Phytochemistry, 1978, Vol. 17, pp 983–985. © Pergamon Press Ltd. Printed in England 0031-9422/78/0501-0983 $02.00/0

LANTHANIDE SHIFT REAGENTS IN NEOLIGNAN ANALYSIS: REVISION OF STRUCTURE OF CANELLIN-B*

SERGIO DE H. CAVALCANTE†, ASTRÉA M. GIESBRECHT, OTTO R. GOTTLIEB, JAMIL C. MOURÃO‡ and MASSAYOSHI YOSHIDA

Instituto de Química, Universidade de São Paulo, c.p. 20780, São Paulo, SP, Brasil

(*Received* 21 *October* 1977)

Key Word Index—*Licaria canella*; *Aniba terminalis*; *Aniba affinis; Aniba burchellii*; Lauraceae; benzofuranoid neolignans; canellin-B; structural analysis; lanthanide shift reagents.

Abstract—PMR studies using lanthanide shift techniques showed that the constitution of canellin-B must be revised to *rel*-(2*S*,3*S*,3a*S*,5*S*)-3a-allyl-5,7-dimethoxy-3-methyl-2-piperonyl-2,3,3a,4,5,6-hexahydro-6-oxobenzofuran and that the previous assignments of H-2, H-4 and H-7 signals of some other benzofuranoid neolignans must be interchanged. The isolation of 5-methoxyguianin from *Licaria canella* (Meissn.) Kosterm. and the characterization of (2*R*,3*S*,5*R*)-5-allyl-5-methoxy-3-methyl-2-piperonyl-2,3,5,6-tetrahydro-6-oxobenzofuran from *Aniba terminalis* Ducke is also reported.

INTRODUCTION

The successful application of lanthanide induced PMR shifts (LIS) to structural problems in the neolignan series [2–4], invited re-examination of several previously encountered problems, such as the structural elucidation of canellin-B from *Licaria canella* (Meissn.) Mez [5] and some spectral assignments of several additional benzofuranoid neolignans, including (2*R*,3*S*,5*R*)-5-allyl-5-methoxy-3-methyl-2-piperonyl-2,3,5,6-tetrahydro-6-oxobenzofuran which had been only isolated in very impure form from *Aniba terminalis* Ducke [6]. Both genera, *Licaria* and *Aniba*, belong to the family Lauraceae.

RESULTS AND DISCUSSION

Licaria canella

The occurrence of elemicin (**1**) and dillapiol, accompanied by the neolignans canellins A, B and C, in the trunk wood of *Licaria canella* has been reported [5]. Canellin-A was isolated in reasonable quantities and its structural proposal relied on spectra, as well as on chemical evidence. By contrast, only relatively minute quantities of the canellins B and C were obtained and the constitutional proposals relied solely on spectral comparisons with model compounds. At the time only porosin (**2**) [7] was available as a model for canellin-B (**3**). However, since the constitution of porosin was subsequently revised to **4** [4], it became probable that canellin-B could conform to a similar formula, i.e. **5**. Indeed, while the original formulation **3** was difficult to rationalize on biogenetic arguments, **5** simply requires oxidative coupling [4, 8] of isoeugenol and 4-hydroxy-3,5-dimethoxy-allylbenzene, precursors also of elemicin.

Re-extraction of *L. canella* gave, in addition to the compounds above, 5-methoxyguianin (**6**) [9]. Although the quantity of canellin-B obtained was again small, it was sufficient for a thorough analysis using Pr $(fod)_3$ induced shifts of PMR bands.

Initially, although in comparison with an aromatic O_2CH_2 substituent, aromatic *o*-diOMe coordinates relatively strongly with the reagent [2], competition for Pr favours coordination with a carbonyl. Indeed, $\Delta\delta$ values are low for the aliphatic protons of the aryl ether functions not only of compounds **7a** [3, 6] and **7b** [3, 10] [$\Delta\delta(O_2C\underline{H}_2)$: resp. 0.4 and −0.2], but also for **4** [$\Delta\delta$(*o*-di$OC\underline{H}_3$): 0.4]. In virtual absence of interference from the alkyl aryl ether moieties, **7a**, **7b** and **4** can thus be used as models for the study of the carbonyl entourage of canellin-B.

