl tosylate and the sodium salts of (E)-isoeugenol and eugenol, analogous substrates in which the cinnamyl moiety is activated by oxy-functions were understandably difficult to obtain. Thus, the tosylate of 3-piperonylallyl alcohol did not give the required ether (**2a**) upon reaction with the sodium salt of (E)-isoeugenol. In order to lessen the reactivity of the tosylate, it was deemed necessary to avoid conjugation of the aromatic ring and the *O*-tosyl-group. Clearly a potential 2,3-double bond had to be retained.

With this purpose, initially, 2-hydroxy-3-piperonyl-1-propyl-2-methoxy-4-(E)-propenylphenyl ether (**3a**) was prepared by the reaction of the sodium salt of (E)-isoeugenol on safrol epoxide. The isomer (**4**) accessible under different reaction conditions was distinguished from **3a** by PMR spectrometry. Unfortunately, however, **3a** proved quite stable in *N,N*-diethylaniline at 240°. In contrast, the 3-hydroxy-derivative (**3c**) gave smoothly (±)-licarin-B under these conditions, either directly or after treatment with $SOCl_2$. In contradistinction to natural licarin-B (**1a**), a crystalline solid, $[\alpha]_D$ +61·4°, synthetic licarin-B is indeed an oil and it can be concluded that eupomatenoid-8, a gum, $[\alpha]_D$ +43° [2], is a mixture of enantiomers. 3-Hydroxy-3-piperonyl-1-propyl-2-methoxy-4-propenylphenyl ether (**3c**) was prepared by a reaction sequence which involved condensation of piperonal and ethyl bromoacetate to ethyl 3-hydroxy-3-piperonylpropionate. $LiAlH_4$ reduction of the ester and selective tosylation of the resulting diol gave the intermediate which was transformed into the required ether by reaction with the sodium salt of (E)-isoeugenol.

EXPERIMENTAL

O-Cinnamylisoeugenol (**2c**). To (E)-isoeugenol (5·0 g) in anhyd. EtOH (60 ml) were added Na (portionwise, 470 mg) and cinnamyl tosylate (6 g). The mixture was stirred overnight and, subsequently, maintained under reflux (0·5 hr). After cooling to room temp., H_2O was added and the mixture extracted with Et_2O. The Et_2O soln was washed with aq. NaOH and H_2O, dried and evaporated. The residue was fractionated by preparative TLC (Merck silica gel PF 254, C_6H_6) giving **2c** as colourless crystals (700 mg), m.p. 55–65°. (Found: M, 280·1459. $C_{19}H_{20}O_2$ requires: M, 280·1463). ν_{max}^{KBr} (cm^{-1}): 1592, 1580, 1508, 1443, 1412, 1385, 1332, 1261, 1219, 1144, 1068, 1038, 1018, 965, 866, 858. PMR ($CDCl_3$, τ): 2·75 (*m*, C_6H_5), 3·3 (*m*, 3 ArH), 3·4 (*d*, *J* 15·0 Hz, PhCH=), 3·6 (*m*, C<u>H</u>CH$_2$O), 3·73 (*d*, *J* 15·0 Hz, ArC<u>H</u>=), 4·0 (*m*, =CHMe), 5·4 (*d*, *J* 5·0 Hz, CH_2O), 6·2 (*s*, OMe), 8·15 (*d*, *J* 5·0 Hz, Me). MS (*m/e*): 280 (2%) M, 164 (3), 163 (5), 117 (100), 116 (11).

O-Cinnamyleugenol (**2d**) was obtained in the same way from eugenol as an oil [8] (800 mg). ν_{max}^{film} (cm^{-1}): 1642, 1592, 1511, 1466, 1453, 1422, 1379, 1335, 1264, 1130, 1143, 1042, 971, 917, 855. PMR (CCl_4, τ): 2·85 (*m*, C_6H_5), 3·2–4·4 (*m*, 3 ArH, 3 CH=), 5·05 (*m*, =CH_2), 5·48 (*d*, *J* 5·0 Hz, CH_2O), 6·3 (*s*, OMe), 6·68 (*d*, *J* 7·0 Hz, $ArCH_2$). MS (*m/e*): 280 (1%) M, 164 (3), 163 (1), 118 (11), 117 (100).

