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BENZOFURANOID NEOLIGNANS FROM *ANIBA SIMULANS*[*]

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Key Word Index—*Aniba simulans*; Lauraceae; neolignans; 3a-allyl-2-aryl-3-methyl-2,3,3a,6-tetrahydro-6-oxobenzofurans; 5-allyl-2-aryl-3-methyl-2,3,5,6-tetrahydro-6-oxobenzofurans; 6-*O*-allyl-2-aryl-3-methyl-1,3-dihydrobenzofurans; 7-allyl-2-aryl-3-methyl-2,3-dihydrobenzofurans; 7-allyl-2-aryl-3-methylbenzofuran.

Abstract—Forteen neolignans, isolated from the benzene extract of *Aniba simulans* (Lauraceae) trunk wood, included the hitherto undescribed (2*S*, 3*S*, 5*R*)-5-allyl-5,7-dimethoxy-2-(3′,4′,5′-trimethoxyphenyl)-3-methyl-2,3,5,6-tetrahydro-6-oxobenzofuran, (2*R*,3*S*,5*R*)-5-allyl-5-methoxy-2-(3′-methoxy-4′,5′-methylenedioxyphenyl)-3-methyl-2,3,5,6-tetrahydro-6-oxobenzofuran, (2*S*,3*S*)-6-*O*-allyl-5-methoxy-2-(3′-methoxy-4′-5′-methylenedioxyphenyl)-3-methyl-2,3-dihydrobenzofuran, (2*R*,3*S*)-6-*O*-allyl-5-methoxy-2-(3′-methoxy-4′,5′-methylenedioxyphenyl)-3-methyl-2,3-dihydrobenzofuran and 7-allyl-6-hydroxy-5-methoxy-2-(3′-methoxy-4,5′-methylenedioxyphenyl)-3-methylbenzofuran.

INTRODUCTION

In a previous paper on an *Aniba* sp. (Lauraceae), the occurrence of the 9 benzofuranoid neolignans **1a**, **1c**, **1f**, **2a**, **2d**, **3a**, **3b**, **4d** and **4f** was described. Inspection of their structures and interconversions by pyrolysis led to the postulate that these compounds belong to series whose representatives can be linked by sequential Cope, retro-Claisen and Claisen rearrangements, e.g. **1a** → **2a** → **3a**, **2d** → **4d**, **1f** → **4f**, and that, consequently, the missing links **3d**, **2f** and **3f**, as well as a precursor of **3b**, should occur naturally [2].

One of the objectives of the present re-investigation thus concerned the isolation and description of such compounds. A new examination of the species was desirable anyway, since in the original paper the absolute stereochemistry at C-2 and C-3 had been established with certainty only for the 2,3-*trans*-dihydrobenzofuranoids **1a**, **2a**, **2d**, **3a**, **3b** and **4d** [2]. The relative configuration of the C-3 vicinal chiral centers in compounds of type **1** was since deduced by ^{13}C NMR [3], and thus the absolute stereochemistry of **1a** is now known. The technique proved of no help, however, in the analysis of the chirality at C-5 of compounds of type **2**, and this feature, as well as the absolute stereochemistry of the 2,3-*cis*-dihydrobenzofuranoids **1c**, **1f** and **4f**, remained to be investigated.

RESULTS

Structural determinations

Botanical material of the previously studied [2], as well as of three additional specimens, was tentatively classified by Dr. K. Kubitzki, Hamburg, as belonging to *Aniba simulans* Allen. Separate work-up revealed the presence in all trunk wood C_6H_6 extracts of sitosterol, benzyl benzoate and benzyl salicylate, common constituents of *Aniba* species [4], and 6,7-dimethoxycoumarin, recently isolated from another Lauraceae species [1]. The distribution of 14 neolignans (Table 1) shows that the chemical composition of specimens numbered 42 237 [2], 46 796 and 46 800 can be considered identical, six of their neolignans bearing a 3,4,5-trimethoxyphenyl and 5 a 3-methoxy-4,5-methylenedioxyphenyl substituent. The composition of a specimen 46 798 is peculiar, in so far as all six isolated compounds bear a 3-methoxy-4,5-methylenedioxyphenyl substituent.