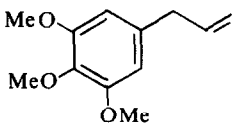
$\Delta\delta$-Values for $OC\underline{H}_3$ are considerably more pronounced if the methoxyls are coplanar (**7a**: 28.2; **7b** 27 [3]) than if they are out of the plane (**4**: 13.4 [4]) of a vicinal carbonyl. Although a CO.COMe.COMe system such as represented in **3** remains to be tested, the $\Delta\delta$ values determined for the OMe protons of canellin-B (**5**: 27.0 and 6.5) are, by this criterion, certainly compatible with structure **5** for canellin-B. Furthermore, if porosin and canellin-B indeed comprised the $CO.CH_2.CHOR$ moieties shown in **2** and **3**, the $\Delta\delta$ values for $C\underline{H}_2$ would be expected to be larger than for $C\underline{H}$. Exactly the opposite is the case (**4**: H-5 > 25, H-4ax 4.3, H-4eq 1.4 [4]; **5**: H-5 21, H-4ax 12), confirming the atomic sequence $CO.CHOR.CH_2$ as shown in the revised formulae **4** and **5**. Finally, when coordination with the shift reagent involves oxygens at C-6 and C-7 as in canellin-B (**5**), H-2 is closer to the coordination site, than when oxygens at C-6 and C-5 are involved as in **7a** and **7b**. This fact may rationalize the relative $\Delta\delta$ values for H-2 and H-3, >1 in **5** (2.9:2.6) and <1 for **7a** (3.4:4.4) and **7b** (2.4:3.3).

* Part 50 in the series 'The Chemistry of Brazilian Lauraceae'. For Part 49 see Ref. [1]. Sponsored by Fundação de Amparo à Pesquisa do Estado de São Paulo.

† CAPES Graduate Fellow, Departamento de Química, Universidade Federal de Alagoas.

‡ Present address: Instituto de Ciências Exatas, Universidade Federal Rural do Rio de Janeiro, Itaguaí, RJ.

The relative stereochemistry for porosin (**4**) was determined by ^{13}C NMR [11]. Chemical shift values for CH_2-3a, which are similar and lower for **4** (τ 7.31 and 7.44) [7] and **5** (τ 7.4 and 7.5) [5] than for the model compound **8** (τ 7.68 and 7.84) [12]] suggest the same *trans*-aryl/allyl stereochemistry for porosin and canellin-B. This argument is based on the anisotropic protection



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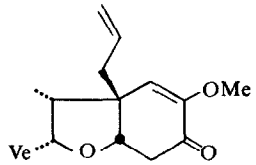

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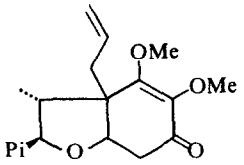

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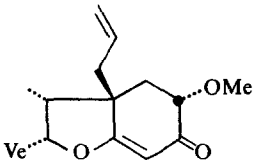

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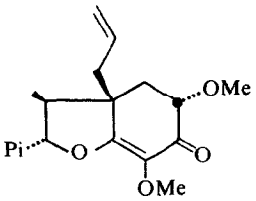

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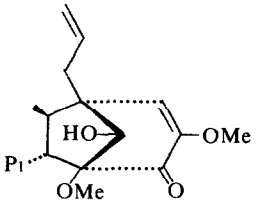

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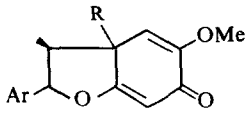
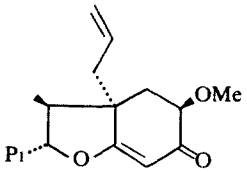


7a Ar = β-Pi, R = α-Al
7b Ar = α-Pi, R = β-Al



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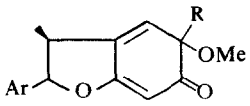