3-Hydroxy-3-piperonyl-1-propyl-2-methoxy-4-(E)-propenyl ether (**3c**). Piperonal in benzene was condensed with ethyl bromoacetate in presence of Zn [9]. The reaction product was chromatographed on neutral Al_2O_3 to give ethyl 3-hydroxy-3-piperonyl propionate (yield 71%) as an oil. ν_{max}^{film} (cm^{-1}): 3509, 1727, 1634, 1610, 1508, 1493, 1443, 1397, 1374, 1282, 1250, 1183, 1163, 1099, 1042, 936, 868. PMR (CCl_4, τ): 3·24 – 3·34 (*m*, 3 ArH), 4·17 (*s*, O_2CH_2), 5·1 (*dd*, *J* 7·0 Hz, C<u>H</u>OH), 5·97 (*t*, *J* 7·0 Hz, OCH_2), 6·40 (*br. s*, OH), 7·44 (*m*, CH_2CO), 8·80 (*d*, *J* 7·0 Hz, Me). MS (*m/e*): 238 (58%) M, 220 (9), 193 (12), 152 (24), 151 (100), 150 (19), 149 (52), 148 (13), 123 (54), 122 (11), 121 (14). The propionate in Et_2O was reduced with $LiAlH_4$ in Et_2O [10a]. The reaction product was chromatographed on neutral Al_2O_3 to give 1,3-dihydroxy-1-piperonylpropane (yield 70%) as an oil. ν_{max}^{film} (cm^{-1}): 3390, 1613, 1504, 1490, 1250, 1101, 1044, 938. PMR (CCl_4, τ): 3·20–3·30 (*m*, 3 ArH), 4·14 (*s*, O_2CH_2), 5·29 (*t*, *J* 6·0 Hz, H-1), 6·07 (*s*, 2 OH), 6·30 (*t*, *J* 6·0 Hz, 2 H-3), 8·17 (*q*, *J* 6·0 Hz, 2 H-2). The diol in C_5H_5N tosylated with an equivalent of TsCl (at 0–10°) [10b]. The crude tosylate (8·9 g) was added to the Na salt of isoeugenol (6 g) in DMF (60 ml). The mixture was stirred at room temp. (12 hr). The solvent was evaporated under vacuum. The residue was extracted with Et_2O. The soln was washed (H_2O), dried and evaporated. The residue (9·7 g) was recrystallized from CCl_4 to give **3c** as colourless solid (4·3 g), m.p. 97–99°. (Found: M, 342·1471. $C_{20}H_{22}O_5$ requires: M, 342·1467). ν_{max}^{KBr} (cm^{-1}): 3333, 1603, 1580, 1499, 1462, 1437, 1404, 1339, 1316, 1264, 1230, 1183, 1166, 1145, 1107, 1056, 1031, 966, 925, 912, 882, 851. PMR ($CDCl_3$, τ): 3·12–3·22 (*m*, 6 ArH), 3·64 (*d*, *J* 15·0 Hz, ArCH=), 3·80–4·00 (*m*, ArCH=C<u>H</u>), 4·10 (*s*, O_2CH_2), 5·07 (*t*, *J* 7·0 Hz, C<u>H</u>OH), 5·72–5·98 (*m*, CH_2O), 6·10 (*s*, OMe), ~6·85 (*br s*, OH), 7·84 (*m*, C<u>H</u>$_2$CH$_2$O), 8·14 (*d*, *J* 5·0 Hz, Me). MS (*m/e*): 342 (37%) M, 324 (6), 179 (12), 165 (13), 164 (100), 161 (12), 152 (12), 151 (27), 149 (37), 148 (30), 131 (19), 123 (12), 121 (12).

