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NEOLIGNANS FROM *NECTANDRA MIRANDA**

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Key Word Index—*Nectandra miranda*; Lauraceae; neolignans; mirandin-A; mirandin-B; licarin-C; (2*S*, 3*S*, 3a*S*)-, (2*S*, 3*S*, 3a*R*)- and (2*R*, 3*S*, 3a*S*)-5-allyl-3a-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3- methyl-2, 3, 3a, 6-tetrahydro-6-oxobenzofuran; 7-allyl-6-hydroxy-5- methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3-methylbenzofuran; (2*R*, 3*R*)-7-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3-methyl-5-(*E*)-propenyl-2,3-dihydrobenzofuran; (2*S*, 3*S*, 3a*S*)-3a-allyl-5-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3-methyl-2, 3, 3a, 6 tetrahydro-6- oxobenzofuran; (2*S*, 3*S* 5*R*)-5-allyl-5-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3-methyl-2, 3, 5, 6-tetrahydro-6-oxobenzofuran; (2*S*, 3*S*)-6-*O*-allyl-5-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3-methyl-2, 3-dihydrobenzofuran.

Abstract—Seven neolignans, isolated from a C_6H_6 extract of *Nectandra miranda* (Lauraceae) trunk wood, included the hitherto undescribed (2*S*, 3*S*, 3a*S*)- and (2*S*, 3*S*, 3a*R*)-5-allyl-3a-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3-methyl-2, 3, 3a, 6-tetrahydro-6-oxobenzofurans (respectively mirandin-A and mirandin-B), 7-allyl-6-hydroxy-5-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3-methylbenzofuran and (2*R*, 3*R*)-7-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3-methyl-5-(*E*)-propenyl-2,3-dihydrobenzofuran (licarin C).

INTRODUCTION

The biosynthesis of the guianin (**4**) [2, 3] and burchellin (**5a**) [3–6] type neolignans of *Aniba* species involves, presumably, the oxidative coupling of propenyl- and allylphenols, either by radical pairing (**1** + **2**) [7] or through ionic intermediates. It suffices to postulate the existence of the allylphenol derived intermediate in a mesomeric form to rationalize the formation (**1** + **3**) of macrophyllin (**6**) [8] and to justify the expectation that the alternative type **7** also should be represented in nature. This is indeed the case and we now report that *Nectandra miranda*, Lauraceae, contains the mirandins A (**7a**) and B (**7b**).

RESULTS AND DISCUSSION

3α-*Methoxybenzofuranoid neolignans*

The mirandins A and B were recognized as neolignans by their formulae, $C_{18}H_{14}O_2(OMe)_4$, and spectra; the similar ^{1}H-NMR and MS (*m/e* 208, 100%) clearly pointing in both cases to partial structure **8** with the Ar and Me groups in a *trans*-relationship [4]. The additional $C_6.C_3$-unit must be represented by a cyclohexadienone [ν_{max} (cm^{-1}) mirandin A 1666; mirandin B 1680] linked at the sole and fully substituted sp^3–C to a methoxyl (τ mirandin A 7.00; mirandin B 6.88) and at a sp^2–C to an allyl group, as in **7**. The allyl can, indeed, be located only on a sp^2–C, the doubly allylic methylene protons being equivalent (τ mirandin A 6.89; mirandin B 6.84, both *d*, $J = 7.0$ Hz). Among the 3 possible sites, C–7 and C–4 are incompatible with the representation of the ring olefinic protons by MR singlets and the biosynthesis which requires the allyl group to be *para*-related with an oxy-function.

Since both compounds are represented by formula **7**, they must differ in the orientation of the aliphatic methoxyl. Indeed, the conspicuous differences in the ^{1}H-NMR spectra, all refer to signals attributed to protons of the immediate vicinity of C–3a. Most significantly, the H–3 signal of mirandin–A appears 0.49 ppm downfield from the H–3 signal of mirandin–B. This seems to indicate association of H–3 to OMe–3a in mirandin–A (**7a**), in contradistinction to the *trans* relation of H–3/OMe–3a in mirandin–B (**7b**). Indeed, the analogous association is apparent in the ^{1}H-NMR spectrum of 2-*epi*-mirandin-A (**7c**), the product of isomerization by acid of **7a**. Comparison of the three spectra reveals additionally the expected relative shielding of methoxyl only in the 2,3a-*cis*-derivative **7a** (Table 1).