Thus, the present work led indeed to the expected intermediates (**3d**, **2f** and **3f**) and precursor (**2b**). Compound **5** was obtained concommitantly. Since it was observed, however, that **4f** (but not **4d**) decomposed into **5** during silica gel TLC, the natural occurrence of this benzofuran derivative is not assured. The constitutions of these five compounds were deduced by spectral comparison with known analogous derivatives. For the compounds of series **1** [1, 2, 5–7], **2** [1, 2, 6, 7], **3** [1, 2, 7] and **4** [2, 7] several models are available. These can be used, inclusively, in conformational and configurational correlations. As has been pointed out [2, 5], and is apparent again in Table 2, the relative shielding of the Me-3 protons by the vicinal Ar reveals the *cis* relation of these groups. It is in this case (**6**) that H-2 is relatively deshielded and must, thus, lie closer to the O—C═C—C═O (in **1** and **2**) or O—Ar (in **3** and **4**) plane than in the 2,3-*trans* isomers (**7**). The identification of **5** relied only on data of two models [1,7]. The sequence of substituents on

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[*] Part 39 in the series 'The Chemistry of Brazilian Lauraceae'. For Part 38 see ref. [1]. Taken from parts of the Doctorate theses presented by O.C.C. (Organization of American States graduate fellow, on leave of absence from Universidad de Costa Rica) and F.M.P. (Coordenação do Aperfeiçoamento de Pessoal de Nível Superior, CAPES, graduate fellow, on leave of absence from Universidade Federal de Santa Maria) to the Universidade de São Paulo (1977). Sponsored by Instituto Nacional de Pesquisas da Amazonia, CNPq, and Fundação de Amparo à Pesquisa do Estado de São Paulo.

Table 1. Benzofuranoid neolignans of *Aniba simulans* (Tp . . . 3,4,5-trimethoxyphenyl, Mp . . . 3-methoxy-4,5-methylenedioxyphenyl, R^2 . . . allyl)

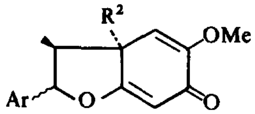
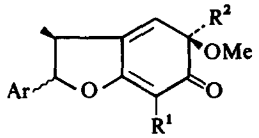
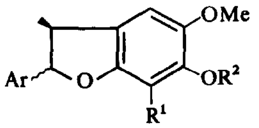
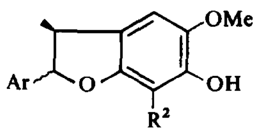
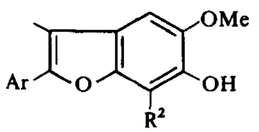
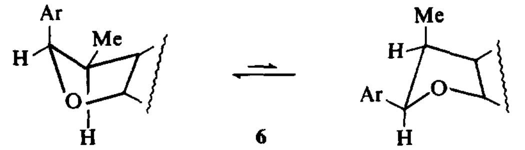
Structure	Ar	R^1	Cmpd.	Specimen Herbarium No 42237 [2]	46796	46800	46798
	α-Tp		**1a**	+	+	+	
	β-Tp		**1c**	+	+	+	
	β-Mp		**1f**	+	+	+	+
	α-Tp	H	**2a**	+	+	+	
	α-Tp	OMe	**2b**		+	+	
	α-Mp	H	**2d**	+	+	+	+
	β-Mp	H	**2f**		+	+	+
	α-Tp	H	**3a**	+		+	
	α-Tp	OMe	**3b**	+			
	α-Mp	H	**3d**				+
	β-Mp	H	**3f**				+
	α-Mp		**4d**	+			
	β-Mp		**4f**	+			
	Mp		**5**				

Table 2. Stereochemically significant PMR data (τ values, all signals are doublets, H-2: $J = 8$ Hz, Me-3: $J = 7$ Hz) of benzofuranoid neolignans

	2,3-*trans*-cmpds. H-2	Me-3		2,3-*cis*-cmpds. H-2	Me-3	Δτ H-2	Me-3
1a	4.71	8.82	**1c**	4.16	9.50	−0.55	+0.68
			1f	4.25	9.50		
2a	5.10*	8.64					
2b	4.96	8.62					
2d	4.94*	8.65	**2f**	4.23	9.07	−0.71	+0.42
3a	5.15	8.66					
3b	5.05	8.64					
3d	4.98	8.62	**3f**	4.30	9.17	−0.68	+0.55
4d	5.09	8.67	**4f**	4.44	9.24	−0.65	+0.57

* These signals were incorrectly considered singlets and assigned to H-7 in ref. [2]. It became clear, subsequently, after shifting of the signals into an interference free region by the LIS technique, that they are doublets. The signals at 4.54 and 3.95 [2] represent, respectively, H-7 and H-4.



