Phytochemistry, 1976, Vol. 15, pp. 1289–1291. Pergamon Press. Printed in England.

NEOLIGNANS FROM A *LICARIA* SPECIES*

OTTO R. GOTTLIEB,† JOSÉ G. S. MAIA‡ and JAMIL C. MOURÃO¶
† Instituto de Química, Universidade de São Paulo; ‡ Instituto Nacional de Pesquisas da Amazônia, Conselho Nacional de Desenvolvimento Científico e Tecnológico, Manaus; ¶ Instituto de Ciências Exatas, Universidade Federal Rural do Rio de Janeiro, Brasil

(*Received* 5 *January* 1976)

Key Word Index—*Licaria* sp.; Lauraceae; neolignans; eusiderin; aurein; *rel*-(2R,3R)-7-allyl-5-methoxy-2-(3,4,5-trimethoxyphenyl)-3-methylbenzodioxan; 2-(4-allyloxy-3,5-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-propane.

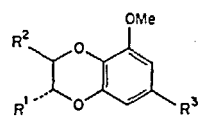
Abstract—The wood of a *Licaria* species (Lauraceae) contains two neolignans, eusiderin, *rel*-(2R,3R)-7-allyl-5-methoxy-2-(3,4,5-trimethoxyphenyl)-3-methylbenzodioxan, and aurein, 2-(4-allyloxy-3,5-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-propane.

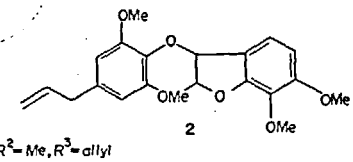
The classification of a *Licaria* species [4], trivial name "louro fígado de galinha", from the vicinity of Manaus, Amazonas, will be possible upon completion of the revision of Lauraceae by Dr. K. Kubitzki, Hamburg. Its trunk wood contains two neolignans: eusiderin, which was located previously in the Indonesian Lauraceae species *Eusideroxylon zwageri* T. *et* B. [2], and a compound which was designated aurein in a plant thought to be *Licaria aurea* (Huber) Kosterm. [3].

Structural proposals for eusiderin, $C_{18}H_{14}O_2(OMe)_4$, based mainly on the recognition that no phenolic degradation products were observed other than pyrogallol derivatives, included not only the benzodioxan alternatives **1a** and **1b**, but also isomeric formulations such as **2** [2]. Re-examination of this problem, by modern spectrometric techniques, invalidated any but the benzodioxan structures, indicated the correct alternative and suggested the *trans*-relationship between the aryl and methyl substituents.

Indeed, the most abundant MS fragment ion revealed the existence of the system $(MeO)_3C_6H_2CHCHMe$ which, according to PMR evidence, includes two equivalent aromatic protons (τ3.40, *s*) and two vicinal aliphatic oxymethines; one linked to phenyl (τ5.46, *d*, *J*8.0 Hz) and the other to methyl (τ5.7–6.3, *m*). The two oxygens must participate in the additional pyrogallol moiety, which, furthermore, supports the fourth methoxyl and an allyl group (*n*-propyl in the dihydroderivative), flanked by two *meta*-related aromatic protons (τ3.63 and 3.51).

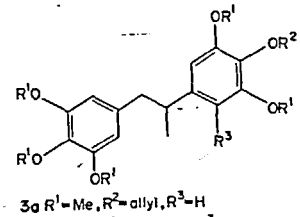
The Pr(fod)$_3$ induced diamagnetic shift of the doublet at τ3.63 (Δ2.4 ppm) is larger than that of the doublet at τ3.51 (Δ2.0 ppm), and the former signal must thus be assigned to the proton in *ortho* relation with respect to the oxy-methoxy coordination site. Equating the LIS value at this site (Δ_{OMe} 4.6 ppm) to 100, the shifts of the *ortho* and *para* proton signals become respectively 52 and 44. While the 52 value is typical for an *ortho*-proton in 1,2-dimethoxybenzenes, the 44 value is about twice as strong as would be expected for a *para*-proton [4]. This indicates the vicinity of the *para*-proton to an additional coordination site identified with the *ortho*-trimethoxy function of the aryl group, since the benzodioxane oxygens associate only feebly with the reagent [4]. Formula **1a**, and not **1b**, thus emerges as the correct