Photolysis or pyrolysis of mirandin-A leads to **9**, a compound which was obtained previously by pyrolysis of the naturally occurring **10** [5], and identified inclusively with respect to stereochemistry. Thus, **7a** registers the absolute configuration of mirandin-A.

In solution, the aryl and cyclodienone moieties of

Table 1. ^{1}H-NMR comparison of the mirandins in $CDCl_3$

	7a	**7b**	**7c**
H-2 (τ)	4.84	4.68	3.94
H-3 (τ)	7.35	7.84	7.30
$J_{H-2,H-3}$ (Hz)	<0.5	9.5	5.0
OMe-3a (τ)	7.00	6.88	6.82
Me-3 (τ)	8.89	8.85	9.48

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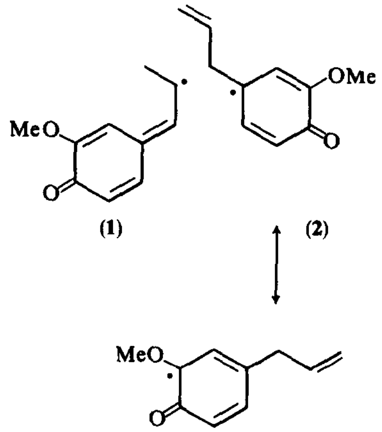
Table 2. ORD extrema ([ϕ]) and UV maxima (ε) of the mirandins in MeOH

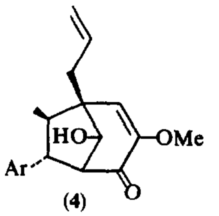
nm	267	275	291	312	335	253	280	300
7a		−21850 *tr*		0	+18490 *pk*	21000	3950	4100
7b	−23490 *tr*	−23020 *pk*	−24500 *tr*	0	+19180 *pk*	12100	3600	4100
7c	+3510 *tr*		+16380 *pk*	0	−19880 *tr*	14150	2850	3850

mirandin-A (**7a**) possess a fair degree of coplanarity, determining relatively intense UV absorption (ε 21000) and low IR carbonyl frequency (1666 cm^{-1}), together with a dihedral angle H–C(2)–C(3)–H of about 90° ($J_{H-2,H-3} = 0.5$ Hz). The Cotton effects associated with the benzenoid and enone chromophores are both positive and cause an unresolved ORD curve between 250–310 nm. In contradistinction, mirandin-B (**7b**) is a twisted structure (ε 12100, ν 1680 cm^{-1}) with the dihedral angle approaching 180° ($J_{H-2,H-3} = 9.5$ Hz). The Cotton effects associated with the two chromophores are of opposite signal in the region of benzenoid (300 nm) and enone (280 nm) absorptions (Table 2), and cause a well resolved ORD curve. Correlation of the signal of these Cotton effects with aryl and methoxyl configuration was effected by analysis of the ORD curve of 2-*epi*-mirandin-A (**7c**). This was derived from mirandin-A (**7a**) by epimerization only of C-2. In consequence, no doubt exists concerning the (2*R*)-configuration, associated with a negative Cotton effect in the 310 nm region, the (3a*S*)-configuration, associated with a positive Cotton effect around 280 nm, and the (3*S*)-configuration of its chiral centres. Mirandin-B, which causes a positive Cotton effect in the 310 nm region and a negative Cotton effect in the 280 nm region, must consequently possess the absolute configuration registered in **7b**.

Configuration and conformation of the mirandins are also discussed in a paper on the ^{13}C–NMR spectra of neolignans [9].