2-Hydroxy-3-piperonyl-1-propyl-2-methoxy-4-(E)-propenyl ether (**3a**). Safrol epoxide (4 g) and Na salt of (E)-isoeugenol in *N,N*-dimethylformamide were stirred (24 hr). H_2O added and the mixture extracted with Et_2O. The Et_2O soln was washed (H_2O), dried and evaporated. The residue was purified by passage through a florisil column giving **3a**, p.f. 54–58°. ν_{max}^{film} (cm^{-1}): 3497, 1603, 1582, 1511, 1490, 1443, 1412, 1374, 1333, 1299, 1250,

1190, 1163, 1142, 1101, 1042, 967, 933, 862. PMR (CCl_4, τ): 3·24–3·44 (*m*, 6 ArH), 3·74 (*d*, *J* 16·0 Hz, ArCH=), 3·90–4·30 (*m*, ArCH=C<u>H</u>), 4·20 (*s*, O_2CH_2), 5·90–6·34 (*m*, 2 H-1′, H-2′), 6·27 (*s*, OMe), 6·50–6·87 (*br s*, OH, disappears with D_2O), 7·29 (*d*, *J* 6·0 Hz, $ArCH_2$), 8·17 (*d*, *J* 6·0 Hz, Me). MS (*m/e*): 342 (13%) M, 279 (4), 165 (15), 164 (100), 163 (16), 149 (28), 136 (41), 135 (84), 131 (13), 121 (13), 119 (29), 117 (29). Reflux in Ac_2O–C_5H_5N (2 hr) gave **3b** as an oil. ν_{max}^{film} (cm^{-1}): 1730, 1597, 1502, 1484, 1441, 1412, 1368, 1233, 1161, 1142, 1098, 1041, 965, 930, 861. PMR (CCl_4, τ): 3·24–3·44 (*m*, 6 ArH), 3·74 (*d*, *J* 16·0 Hz, ArCH=), 3·87–4·34 (*m*, ArCH=C<u>H</u>), 4·20 (*s*, O_2CH_2), 4·67–5·07 (*m*, CHOAc), 6·14 (*d*, *J* 5·0 Hz, CH_2O), 6·24 (*s*, OMe), 7·44 (*d*, *J* 7·0 Hz, $ArCH_2$), 8·07 (*s*, COMe), 8·20 (*d*, *J* 6·0 Hz, =CHC<u>H</u>$_3$). MS (*m/e*): 384 (1%) M, 222 (4), 221 (32), 162 (15), 161 (100), 149 (15), 135 (27), 132 (11), 131 (100).

1-*Hydroxy*-3-*piperonyl*-2-*propyl*-2-*methoxy*-4-(E)-*propenyl ether* (**4**). Safrol and *m*-chloroperbenzoic acid in CH_2Cl_2 gave safrol epoxide acc. to a described procedure [10c]. PMR (CCl_4, τ): 3·37–3·24 (*m*, 3 ArH), 4·19 (*s*, O_2CH_2), 6·9–7·2 (*m*, CHO), 7·3–7·5 (*m*, C<u>H</u>HO), 7·35 (*d*, *J* 5·0 Hz, $ArCH_2$), 7·64 (*dd*, *J* 5·5, 2·5 Hz, C<u>H</u>HO). To anhyd. EtOH were added Na (0·51 g), (E)-isoeugenol (5·5 g), and safrol epoxide (4 g) in EtOH soln [11]. After stirring (24 hr), H_2O was added and the mixture extracted with Et_2O. The Et_2O soln was washed (H_2O), dried and evaporated. The residue was purified by passage through a florisil column giving **4** as an oil (Found: M, 342·1465. $C_{20}H_{22}O_5$ requires: M, 342·1467). PMR (CCl_4, τ): 3·47–3·17 (*m*, 6 ArH), 3·37 (*d*, *J* 15·0 Hz, ArCH–), 4·34–3·87 (*m*, ArCH=C<u>H</u>), 4·14 (*s*, O_2CH_2), 5·64–6·07 (*m*, 2 H-1′, H-2′, OH), 6·17 (*s*, OMe), 6·70 (*dd*, *J* 14·0, 5·0 Hz, H-3′), 7·10 (*dd*, *J* 14·0, 7·0 Hz, H-3′), 8·14 (*d*, *J* 5·0 Hz, Me).