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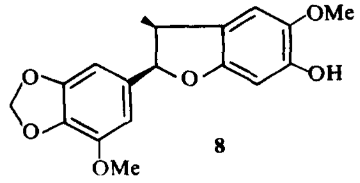

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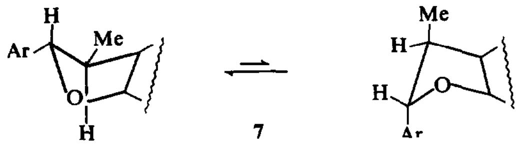

7

the benzene ring of the benzofuran system must be, nevertheless, correct, in view of the following evidence. First, a pyridine induced PMR solvent shift [8] demonstrated the vicinity of the allyl-CH_2 (Δτ 0.28 ppm) and the hydroxyl. This forms an intramolecular hydrogen bridge [9] to the methoxyl oxygen [$\nu(CH_2Cl_2)$ 3530 cm^{-1}, invariant upon dilution]. Finally, double irradiation at the PMR methoxyl frequency (τ 6.05) caused a 23 % NOE enhancement of the intensity of the aromatic H singlet at τ 3.20.

The proposed structures were confirmed by synthesis. This involved precursors of established structure [2], which were subjected to pyrolysis (**2d** → **3d**, **1f** → **2f** → **3f** → **4f**, **8**) or air oxidation (**4f** → **5**). The Cope rearrangement of **1f** → **2f** is of special significance. Indeed, since the relative configuration of **1f** is known [3] and the thermal reaction operates by suprafacial allyl migration, the relative configuration of the product can only be expressed as in **2f**.

In additional interconversions, acid isomerization of **3f** and **4f** (negative Cotton effects at 290 nm) led, as expected, respectively to **3d** and **4d** (positive Cotton effects at 290 nm). Clearly, this reaction proceeds by epimerization only of C-2. Absolute configurations can thus be formulated not only for **3f** and **4f**, but also for the additional 2,3-*cis*-derivatives **1f** and **2f**, on account of the aforementioned conversion to **3f**, and for **1c**, whose ORD curve is superimposable on the analogous curve of **1f**.

Deduction of the absolute configuration of **2a**, **2b** and **2d** will be part of a forthcoming general discussion on the stereochemistry of benzofuranoid neolignans.

EXPERIMENTAL

Isolation of the constituents. All plant material was collected at Ducke Forest Reserve, Manaus, Amazonas. The procedure used for Herbarium (INPA, Manaus) Specimen No 46798 is typical. Powdered wood (8 kg) was percolated at room temp. with C_6H_6. The extract (70 g) was freed of fatty esters (2.2 g) by washing with petrol and chromatographed on a Si gel column, giving the following fractions with C_6H_6–AcOEt mixtures of the indicated vol/vol compositions: A (1:0), B (9:1), C (8:2), D (6:4), E (4:6). A (4.3 g) was separated by TLC (petrol–C_6H_6, 3:7) into benzyl benzoate and benzyl salicylate. B (2.8 g) was separated by TLC (C_6H_6–AcOEt, 98:2), in order of increasing R_f, into a 7:3 mixt. of **3d** and **3f** (250 mg) and **5** (30 mg). The mixture was septd by fractional cryst. from MeOH. The initial fractions contained pure **3d**. C (3.6 g) is mainly sitosterol. D (20.6 g) was septd by filtration into crystalline **1f** (10 g). The oily filtrate was septd by TLC (Et_2O), into **1f** (R_f 0.19) and a 7:3 mixt. of **2d** and **2f** (R_f 0.58). The mixture was septd by Al_2O_3 TLC (Et_2O) into **2d** (200 mg) and **2f** (50 mg). E (9.4 g) was septd by TLC ($CHCl_3$–MeOH 96:4) into a mixture of **1f**, **2d** and **2f** (R_f 0.64) and a mixture of 6,7-dimethoxycoumarin and bicyclo[3,2,1]octanoid neolignans (to be reported). Similar work-up of a C_6H_6 extract (5 g) from trunk wood of Specimen No 46796 gave, in fraction D, additionally **2b** (50 mg).