(1) **(2)** **(3)**



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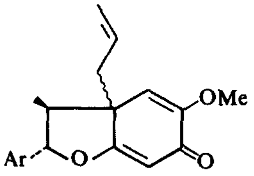
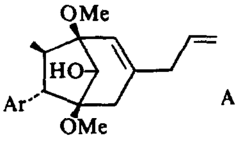


(5) Allyl
(5a) β
(5b) α



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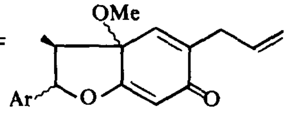
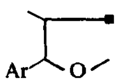


(7) Ar OMe
(7a) α α
(7b) α β
(7c) β α



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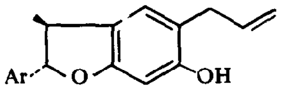

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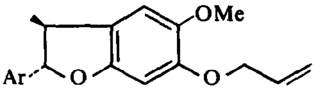

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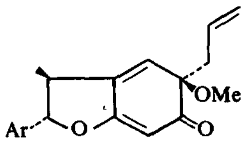

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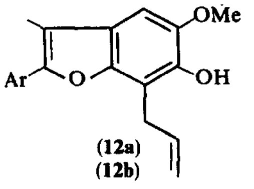
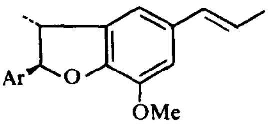


(12a)
(12b)



(13a)
(13b)

■ fully substituted sp^3-C
In **7–10**, **12a** and **13a** Ar = 3,4,5-trimethoxyphenyl
In **12b** Ar = 3,4-methylenedioxyphenyl
In **13b** Ar = 3,4-dimethoxyphenyl

Other benzofuranoid neolignans

Further compounds of *Nectandra miranda* include sitosterol, the ferulate of a fatty alcohol, 6,7-dimethoxycoumarin and 5 neolignans: the known [5] (2*S*, 3*S*, 3a*S*)-3a-allyl-5-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3-methyl-2, 3, 3a, 6-tetrahydro-6-oxobenzofuran (**5b**), (2*S*, 3*S*, 5*R*)-5-allyl-5-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3-methyl-2, 3, 5, 6-tetrahydro-6-oxobenzofuran (**11**) and (2*S*, 3*S*)-6-*O*-allyl-5-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl)-3-methyl-2,3-dihydrobenzofuran (**10**), and the previously unknown $C_{18}H_{11}O.OH(OMe)_4$ (**12a**) and $C_{18}H_{14}O(OMe)_4$ (**13a**).

Both **12a** and **13a** were recognized as neolignans through their molecular formulae and classified according to type by ^{1}H-NMR, the spectra being partly superimposable, respectively, on the spectra of 7-allyl-6-hydroxy-5-methoxy-3-methyl-2-piperonylbenzofuran (**12b**) [6] and of the licarin-type [10] compound (2*R*, 3*R*)-7-methoxy-3-methyl-5-(*E*)-propenyl-2-veratryl-2, 3-dihydrobenzofuran (**13b**) [3] from *Aniba* species. The differences in these pairs of spectra refer only to signals due to the aryl substituents of **12a** and **13a** (3 OMe) and **12b** and **13b**. The closeness of the ORD curves of **13a**, designated licarin-C[11], and **13b** [3] demonstrates their identical absolute stereochemistry.

EXPERIMENTAL

Isolation of the constituents. The C_6H_6 ext. (50 g) of a trunk wood sample (7.1 kg) of *Nectandra miranda* Sandw. (Voucher: Herbarium IPEAN, Belém, 120.907) from the IPEAN Forest Reserve near Belém, Pará) was separated into petrol soluble and insoluble portions. The former (8 g) was chromatographed on Si gel, C_6H_6 eluting in order the ferulate of a fatty alcohol (220 mg), **12a** (80 mg), a mixture of **13a** (1.7 g) and **10** (40 mg) which was separated by preparative TLC, **7b** (15 mg) and **7a** (5 g). The insoluble portion (34 g) was freed from fatty material with hot MeOH. The residue (9 g) was chromatographed on Si gel, solvent of increasing polarity eluting in order **7a** (2 g), sitosterol (550 mg), 6,7-dimethoxycoumarin (350 mg), **11** (1.9 g), **5b** (50 mg) and a complex mixture (27 g). The known compounds were identified by direct comparison. Previously reported as a viscous oil [5], **11** was obtained as crystals, mp 110–111° (hexane–C_6H_6).