Pyrolysis procedure. The particular aryl cinnamyl ether (1·0 g) in *N*,*N*-diethylaniline (25 ml) was maintained at the indicated temp. for the indicated time. The cooled reaction mixture was dissolved in Et_2O and washed with 30% aq. HCl to eliminate the aniline and H_2O, dried and evaporated. The residue was fractionated by preparative TLC (SiO_2, C_6H_6).

(±)-*Licarin-B* (**1a**). Pyrolis of **3c** (235°, 10 hr) gave (±)-**1a** (20 mg), accompanied by starting material (>0·8 g). Alternatively, freshly distilled $SOCl_2$ (0·5 g) was added to a soln of **3c**. The mixture was stirred at room temp. (2 hr) and dissolved in Et_2O. The soln was washed with 10% aq. $CuSO_4$, dried and evaporated. Pyrolysis of the residue (235°, 10 hr) gave (±)-**1a** (0·1 g). (±)-**1a** is an oil, UV, IR, PMR and MS superimposable on the analogous spectra of natural (+)-licarin-B, m.p. 91–92°.

7-*Methoxy*-3-*methyl*-2-*phenyl*-5-(E)-*propenyl*-trans-*coumaran* (**1c**). Pyrolysis of **2c** (250°, 24 hr) gave **1c** (240 mg) as an oil. (Found: M, 280·1468. $C_{19}H_{20}O_2$ requires: M, 280·1463). ν_{max}^{film} (cm^{-1}): 1603, 1488, 1447, 1364, 1326, 1292, 1267, 1206, 1144, 1076, 1032, 967, 868, 822. PMR (CCl_4, τ): 2·72 (*s*, C_6H_5), 3·36 (*br s*, H-4, H-6), 3·73 (*d*, *J* 15·0 Hz, ArCH=), 4·0 (*m*, ArCH=C<u>H</u>), 4·88 (*d*, *J* 9·0 Hz, H-2), 6·15 (*s*, OMe), 6·65 (*m*, H-3), 8·15 (*d*, *J* 5·0 Hz, =CHC<u>H</u>$_3$), 8·58 (*d*, *J* 7·0 Hz, Me-3). MS (*m/e*): 280 (100%), M, 265 (12), 253 (12).

5-*Allyl*-7-*methoxy*-3-*methyl*-2-*phenyl*-trans-*coumaran* (**1d**). Pyrolysis of **2d** (250°, 24 hr) gave **1d** (280 mg) as an oil. (Found: M, 280·1469. $C_{19}H_{20}O_2$ requires: M, 280·1463). ν_{max}^{film} (cm^{-1}): 1642, 1603, 1490, 1449, 1431, 1326, 1292, 1225, 1209, 1142, 1080, 1031, 969, 915, 845, 817. PMR (CCl_4, τ): 2·66 (*s*, C_6H_5), 3·50 (*d*, *J* 2·0 Hz, H-4, H-6), 4·12 (*m*, CH=), 4·88 (*d*, *J* 9·0 Hz, H-2), 5·0 (*m*, =CH_2), 6·12 (*s*, OMe), 6·6 (*m*, H-3), 6·68 (*d*, *J* 7·0 Hz, $ArCH_2$), 8·55 (*d*, *J* 7·0 Hz, Me-3). MS (*m/e*): 280 (100%) M, 265 (8), 239 (13).

Acknowledgements—The MS were registered by Dr. P. M. Baker, Universidade Federal do Rio de Janeiro; and by Dr. A. Aragão Craveiro by courtesy of Prof. E. Wenkert, Rice University, Houston, Texas, U.S.A.

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