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MACROPHYLLIN, A NEOLIGNAN FROM *LICARIA MACROPHYLLA**

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Key Word Index—*Licaria macrophylla*, Lauraceae; neolignan, macrophyllin, 3-allyl-8-hydroxy-1,5-dimethoxy-7-methyl-4(or 2)-oxo-6-(3',4'-methylenedioxy-5'-methoxyphenyl)-bicyclo [3,2,1]oct-2(or 4)-ene

Abstract—The trunk wood of *Licaria macrophylla* (A C Smith) Kosterm (Lauraceae) contains, in addition to sitosterol, terpene (borneol) and sesquiterpene (nerolidol, elemol) alcohols, a novel neolignan, macrophyllin, for which the structure of 3-allyl-8-hydroxy-1,5-dimethoxy-7-methyl-4(or 2)-oxo-6-(3',4'-methylenedioxy-5'-methoxyphenyl)-bicyclo [3,2,1] oct-2(or 4)-ene is proposed

Licaria macrophylla (A. C. Smith) Kosterm. is a tree which grows in the Amazon region. The trunk wood yielded borneol, nerolidol, elemol, sitosterol and a new compound, $C_{22}H_{26}O_7$, designated macrophyllin. Functional analysis, warranting expansion of the formula to $C_{18}H_{14}O . OH(OMe)_3 . O_2CH_2$, suggested this to be a bis-$C_6 . C_3$-derivative. One of the $C_6 . C_3$-moieties must have structure **1**, since the MS indicates cleavage of the molecular ion into a fragment, *m/e* 192 (80%), which, in analogy with the predominant fragment ions of related *bis*-$C_6 . C_3$-compounds, such as guianin (**2**),[2] canellin-A (**3**)[1] and canellin-C (**4**),[1] must be represented by **5**. The PMR spectrum contains all the required proton signals and shows that the two aromatic protons are *meta* related. It is biogenetically improbable that they are situated at the alternative *meta*-positions, because this would require the C_3-side chain to occupy the *para*-position to an unoxygenated carbon.

The structure of the additional C_9-moiety can be deduced from the remaining PMR signals. These reveal the existence of the three C_3-sequences represented in **6**. The secondary nature of the carbinol is documented by the large paramagnetic shift of the oxymethine PMR singlet at τ 5 80 which accompanies acetylation of macrophyllin (Δ 1·35 ppm). In addition, this reaction produces virtually identical (Δ 0·08 and 0·09 ppm) diamagnetic

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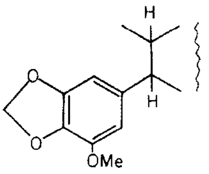
[1] GILSBRECHT, A M, FRANCA, N C, GOTTLIEB, O R and ROCHA, A I da (1974) *Phytochemistry* **13**, 2285

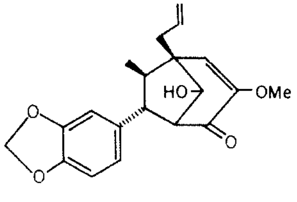
[2] BULOW, M V VON, FRANCA, N C, GOTTLIEB, O R and PUENTES SUAREZ, A M (1973) *Phytochemistry* **12**, 1805

shifts of the singlets at τ 6·53 and 6 68 attributed to aliphatic methoxyls. These must thus occupy symmetrical positions with respect to the carbinol, and, no additional oxymethine signals being observable, not even in the spectrum of tetrahydromacrophyllin, be placed on non-protonated sp^3-carbons.

The α,β-unsaturated carbonyl, whose presence can be inferred through the IR spectrum (ν_{max} 1685 cm^{-1}), has a single hydrogen, most probably at the β-carbon since the corresponding PMR singlet occurs at relatively low field (τ 3 15) The α-carbon must be occupied by the allyl group The appearance of the $C\underline{H}_2$ doublet at relatively low field (τ 6·94, J 7·0 Hz) can be rationalized only if the methylene group is flanked by an additional double bond Accordingly, there is only one way in which the C_3-sequences of **6** can be joined. The carbinolic proton of the resulting unit **7** must lie over the ring. Saturation of the cyclic double bond (as in tetrahydromacrophyllin), depriving it of anisotropic protection, results in a considerable paramagnetic shift (Δ 0·20 ppm) of the corresponding singlet.