(2S, 3S, 3aS)-5-*Allyl*-3a-*methoxy*-2-(3′, 4′, 5′-*trimethoxyphenyl*)-3-*methyl*-2, 3, 3a, 6-*tetrahydro-6-oxobenzofuran* (**7a**). mp 89–91° (C_6H_6–hexane) [Found: C, 68.38; H, 6.70.$C_{22}H_{26}O_6$ requires: C, 68.39; H, 6.73%]. ν_{max}^{KBr} (cm^{-1}): 1666, 1624, 1515, 1470, 1430, 1369, 1250, 1136, 1063, 925, 848. ^{1}H-NMR ($CDCl_3$, 220 MHz, τ): 3.46 (*s*, H-2′, 6′), 3.86 (*s*, H-4), 4.19–4.28 (*m*, CH=), 4.16 (*s*, H-7), 4.84 (sec. split *s*, H-2), 4.89–5.00 (*m*, =CH_2), 6.19 (*s*, OMe-3′, 4′, 5′), 6.89 (*d*, *J* = 7.0 Hz, CH_2), 7.00 (*s*, OMe-3a), 7.35 (sec. split *q*, *J* = 7.0 Hz, H-3), 8.89 (*d*, *J* = 7.0 Hz, Me-3). MS *m/e* (rel. int.): 386 (95%) M, 357 (10), 317 (27), 221 (45), 209 (14), 208 (100), 193 (50), 178 (25), 166 (40), 165 (67), 137 (15), 135 (10), 105 (10).

Photolysis of mirandin-A. A 2 mM soln of **7a** in MeOH under N_2 was irradiated by a 450 W medium pressure mercury lamp (Hanovia) either for 30 min (without Pyrex filter) or for 120 min (with Pyrex filter). The solns were evap. and the residues fractionated into constituents by TLC. Relative yield of **9**: 8% (with filter) and 25% (without filter). The compound was identical in all respects, including ORD to (2*S*, 3*S*)-5-allyl-6-hydroxy-2-(3′, 4′, 5′-trimethoxyphenyl-3-methyl-2, 3-dihydrobenzofuran (**9**). The published data [5] must be revised with respect to mp 196–198° (C_6H_6–petrol) and ORD [ϕ]-values to be reduced by a factor of 7.

Pyrolysis of mirandin-A. Solns of **7a** in $C_6H_5NEt_2$ under N_2 were maintained at 100° and 200° for 5 hr. The cooled reaction mixtures were treated by a described procedure [5]. TLC indicated recovery of starting material in the run at 100°. The run at 200° gave **7a** and **9** (50% yield).

Isomerization of mirandin-A. A soln of **7a** (240 mg) and TsOH (1 mg) in dry MeOH (15 ml) was kept at room temp. (48 hr). The soln was then neutralized with $NaHCO_3$ and evap. The residue was separated by Si gel–TLC C_6H_6–AcOEt (8:2) into **7c** (50 mg), **7a** (140 mg) and a mixture (30 mg).

(2S, 3S, 3aR)-5-*Allyl*-3a-*methoxy*-2-(3′, 4′, 5′- *trimethoxyphenyl*)-3-*methyl*-2, 3, 6-*tetrahydro-6-oxobenzofuran* (**7b**). mp 88–92° (C_6H_6–CCl_4) [M found: 386.1722. $C_{22}H_{26}O_6$ requires: 386.1729]. ν_{max}^{film} (cm^{-1}): 1680, 1639, 1515, 1470, 1430, 1369, 1250, 1136, 1075, 925, 850. ^{1}H-NMR ($CDCl_3$, 100 MHz, τ): 3.50 (*s*, H-2′, 6′), 3.74 (*s*, H-4), 4.18 (*s*, H-7), 4.0–4.3 (*m*, CH=), 4.68 (*d*, *J* = 9.5 Hz, H-2), 4.75–4.95 (*m*, =CH_2), 6.15 (*s*, OMe-3′, 4′, 5′), 6.84 (*d*, *J* indet., CH_2), 6.88 (*s*, OMe-3a), 7.84 (*dq*, *J* = 7.0, 9.5 Hz, H-3), 8.85 (*d*, *J* = 7.0 Hz, Me-3). MS *m/e* (rel. int.): 386 (84%) M, 356 (22), 317 (9), 275 (11), 223 (15), 222 (28), 209 (14), 208 (100), 204 (25), 193 (31), 189 (13), 178 (23), 165 (26), 137 (14), 135 (22).