9a Ar = α-Pi, R = α-Al
9b Ar = β-Pi, R = α-Al
9c Ar = α-Pi, R = β-Al
9d Ar = α-Ve, R = β-Al
9e Ar = α-Ve, R = α-Al

Al = allyl
Pi = piperonyl
Ve = veratryl

offered by a *cis*-aryl, a phenomenon which also reveals the 2,3-*cis* stereochemistry of porosin (Me-3, τ 9.48) [7] versus the 2,3-*trans* stereochemistry of canellin-B (Me-3, τ 8.96) [5]. The relative configurations of OMe-5 are again identical for **4** and **5**, both compounds showing H-4ax, H-5ax interactions (J = 12 Hz) [5, 7].

Aniba terminalis

A previous analysis of the trunk wood of *Aniba terminalis* referred to the presence of 8 benzofuranoid neolignans [6], including (2*R*,3*S*,3a*S*)-3a-allyl-5-methoxy-3-methyl-2-piperonyl-2,3,3a,6-tetrahydro-6-oxobenzofuran (**7a**), (2*S*, 3*S*, 5*R*)- [13], and not (2*S*,3*S*,5*S*)- as indicated in the original paper, and (2*R*,3*S*,5*R*)-5-allyl-5-methoxy-3-methyl-2-piperonyl-2,3,5,6-tetrahydro-6-oxobenzofurans (resp. **9a** and **9b**). The separation of the neolignans **9a** and **9b**, which had been obtained as a 9:1 mixture, was now achieved. Their spectral and ORD characteristics (see Experimental) confirm the proposed structures. The LIS data for **9a** and **9b** (registered in [3]) are comparable; with exception of the shift values for H-2 which are, as expected [3], lower for the β-proton of **9a** ($\Delta\delta$ 1.6) than for the α-proton of **9b** ($\Delta\delta$ 3). In the PMR spectrum of **9a** in pure $CDCl_3$, the H-2 band is overlapped by the $=CH_2$ band and thus not clearly discernible as a doublet. This fact led to band assignments [6] which must now, according to LIS measurements, be corrected for H-2 to τ 4.94 (*d*, J = 7 Hz), for H-4 to τ 3.94 (*d*, J = 3 Hz) and for H-7 to τ 4.54 (*s*). Analogous measurements for **7a** [3] require correction of the assignment [6] for H-2 to τ 4.1 (*d*, J = 5 Hz).

Aniba affinis *and* A. burchellii

The most interesting feature of these re-assignments refers to the H-4 signal of the compounds of type **9** which appears as a doublet (J = 3 Hz) due to allylic coupling, a fact which was confirmed by double irradiation experiments and by registry of the LIS data [3] for **9c** from *A. burchellii* Kosterm. [13]. Reported band assignments for this compound must be corrected for H-2 to τ 4.81 (*d*, J = 7 Hz), for H-4 to τ 3.77 (*d*, J = 3 Hz) and for H-7 to τ 4.34 (*d*, H-7).

Analogously, band assignments for a compound from *A. affinis* (Meissn.) Mez, written **9d** in the original paper [9] but which is now known to be represented by **9e** [3], must be corrected for H-2 to τ 5.03 (*d*, J = 8 Hz) and for H-4 to τ 3.94 (*d*, J = 3 Hz). The recognition of the correct stereochemistry for this metabolite was described [3] and confirms the structure of **9d** for an isomer from *A. burchellii* [13] by ORD comparison (see Experimental).

EXPERIMENTAL

PMR-shift studies were carried out by stepwise addition of known amounts of $Pr(fod)_3$ to *ca* 8 × 10^{-5} M solns of substrate in $CDCl_3$. The LIS data were obtained by graphic extrapolation of observed shifts to 1:1 shift reagent–substrate ratio.