(1)



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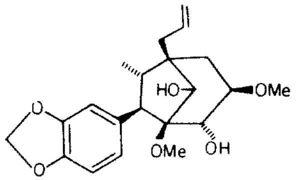

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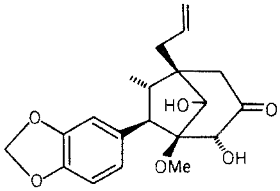

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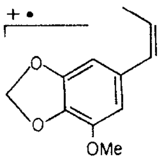

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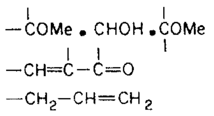
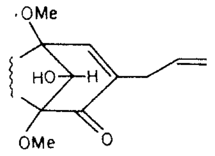


$$\begin{array}{l} -\overset{|}{C}OMe \cdot CHOH \cdot \overset{|}{\underset{|}{C}}OMe \\ -CH{=}\overset{|}{C}-\overset{|}{C}{=}O \\ -CH_2-CH{=}CH_2 \end{array}$$

(6)



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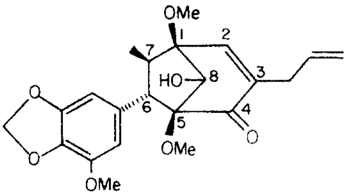

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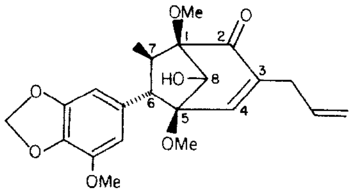

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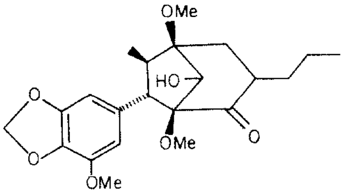
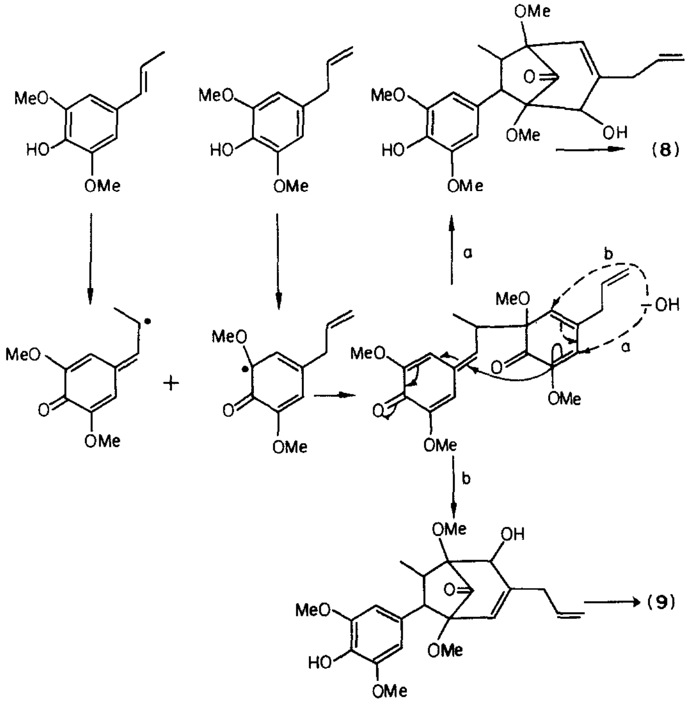


(10)