(2R, 3S, 3*a*S)-5*Allyl-3a-methoxy*-2-(3′, 4′, 5′-*trimethoxyphenyl*)-3-*methyl*-2, 3, 3a, 6-*tetrahydro-6-oxobenzofuran* (**7c**). Viscous oil [Found: C, 68.45; H, 6.61. $C_{22}H_{26}O$ requires: C, 68.39; H, 6.73%]. ν_{max}^{film} (cm^{-1}): 1672, 1629, 1244, 1189, 1135, 1076, 1014, 945, 918, 852. ^{1}H-NMR ($CDCl_3$, 100 MHz, τ): 3.56 (*s*, H-2′, 6′), 3.74 (broad *s*, H-4), 3.94 (*d*, *J* = 5.0 Hz, H-2), 4.06 (*s*, H-7), 3.85–4.35 (*m*, CH=), 4.8–5.0 (*m*, =CH_2), 6.14 (*s*, OMe-3′, 4′, 5′), 6.82 (*s*, OMe-3a), 6.75–6.90 (*m*, CH_2), 7.30 (*dq*, *J* = 7.0, 5.0 Hz, H-3), 9.48 (*d*, Me-3). MS *m/e* (rel. int.): 386 (93%) M, 356 (27), 341 (13), 317 (33), 289 (10), 252 (13), 221 (40), 208 (100), 193 (47), 168 (40), 165 (40), 149 (80), 139 (53).

7-*Allyl-6-hydroxy-5-methoxy*-2-(3′, 4′, 5′-*trimethoxyphenyl*)-3-*methylbenzofuran* (**12a**). Crystals, mp 133–135° (petrol) [Found: C, 68.19; H, 6.23. $C_{22}H_{24}O_6$ requires: C, 68.75; H, 6.25%]. ν_{max}^{KBr} (cm^{-1}): 3500, 1600, 1340, 1250, 1135, 845. λ_{max}^{EtOH} (nm): 250, 290, 325 (ε 6300, 11350, 19200). ^{1}H-NMR ($CDCl_3$, τ, 60 MHz): 3.10 (*s*, H-2′, 6′), 3.24 (*s*, H-4), 3.5–4.1 (*m*, CH=), 4.24 (OH-6), 4.65–5.15 (*m*, =CH_2), 6.10 (*s*, OMe), 6.14 (*s*, 2 OMe), 6.20 (*s*, OMe), 6.34 (sec. split *d*, *J* = 5.9 Hz, CH_2), 7.67 (*s*, Me-3). MS *m/e* (rel. int.): 384 (100%) M, 368 (56), 192 (16).

(2R, 3R)-7-*Methoxy*-2-(3′, 4′, 5′-*trimethoxy phenyl*)-3- *methyl*-5-(*E*)-*propenyl*-2, 3-*dihydrobenzofuran* (**13a**). Crystals, mp 100–101° (MeOH) [M found: 370.1775. $C_{22}H_{26}O_5$ requires: 370.1780]. λ_{max}^{MeOH} (nm): 222, 268 (ε 36300, 21500). ^{1}H-NMR (CCl_4, τ): 3.35–3.50 (*m*, 4 ArH), 3.75 (*d*, *J* = 15.0 Hz, ArCH=), 4.05 (*dq*, *J* = 15.0, 5.5 Hz, = CH); 5.07 (*d*, *J* = 9.1 Hz, H-2), 6.14 (*s*, OMe), 6.20 (*s*, 2 OMe), 6.27 (*s*, OMe), 6.6–7.2 (*m*, H-3), 8.15 (*d*, *J* = 5.5 Hz, Me), 8.60 (*d*, *J* = 6.5 Hz, Me-3). MS *m/e* (rel. int.): 370 (100%) M, 355 (43), 339 (7), 295 (4), 281 (4), 256 (4), 202 (4), 192 (7), 190 (8), 185 (23), 181 (17), 167 (10), 165 (7), 153 (6). 115 (5). ORD (*c*, 1.35 mg/100 ml, MeOH, 320–220 nm): $[\phi]_{340}$ 0, $[\phi]_{295}^{pk}$ + 10400, $[\phi]_{280}$ 0, $[\phi]_{255}^{tr}$ − 40000, $[\phi]_{235}$ 0.

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