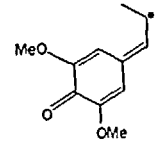


2

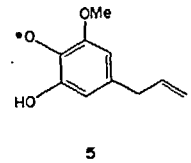
1a R¹=3,4,5-trimethoxyphenyl, R²=Me, R³=allyl
1b R¹=Me, R²=3,4,5-trimethoxyphenyl, R³=allyl
1c R¹=3,4,5-trimethoxyphenyl, R²=Me, R³=*n*-propyl



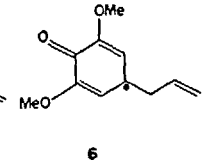
3a R¹=Me, R²=allyl, R³=H
3b R¹=Me, R²=*n*-propyl, R³=H
3c R¹=R²=R³=H
3d R¹=R²=Ac, R³=H
3e R¹=Me, R²=R³=H
3f R¹=Me, R²=Ac, R³=H
3g R¹=Me, R²=H, R³=allyl
3h R¹=Me, R²=Ac, R³=allyl
3i R¹=Me, R²=H, R³=*n*-propyl
3j R¹=Me, R²=Ac, R³=*n*-propyl



4



5



6

* Part 36 in the series "The Chemistry of Brazilian Lauraceae". For Part 35 see ref. [1]. Abstracted from the M.S. thesis presented by J.G.S.M. to the Universidade Federal Rural do Rio de Janeiro (1973). Sponsored by Ministério do Planejamento (Financiadora de Estudos e Projetos S.A.) through Academia Brasileira de Ciências and by Fundação de Amparo à Pesquisa do Estado de São Paulo.

representation of eusiderin. The *trans*-arrangement of the substituents on this benzodioxane, compatible with the relatively low field Me-3 signal (τ8.77) and the relatively large $J_{2,3}$ (8.0 Hz) of the PMR spectrum [5], was inferred from the ^{13}C NMR spectrum. This showed, by comparison with model neolignan spectra, that the methyl group must be beyond non-bonded interaction range of the neighbouring aryl substituent [11].

The formula $C_{18}H_{15}O(OMe)_5$, determined for aurein by HR MS and PMR, suggested its structural relation to eusiderin (**1a**). It became clear immediately, however, that here the two C_9-moieties cannot be linked by an oxygen bridge. While dihydroeusiderin (**1c**) is cleaved into 1,2,3-trihydroxy-5-*n*-propylbenzene by HI/AcOH at reflux temperature [2], dihydroaurein (later formulated **3b**) leads to a phenol $C_{15}H_{10}(OH)_6$ (**3c**). The PMR spectrum of this phenol and of its hexaacetate (**3d**) are devoid of signals due to an *n*-propyl group, and, hence, the allyl group of aurein must etherify the undefined oxygen of its formula given above. Indeed, pyrolysis (to **3e** 56% yield) and acid treatment (to **3g** 76% yield) of aurein easily cleave this *O*-allyl. The former reaction is relevant, since loss of the allyl group shows that the *o*- and *p*-positions relative to the O-allyl group are substituted. In the latter reaction, comparison of the PMR spectrum shows that the O-allyl group (OCH_2, τ5.53) of aurein is replaced in the rearrangement product (**3g**) by a C-allyl group (CCH_2, τ6.75) which generates a C-*n*-propyl group (CCH_2, τ8.44) after hydrogenation (**3i**). In **3g**, one of the two pairs of equivalent aromatic protons (τ3.68, *s*) in aurein is reduced to one lone proton (τ3.56, *s*), while the other pair (τ3.80) gives rise again to a 2H-singlet (τ3.75). The 1:2 relation of the aromatic signals is evidence of the purity of the rearranged product.