(2S,3S,5R)-5-*Allyl*-5,7-*dimethoxy*-2-(3′,4′,5′-*trimethoxyphenyl*-3-*methyl*-2,3,5,6-*tetrahydro*-6-*oxobenzofuran* (**2b**). Viscous oil (found: M 416.1829, $C_{22}H_{24}O_7$ requires 416.1835). UV λ^{MeOH}_{max} nm: 260 inf., 280 *sh*., 335 (ε 2750, 2000, 4000). IR ν^{film}_{max} cm^{-1}: 1656, 1608, 1458, 1355, 1241, 1131, 1011, 923, ^{1}H-NMR ($CDCl_3$, 100 MHz, τ): 3.44 (*s*, H-2′, H-6′),4.00 (*d*, *J* = 3.0Hz, H-4); 4.10–4.40 (*m*, CH=), 4.80–5.04 (*m*, =CH_2), 4.96 (*d*, *J* = 8.0 Hz, H-2), 6.70–7.00 (*m*, H-3), 6.86 (*s*, OMe-5), 7.46 (*d*, *J* = 8.0Hz, CH_2), 8.62 (*d*, *J* = 7.0Hz, Me-3). MS (*m/e*): 416 (20 %) M, 370 (40), 329 (15), 196 (15), 179 (25), 165 (25), 149 (30), 119 (100), 105 (25), 77 (30), 57 (50), 47 (60), 43 (50), 41 (50). ORD (c 1.26 mg/100 ml, MeOH, 225–355 nm): $[\theta]^{tr}_{353}$ − 15800; $[\theta]_{322}$ 0; $[\theta]^{pk}_{288}$ + 10200, $[\theta]_{242}$ 0, $[\theta]^{tr}_{233}$ − 3140, $[\theta]_{225}$ 0.

(2R, 3S, 5R)-5-*Allyl*-5-*methoxy*-2-(3′-*methoxy*-4′,5′-*methylenedioxyphenyl*)- 3-*methyl*-2,3,5,6-*tetrahydro*-6-*oxobenzofuran* (**2f**). 109–110° (petrol–C_6H_6) (found: M 370.1409, $C_{21}H_{22}O_6$ requires: 370.1415). UV λ^{MeOH}_{max} nm: 245, 290, 317 (ε 11900, 4350, 6400). IR ν^{film}_{max}cm^{-1}: 1632, 1601, 1504, 1490, 1372, 1136, 978, 917. ^{1}H-NMR (60 MHz, $CDCl_3$, τ): 3.63 (*s*, H-2′, H-6′), 3.80 (*d*, *J* = 3.0Hz, H-4), 4.00 (*s*, O_2CH_2), 4.23 (*s*, H-7), 4.25 (*d*, *J* = 8.0Hz, H-2), 3.92–4.60 (*m*, CH=), 4.73–5.22 (*m*, =CH_2), 6.10 (*s*, OMe-3′), 6.30–6.80 (*m*, H-3), 6.85 (*s*, OMe-5), 7.47 (*d*, *J* = 7.0Hz, CH_2), 9.08 (*d*, *J* = 7.0Hz, Me-3). Upon double irrad. at 6.30–6.76 (H-3), the doublets at 4.25 (H-2) and 9.08 (Me-3) collapse into singlets. MS (*m/e*): 370 (39 %) M, 371 (11), 329 (22), 192 (13), 179 (12), 177 (19), 165 (30), 149 (27), 101 (15), 91 (12), 77 (13), 69 (19), 59 (47), 57 (20), 43 (100), 41 (26). ORD (c 1.45 mg/50 ml, MeOH, 235–390 nm): $[\theta]_{382}$ 0, $[\theta]^{tr}_{345}$ − 44700, $[\theta]_{317}$ 0, $[\theta]^{pk}_{295}$ + 34500, $[\theta]^{pk}_{270}$ + 32000, $[\theta]_{238}$ 0.

(2S, 3S)-6-O-*Allyl*-5-*methoxy*-2-(3′-*methoxy*-4′,5′-*methylenedioxyphenyl*)-3-*methyl*-2,3-*dihydrobenzofuran* (**3d**). Needles, mp 81–82° (MeOH) (found: M 370.1410, $C_{21}H_{22}O_6$ requires: M 370.1415). UV λ^{MeOH}_{max} nm: 238 inf., 297 (ε 13700, 9400). IR ν^{film}_{max} cm^{-1}: 1638, 1496, 1460, 1430, 1118, 1087, 935, 830. ^{1}H-NMR (60 MHz, $CDCl_3$, τ): 3.27 (*s*, H-4), 3.38 (*s*, H-2′, H-6′), 3.47 (*s*, H-7), 3.53–4.20 (*m*, CH=), 4.03 (*s*, O_2CH_2), 4.40–4.85 (*m*, =CH_2), 4.98 (*d*, *J* = 8.0Hz, H-2), 5.34–5.50 (*m*, CH_2), 6.08 (*s*, OMe-3′), 6.17 (*s*, OMe-5), 6.47–6.97 (*m*, H-3), 8. 62 (*d*, *J* = 7.0Hz, Me-3). Upon double irrad. at 6.50–6.93 (H-3), the doublets at 4.98 (H-2) and 8.62 (Me-3) collapse into singlets. MS (*m/e*): 370 (100 %) M, 371 (25), 329 (28), 269 (14), 177 (60), 165 (17), 121 (14), 106 (14), 91 (11), 77 (11), 69 (11), 41 (26). ORD (c 3.82 mg/50 ml, MeOH, 220–360 nm): $[\theta]_{355}$ 0, $[\theta]^{tr}_{320}$ − 6650, $[\theta]_{305}$ 0. $[\theta]^{pk}_{287}$ + 9500, $[\theta]^{pk}_{260}$ + 10650, $[\theta]_{245}$ 0.