Macrophyllin must thus be represented by one of the two formulae which can be constructed through linkage of **1** and **7** Although **8** is preferred on account of its slightly greater structural resemblance to guianin (**2**), and the canellins A (**3**) and C (**4**), biogenetically both **8** and **9** are equally probable (Scheme) and no argument is presently available by which **9** can be excluded. This is due to the fact that the aryl group occupies the *endo*-face of the molecule and thus, in contradistinction to the aryl group of the canellins (**3**, **4**), does not help in the discrimination of the methoxyls through differential shielding. Evidence for the *endo*-arrangement was seen in the fact that the hydroxyl at C-8 of macrophyllin is as completely acetylated at room temp. as that of guianin (**2**), while under identical conditions only monoacetates are formed from the canellins A (**3**) and C (**4**).[1] In these cases, esterification of the hydroxyl at C-8 is incomplete, even at 60°, due, conceivably, to the steric hindrance exerted by the *exo*-aryl group. The *trans*-relationship of the aryl-methyl substituents, as shown in the relative spacial representations of macrophyllin (**8** and **9**), is based on the large coupling constant which characterizes $J_{H-6,H-7}$ (8·7 Hz) and the normal chemical shift of the C–Me protons (τ 9·08). A smaller coupling and a chemical shift above τ 9·3 would be expected for the *cis*-arrangement.[1]



SCHEME 1 PROBABLE BIOGENETIC PATHWAY TO MACROPHYLLIN

EXPERIMENTAL

Licaria macrophylla Collection Site Ducke Forest Reserve, Manaus, Amazonas Tree 15 m high. Herbarium sample INPA, Manaus, no 15536 *Solvent extraction* Dry, powdered trunk wood (6 kg) was extracted successively with C_6H_6 and with EtOH The C_6H_6-soln deposited, after conc under vacuum 2 crops of macrophyllin (3·2 g) which was separated by filtration Part (22 g) of the residual C_6H_6 extract (195 g) was chromatographed on silica. C_6H_6 eluted sitosterol and C_6H_6–$CHCl_3$ 1:1 eluted an additional quantity of macrophyllin (800 mg). Chromatography on silica of the EtOH extract (330 g) also yielded macrophyllin (2·5 g) *Vapour entrainment* Essential oils were obtained from bark (yield 0·45%, $n_D^{20°}$ 1·4975) and wood (yield 0·50%, $n_D^{20°}$ 1·5055) Composition of wood oil determined by GLC borneol 3%, nerolidol 5%, elemol 25%, sesquiterpene alcohols 40%. The constituents were identified, after isolation by preparative GLC, through direct comparison with authentic samples