Six OR-groups and two pairs of equivalent protons can only be accommodated on two phenyl units, containing the phloroglucinol or pyrogallol oxygenation patterns. As a further consequence of symmetry, the *O*-allyl group must be located on the *para*-carbon of one of the units. At least for this ring, the phloroglucinol pattern can be immediately disregarded as a plausible alternative, since acetylation of the pyrolysis product (**3e** → **3f**) causes a negligible PMR shift of the ArH signals. Thus, the corresponding protons cannot be located on the *ortho*-carbons. The other ring must possess an identical oxgenation pattern. PMR shifts of identical magnitude for the ArH signals due to both rings are observed (τ −0.57 and −0.53 ppm) upon comparing the spectra of the pyrolysis product (**3e**) and the hexaacetate (**3d**).

The three-carbon moiety which bridges the two rings comprises a $C\underline{H}_3CH$ group (τ8.77, *d*, *J* 6.0 Hz). The CH PMR band for this unit was included in a signal representing a total of three benzylic (τ7.1–7.3) protons. Neither in the 220 MHz spectrum of aurein itself, nor in the 60 MHz spectra of the series of derivatives **3b–3j** was this signal resolvable. Although thus, *a priori*, the $-CH_2CHMe-$ bridge may be inserted between the two phenyl units in two ways, only structure **3a** is compatible with the masses of the two most abundant MS fragment ions (*m/e* 181 and 221), resulting from cleavage of the doubly benzylic C–C bond.

Clearly, eusiderin (**1a**) and aurein (**3a**) stem from an identical pair of precursors, a trioxygenated propenylbenzene and a trioxygenated allylbenzene. Assuming that their oxidative coupling involves radical pairs, **4** and **5** could lead to eusiderin (**1a**) [6], whose synthesis patterned on this postulate was achieved [7], while **4** and **6** would give an intermediate which, upon hydrogen addition and retro-Claisen rearrangement, would lead to aurein (**3a**). This singular process recalls the biosynthesis of thyroxin [8] where, however, the final dienone–phenol rearrangement causes the loss of a three-carbon fragment. The retro-Claisen reaction was postulated previously to rationalize the biosynthesis of another neolignan type [9,10].

EXPERIMENTAL

Isolation of the constituents. A specimen of *Licaria* sp. (voucher: Herbarium INPA, Manaus 42209) was collected at the Ducke Forest Reserve, near Manaus. Its trunk wood (8 kg) was freed from bark, ground and extracted successively with C_6H_6 and EtOH. The C_6H_6-extract (150 g) gave crystals of **1a** (17.2 g) which were separated by filtration from an oil. This was chromatographed on a SiO_2 column. Elution with C_6H_6 gave **1a** (4 g) and with C_6H_6–EtOAc (7:3) gave **3a** (7.4 g). SiO_2-Chromatography of the EtOH extract gave additional quantities of **3a**.