(2R, 3S)-6-O-*Allyl*-5-*methoxy*-2-(3′-*methoxy*-4′,5′-*methylenedioxyphenyl*)-3-*methyl*-2,3-*dihydrobenzofuran* (**3f**). Viscous oil (found: M 370.1410, $C_{21}H_{22}O_6$ requires: M 370.1416). UV λ^{MeOH}_{max} nm: 238 inf., 298 (ε 10350, 6850). IR ν^{film}_{max}cm^{-1}: 1637, 1493, 1460, 1429, 1124, 1094, 948, 851, 833. ^{1}H-NMR (60 MHz, $CDCl_3$, τ): 3.25 (*s*, H-4), 3.43 (*s*, H-7), 3.47 (*s*, H-2′, H-6′), 3.56–4.26 (*m*, CH=), 4.00 (*s*, O_2CH_2), 4.32 (*d*, *J* = 8.0Hz, H-2), 4.40–4.84 (*m*, =CH_2), 5.30–5.46 (*m*, CH_2), 6.08 (*s*, OMe-3′), 6.13 (*s*, OMe-5), 6.27–6.76 (*m*, H-3), 9.17 (*d*, *J* = 7.0Hz, Me-3). Upon double irrad. at 6.27–6.80 (H-3), the doublets at 4.32 (H-2) and 9.17 (Me-3) collapse into singlets MS (*m/e*): 370 (21 %) M, 279 (10), 222 (18), 180 (26), 179 (24), 149 (100), 135 (14), 83 (12), 71 (20), 57 (48), 43 (48), 41 (35). ORD (c 2.15 mg/50 ml, MeOH, 235–360 nm): $[\theta]_{355}$ 0, $[\theta]^{pk}_{320}$ + 14500, $[\theta]_{304}$ 0, $[\theta]^{tr}_{284}$ − 18200, $[\theta]_{260}$ 0, $[\theta]_{248}$ + 34400, $[\theta]_{235}$ 0.

7-*Allyl*-6-*hydroxy*-5-*methoxy*-2-(3′-*methoxy*-4′,5′-*methylenedioxyphenyl*)-3-*methylbenzofuran* (**5**). Yellow crystals, mp 141–142° (MeOH) (found: M 368.1322, $C_{21}H_{20}O_6$ requires: M 368.1311). UV λ^{MeOH}_{max} nm: 218, 290, 327 (ε 30400, 10450, 27000). UV $\lambda^{MeOH+NaOH}_{max}$ nm: 218, 270, 352 (ε 30400, 5750, 24400). IR ν^{KBr}_{max}cm^{-1}: 3495, 3412, 1642, 1512, 1440, 1346, 928, 837, 808. ^{1}H-NMR (60 MHz, $CDCl_3$, τ): 3.02 (*s*, H-2′, H-6′), 3.18 (*s*, H-4), 3.60–4.26 (*m*, CH=), 3.97 (*s*, O_2CH_2), 4.20 (*s*, OH-6), 4.63–5.06 (*m*, =CH_2), 6.00 (*s*, OMe-3′), 6.03 (*s*, OMe-5), 6.28 (*d*, *J* = 6.0Hz, CH_2), 5.58 (*s*, Me-3). τ ($CDCl_3$) − τ(C_5D_5N): 0.19 (H-2′, H-6′), 0.23 (H-4). MS (*m/e*): 368 (100 %) M, 184 (9).

Pyrolyses. Performed according to a procedure described in refs. [1] and [2] at 105° (**1f** → **2f**), 115° (**2f** → **3f**,**2d** → **3d**), 145° (**3f** → **4f**,**8**). Acid isomerizations were performed according to a procedure described in ref. [1] (**3f** → **3d**; **4f** → **4d**). **1f**, **4f**, **4d** and **8** were identified by direct comparison with authentic samples [2].

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