Macrophyllin (**8**). Colourless crystals, m p 175–178 (CHCl$_3$ MeOH). M found 402 1681, calc for $C_{22}H_{26}O_7$ 402 1679 UV λ_{max}^{EtOH} (nm): 215, 235 sh., 270 sh. (ϵ 53 100, 20 500, 6000). IR ν_{max}^{KBr} (cm^{-1}): 3420, 1685 1627, 1507, 1450, 1305, 1205 1140, 1120, 1095, 928 PMR (CDCl$_3$, 220 MHz τ) 3 15 (s H-2), 3 30 (*d* *J* 1 5 Hz, ArH), 3 50 (*d*, *J* 1 5 Hz, ArH), 4 10 (s, O_2CH_2), 4 05–4 45 (*m*, $C\underline{H}=CH_2$), 4 70–5 10 (*m*, $CH=C\underline{H}_2$), 5 80 (*s*, H-8), 6 15 (*s*, ArOMe), 6 53 (*s*, OMe-5), 6 68 (*s*, OMe-1) 6 94 (*d*, *J* 7 0 Hz, $C\underline{H}_2$-CH=), 7 06–7 19 (*m*, H-7) 7 15 (*s*, OH) 7 61 (*d*, *J* 8 7 Hz, H-6), 9 08 (*d*, 6 8 Hz, Me-7) MS (*m/e*) 402 (100%)M, 221 (15), 210 (16), 195 (20), 192 (80), 191 (31) 190 (22), 181 (28) 179 (20), 169 (31), 165 (12), 86 (28), 84 (38) 57 (10), 55 (10), 44 (36), 43 (18) *Acetate* Obtained with Ac_2O-C_5H_5N at room temp. (48 hr) as an oil, ν_{max}^{film} (cm^{-1}): 1735 1690, 1630, 1455 1435 1375, 1235 1100 760 PMR (CDCl$_3$, 60 MHz, τ): 3 05 (*s*, H-2), 3 30 (*d*, *J* 1 5 Hz, ArH), 3 57 (*d*, *J* 1 5 Hz, ArH), 4 06 (*s*, O_2CH_2), 4 00–4 40 (*m*, $C\underline{H}=CH_2$), 4 45 (*s*, H-8), 4 63–5 03 (*m*, $CH=C\underline{H}_2$), 6 17 (*s*, ArOMe), 6 61 (*s*, ROMe), 6 77 (*s*, ROMe), 6 86 (*d*, *J* 7 0 Hz $C\underline{H}_2$-CH=), 7 21 (*m*, H-7), 7 21 (*m*, H-7) 7 59 (*d*, *J* 9 0 Hz, H-6) 7 70 (*s*, COMe), 9 10 (*s*, Me-7) MS (*m/e*) 444 (5%) M, 210 (55), 195 (20), 194 (18) 193 (20) 192 (33), 179 (13) 165 (15) 150 (40), 149 (58), 113 (13) 105 (13), 79 (16), 78 (16), 77 (20), 71 (33), 69 (20) 65 (13) 57 (45), 55 (20), 43 (100)

Tetrahydromacrophyllin (**10**). Macrophyllin (300 mg) in EtOH (10 ml) was added to a suspension of 10% Pd/C (80 mg) in EtOH (5 ml) and hydrogenated (4 hr) The solution was filtered and evaporated The residue was separated by preparative TLC (silica, C_6H_6-AcOEt 1 1) into the more polar tetrahydro-derivative (180 mg) and a less polar mixture of di- and hexahydro-derivatives (35 mg) Tetrahydromacrophyllin, m p 139–141 (C_6H_6, hexane) ν_{max}^{KBr} (cm^{-1}): 3450 1720, 1630 1520, 1460, 1370, 1340 1315, 1240, 1200, 1130 1110 1090 1045 1030 990, 965, 930, 830 PMR (220 MHz, CDCl$_3$, τ), 3 45 (*d* 1 5 Hz ArH), 3 64 (*d* 1 5 Hz ArH), 4 12 (*s*, O_2CH_2), 5 60 (*s*, H-8), 6 16 (*s*, ArOMe), 6 56 (*s*, OMe-5), 6 79 (*s*, OMe-1), 7 21 (apparent quintuplet, *J* ~ 8, H-7), 7 57 (*s*, OH), 7 5–7 6 (*m*, H-3), 7 69 (*d*, *J* 10 0 Hz H-6), 7 85 (apparent *t*, *J* ~ 13 Hz, H-2), 7 9–8 1 (*m*, $C\underline{H}HEt$), 8 32 (*dd*, *J* 14 0, 9 0 Hz H-2), 8 5–8 9 (*m*, $CH\underline{H}C\underline{H}_2Me$), 9 05 (*t*, *J* 7 5 Hz, $CH_2C\underline{H}_3$), 9 08 (*d*, *J* 7 0 Hz Me-7), MS (*m/e*) 406 (13%) M, 197 (45) 194 (9), 192 (9), 165 (11), 152 (11), 149 (9), 137 (9), 135 (9) 125 (10), 123 (11) 93 (8) 91 (15) 85 (14), 83 (22) 81 (24), 79 (17) 78 (99), 77 (32), 71 (24), 69 (29), 67 (18) 57 (71) 43 (100).

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