Eusiderin (**1a**), mp and UV spectrum as required by lit. [2] (M^+ found: 386.1720; $C_{22}H_{26}O_6$ requires: 386.1729). ν_{max}^{KCl} (cm^{-1}): 1590, 1500, 1240, 1225, 1150, 1135, 1100. PMR ($CDCl_3$, τ): 3.40 (*s*, 2ArH), 3.51 (*d*, *J* 2.0 Hz, H-8), 3.63 (*d*, *J* 2.0 Hz, H-6), 3.8–4.3 (*m*, =CH), 4.75–5.15 (*m*, $=CH_2$), 5.46 (*d*, *J* 8.0 Hz, H-2), 5.7–6.3 (*m*, H-3), 6.15 (*s*, 4 OMe), 6.73 (*d*, *J* 6.0 Hz, CH_2), 8.77 (*d*, *J* 6.0 Hz Me-3). MS (*m/e*): 386 (100%) M^+, 302 (25), 209 (50), 208 (85), 193 (66), 191 (54), 165 (30), 135 (36), 133 (24), 107 (38), 105 (26). LIS studies were carried out by stepwise addition of known amounts of $Pr(fod)_3$ to *ca* 0.15 M solns of **1a** in $CDCl_3$. The data were obtained by graphic extrapolation of observed shifts to 1:1 shift reagents–**1a** ratio and are reported in full elsewhere [4]. *Dihydroeusiderin* (**1c**), mp and UV spectrum as required by lit. [2] (M^+found: 388; $C_{22}H_{28}O_6$ requires: 388). PMR ($CDCl_3$, τ): 3.40 (*s*, 2 ArH), 3.51 (*d*, *J* 2.0 Hz, H-8), 3.62 (*d*, *J* 2.0 Hz, H-6), 5.40 (*d*, *J* 8.0 Hz, H-2), 5.6–6.1 (*m*, H-3), 6.08 (*s*, 4 OMe), 7.48 (*t*, *J* 6.0 Hz, $ArCH_2$), 8–9 (*m*, CH_2), 8.72 (*d*, *J* 6 Hz, Me-3), 9.05 (*t*, *J* 6 Hz, Me).

Aurein (**3a**), mp 80–81° (hexane–C_6H_6) (M^+ found: 402.2047; $C_{23}H_{30}O_6$ requires: 402.2042). ν_{max}^{KBr} (cm^{-1}): 1587, 1498, 1452, 1325, 1240, 1132, 1005. λ_{max}^{EtOH} (nm): 235 inf., 270 (ε 12500, 1200). PMR ($CDCl_3$, 220 MHz, τ): 3.68 (*s*, 2 ArH), 3.80 (*s*, 2 ArH), 3.93 (*ddt*, *J* 6.0, 10.0, 17.0, =CH), 4.72 (*ddt*, *J* 1.8, 2.0, 17.0, =CH), 4.85 (*ddt*, *J* 1.6, 1.8, 10.0, =CH), 5.53 (sec. split *d*, *J* 6.0 Hz, OCH_2), 6.19 (*s*, 3 OMe), 6.25 (*s*, 2 OMe), 7.05–7.35 (*m*, $ArCH_2$, ArCH), 8.74 (*d*, *J* 6.0 Hz, CMe). MS (*m/e*): 402 (100%) M^+, 222 (36), 221 (60), 182 (36), 181 (72), 162 (40), 151 (31), 150 (32), 137 (28), 136 (28), 91 (20). *Dihydroaurein* (**3b**) [hydrogenation of **3a** (100 mg) + 15% Pd–C (15 mg)], mp 89–91° (petrol–C_6H_6) (M^+ found: 404; $C_{23}H_{32}O_6$ requires: 404). ν_{max}^{KCl} (cm^{-1}): 1335, 1240, 1130. PMR ($CDCl_3$, τ): 3.62 (*s*, 2 ArH), 3.75 (*s*, 2 ArH), 6.07 (*t*, *J* 7 Hz, OCH_2), 6.20 (*s*, 4 OMe), 6.22 (*s*, 1 OMe), 7.1–7.3 (*m*, $ArCH_2$, ArCH), 8.0–8.4 (*m*, CH_2), 8.70 (*d*, *J* 6 Hz, CMe), 9.00 (*t*, *J* 7 Hz, CMe).