Isolation of constituents of Licaria canella. A sample of trunk wood (2.5 kg) [5] was extracted with C_6H_6. The extract (10 g) was crystallized from C_6H_6 to yield canellin-A (7.4 g). The mother-liquour was evapd and the residue separated by repeated TLC (Si gel, C_6H_6–EtOAc, 4:1) into **6** (36 mg), **5** (30 mg) and canellin-C (trace).

Separation of mixture of **9a** + **9b** *from* Aniba terminalis. Repeated TLC (Si gel, C_6H_6–EtOAc, 4:1) of A_5 (350 mg, see Experimental of Ref. [6]) gave **7a** (200 mg), **9a** (80 mg) and **9b** (30 mg).

(2R,3S,3aS)-*3a-Allyl-5-methoxy-3-methyl-2-piperonyl-2,3,3a,6-tetrahydro-6-oxobenzofuran* (**7a**). Mp 121–122° (MeOH) For other data see Discussion and [6]

(2R, 3S, 5R)-*5-Allyl-5-methoxy-3-methyl-2-piperonyl-2, 3, 5, 6-tetrahydro-6-oxobenzofuran* (**9a**). Mp 119–121° (petrol). ORD (*c* 8.8 mg/100 ml, MeOH): $[\phi]_{400}$ + 11270, $[\phi]_{375}$ 0, $[\phi]^{tf}_{342}$ −36930, $[\phi]_{314}$0, $[\phi]^{sh}_{292}$ + 28160, $[\phi]^{infl}_{277}$ + 28790, $[\phi]^{pk}_{265}$ +37550 For other data see [6]

(2R,3S,5R)-*5-Allyl-5-methoxy-3-methyl-2-piperonyl-2,3,5,6-tetrahydro-6-oxobenzofuran* (**9b**). Viscous oil. λ_{max} (MeOH, nm):

237, 288, 315 (ε 10550, 7650, 6800). λ_{max} (film, cm^{-1}): 1678, 1639, 1608. PMR (100 MHz, $CDCl_3$, τ): 3.21 (*d*, $J = 8.5$ Hz, ArH-5), 3.3 (*dd*, $J = 8.5$ and 2 Hz, ArH-6), 3.4 (*d*, $J = 2$ Hz, ArH-2), 3.81 (*d*, $J = 2$ Hz, H-4), 4.04 (*s*, O_2CH_2), 4.2–4.5 (*m*, CH=), 4.26 (*d*, $J = 8$ Hz, H-2), 4.28 (*s*, H-7), 4.97 (2 *dd*, $J = 15$ and 1.5 Hz, $J = 10.5$ and 1.5 Hz, $=CH_2$), 6.58 (*ddq*, $J = 8$, 2 and 7 Hz, H-3), 6.86 (*s*, OMe-5), 7.48 (*d*, $J = 7$ Hz, CH_2), 9.11 (*d*, $J = 7$ Hz, Me-3). MS (*m/e*): 340 (100%) M^+, 310 (19), 299 (54), 271 (11), 239 (14), 178 (10), 175 (11), 162 (14), 149 (30), 135 (40). ORD (*c* 4.8 mg/100 ml, MeOH): $[\phi]_{400}$ + 10480, $[\phi]_{377}$ 0, $[\phi]^{tr}_{343}$ −37220, $[\phi]_{315}$ 0, $[\phi]^{pk}_{295}$ + 40880, $[\phi]^{infl}_{282}$ + 35640, $[\phi]^{sh}_{270}$ + 34590.

(2S,3S,5S)-*5-Allyl-5-methoxy-3-methyl-2-veratryl-2,3,5,6-tetrahydro-6-oxobenzofuran* (**9d**). ORD (*c* 4.6 mg/100 ml., MeOH): $[\phi]_{400}$ −2520, $[\phi]_{388}$ 0, $[\phi]^{pk}_{342}$ + 36400, $[\phi]_{312}$ 0, $[\phi]^{tr}_{290}$ −25200, $[\phi]^{infl}_{277}$ −22260, $[\phi]^{sh}_{270}$ −21840, $[\phi]_{235}$ 0.

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