1,2-Di-(3,4,5-trihydroxyphenyl)-propane (**3c**). **3a** (440 mg) in 68% HI (3.3 ml) + AcOH (33 ml) and red P (3 g) was maintained under reflux (1 hr) and evaporated under vacuum at 100°. Cooled residue was suspended in H_2O and extracted with $CHCl_3$. Solvent was evaporated and residue purified by SiO_2 column chromatography to give a solid (320 mg), mp 201–204° (petrol–MeOH) (M^+ found: 292; $C_{15}H_{16}O_6$ requires: 292). ν_{max}^{KBr} (cm^{-1}): 3330 (broad), 1320 (broad), 1235, 1025. PMR [$(CD_3)_2CO$, τ]: 2.64 (*broad*, 5 OH), 3.72 (*s*, 2 ArH), 3.80 (*s*, 2 ArH), 7.2–7.4 (*m*, $ArCH_2$, ArCH), 8.90 (*d*, *J* 6 Hz, CMe). *Hexacetate* (**3d**), oil. ν_{max}^{film} (cm^{-1}): 1745, 1200 (broad), 1045. PMR ($CDCl_3$, τ): 3.10 (*s*, 2 ArH), 3.20 (*s*, 2 ArH), 7.1–7.3 (*m*, $ArCH_2$, ArCH), 7.80 (*s*, 6 COMe), 8.80 (*d*, *J* 6 Hz, CMe).

2-(4-*Hydroxy*-3,5-*dimethoxyphenyl*)-1-(3,4,5-*trimethoxyphenyl*)-*propane* (3e). 3a (100 mg) in $C_6H_5NEt_2$ (0.5 ml) under N_2 was heated under reflux (4 hr). The cooled reaction mixture was treated with excess 2N HCl and extracted with $CHCl_3$. Evaporation of solvent gave a residue which was purified by SiO_2 column chromatography to give an oil (50 mg) (M^+ found: 362; $C_{20}H_{26}O_6$ requires: 362). ν_{max}^{film} (cm^{-1}): 3430, 1335, 1240, 1220, 1130. PMR (CCl_4, τ): 3.63 (*s*, 2 ArH), 3.77 (*s*, 2 ArH), 4.55 (*bs*, OH), 6.20 (*s*, 3 OMe), 6.25 (*s*, 2 OMe), 7.1–7.3 (*m*, $ArCH_2$, ArCH), 8.77 (*d*, *J* 6 Hz, CMe). *Acetate* (3f), mp 119–122° (M^+ found: 404; $C_{22}H_{28}O_7$ requires: 404. ν_{max}^{KCl} (cm^{-1}): 1760, 1250, 1205, 1130. PMR ($CDCl_3$, τ): 3.62 (*s*, 2 ArH), 3.75 (*s*, 2 ArH), 6.16 (*s*, 5 OMe), 7.1–7.3 (*m*, $ArCH_2$, ArCH), 7.63 (*s*, COMe), 8.66 (*d*, *J* 6 Hz CMe).

2-(2-*Allyl*-4-*hydroxy*-3,5-*dimethoxyphenyl*)-1-(3,4,5-*trimethoxyphenyl*)-*propane* (3g). 3a (300 mg) in HOAc (12 ml) was treated with a soln of H_2SO_4 (0.15 ml) in HOAc (3 ml). After 48 hr at room temp., H_2O was added and the mixture extracted with $CHCl_3$. Evaporation of solvent gave a residue which was separated by SiO_2 column chromatography into unchanged 3a (25 mg) and 3g (209 mg), oil (M^+ found: 402.2048; $C_{23}H_{30}O_6$ requires: 402.2042). ν_{max}^{film} (cm^{-1}): 3420, 1308, 1240, 1120. PMR (CCl_4, τ): 3.56 (*s*, 1 ArH), 3.86 (*s*, 2 ArH), 3.9–4.4 (*m*, =CH), 4.9–5.3 (*m*, $=CH_2$), 6.20 (*s*, OMe), 6.22 (*s*, OMe), 6.30 (*s*, 2 OMe), 6.32 (*s*, OMe), 6.75 (*d*, *J* 6 Hz, $C\underline{H}_2CH=$), 7.3–7.5 (*m*, $ArCH_2$, ArCH), 8.88 (*d*, *J* 6 Hz, CMe). *Acetate* (3h), mp 49–51° (hexane) (M^+ found: 444; $C_{25}H_{32}O_7$ requires: 444). ν_{max}^{KCl} (cm^{-1}): 1745, 1240, 1200, 1125. PMR ($CDCl_3$, τ): 3.34 (*s*, ArH), 3.75 (*s*, 2 ArH), 3.9–4.4 (*m*, =CH), 4.9–5.3 (*m*, $=CH_2$), 6.15 (*s*, OMe), 6.18 (*s*, OMe), 6.22 (*s*, 2 OMe), 6.26 (*s*, OMe), 6.72 (*d*, *J* 6 Hz, $C\underline{H}_2CH=$), 7.1–7.4 (*m*, $ArCH_2$, ArCH), 7.63 (*s*, COMe), 8.73 (*d*, *J* 6 Hz, CMe).

2-(4-*Hydroxy*-3,5-*dimethoxy*-2-n-*propylphenyl*)-1-(3,4,5-*trimethoxyphenyl*)-*propane* (3i). [Hydrogenation of 3g (119 mg) + 15% Pd-C (15 mg) in EtOH (15 mg)], oil (M^+ found: 404, $C_{23}H_{32}O_6$ requires: 404). ν_{max}^{film} (cm^{-1}): 3290, 1312, 1248, 1125. PMR ($CDCl_3$, τ): 3.42 (*s*, ArH), 3.72 (*s*, 2 ArH), 4.60 (*bs*, OH), 6.10 (*s*, OMe), 6.16 (*s*, 2 OMe), 6.21 (*s*, 2 OMe), 7.1–7.6 (*m*, $2\,ArCH_2$, ArCH), 8.44 (*d*, *J* 6 Hz, CH_2), 8.72 (*d*, *J* 6 Hz, CMe), 9.00 (*t*, *J* 6 Hz, CMe). *Acetate* (3j), oil (M^+ found: 446, $C_{25}H_{34}O_7$ requires: 446). PMR (CCl_4, 3.52 (*s*, ArH), 3.95 (*s*, 2 ArH), 6.20 (*s*, OMe), 6.30 (*s*, 4 OMe), 7.1–7.4 (*m*, $2\,ArCH_2$, ArCH), 7.70 (*s*, COMe), 8.6–8.8 (*m*, COMe, CH_2), 9.05 (*t*, *J* 6 Hz, CMe).

REFERENCES

1. Aiba, C. J., Gottlieb, O. R., Yoshida, M., Mourão, J. C. and Gottlieb, H. E. (1976) *Phytochemistry* **15**, 1031.
2. Hobbs, J. J. and King, F. E. (1960) *J. Chem. Soc.* 4732.
3. Gottlieb, O. R. (1974) *Rev. Latinoamer. Quím.* **5**, 1.
4. Braz F°., R., Mourão, J. C., Gottlieb, O. R. and Maia, J. G. S. (1976) *Tetrahedron Letters* 1157.
5. Giesbrecht, A. M., Franca, N. C., Gottlieb, O. R. and Rocha, A. I. da (1974) *Phytochemistry* **13**, 2285.
6. Gottlieb, O. R. (1972) *Phytochemistry* **11**, 1537.
7. Merlini, L. and Zanarotti, A. (1975) *Tetrahedron Letters* 3621.
8. Cahnmann, H. J. (1971) *Annual Report*, p. 5, Tanabe Amino Acid Research Foundation, Osaka, Japan.
9. Aiba, C. J., Fernandes, J. B., Gottlieb, O. R. and Maia, J. G. S. (1975) *Phytochemistry* **14**, 1597.
10. Gottlieb, O. R., Silva, M. L. da and Ferreira, Z. S. (1975) *Phytochemistry* **14**, 1825.
11. Wenkert, E., Gottlieb, H. E., Gottlieb, O. R., Pereira, M. O. da S. and Formiga, M. D. (1976) *Phytochemistry* (in press).