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2,5-DIARYL-3,4-DIMETHYLTETRAHYDROFURANOID LIGNANS

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Key Word Index—*Aristolochia chilensis*; Aristolochiaceae; Magnoliales; (+)-aristolignin; (−)-zuonin-A; malabaricanol.

Abstract—*Aristolochia chilensis* has yielded the new 2,5-diaryl-3,4-dimethyltetrahydrofuranoid lignans (+)-aristolignin and (−)-zuonin-A. These and related tetrahydrofuranoids have been classified into six stereochemical groups.

INTRODUCTION

The 2,5-diaryl-3,4-dimethyltetrahydrofurans are a group of lignans found mainly among members of the botanical families Magnoliaceae, Himantandraceae, Schisandraceae, Lauraceae, Trimeniaceae, Austrobaileyaceae and Myristicaceae [1–12], all of which belong to the order Magnoliales [13]. They have also been found in the botanically related family Aristolochiaceae [14], of the order Aristolochiales [13].

No review dedicated solely to these tetrahydrofurans has appeared, but six stereochemical groups may be distinguished. Group I (Table 1) includes the *meso* or quasi-*meso* series represented by galgravin (**1**) [1], (+)-nectandrin-A (**2**), nectandrin-B (**3**) [2] and zuonin-B (**4**) [3]. From the literature data, it would appear that the tetrahydrofuran recently characterized as malabaricanol [4] corresponds to nectandrin-B (**3**) previously isolated by LeQuesne *et al.* [2]. The assignment of the positions of the hydroxyl and methoxyl aromatic substituents in (+)-nectandrin-A is based on biogenetic grounds, while the absolute configuration of this compound still remains to be established.

Groups II and III consist of (−)-galbacin (**5**) [1], (−)-galbelgin (**6**) [5] and (−)-grandisin (**7**) [6] on the one hand, and (+)-galbacin (**8**) and (+)-galbelgin (**9**) [12] on the other. The absolute configurations still remain to be assigned.

The tetrahydrofurans (+)-veraguesin (**10**) [7], (+)-calopiptin (**11**) [8], (+)-austrobailignan-7 (**12**) [9] and (+)-verrucosin (**13**) [10] made up Group IV until the present results. The absolute configuration of (+)-calopiptin (**11**) is known from chemical degradation, and the other members of Group IV were correlated chemically with this species.

Group V consists of (+)-chicanin (**15**) [11], (+)-zuonin-A (**16**) [3] and (+)-zuonin-C (**17**) [3]. The absolute configuration of (+)-chicanin (**15**) has been settled through chemical degradation. It should be noted that the spectroscopic data available for (+)-zuonin-C (**17**) does not allow for an unequivocal structure assignment (Table 1).

(−)-Machilusin (**18**) [12] was the sole constituent of Group VI until the present results. Again, chemical and spectroscopic data did not permit a clear cut assignment of structure to this product (Table 1). It is relevant to point out that individual members of Groups V and VI may be enantiomeric as in the case of (+)-zuonin-A (**16**) and (−)-zuonin-A (**19**) described below.

RESULTS AND DISCUSSION

An investigation of the roots of *Aristolochia chilensis* Miers (Aristolochiaceae) has supplied the known lignans (+)-calopiptin (**11**) and (+)-austrobailignan-7 (**12**), together with the new (−)-zuonin-A (**19**) and (+)-aristolignin (**14**).

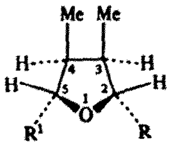
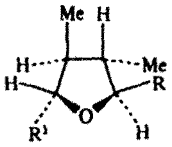
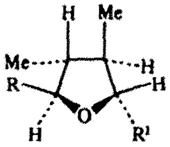
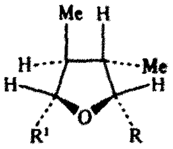
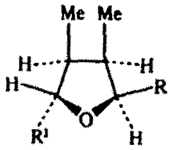
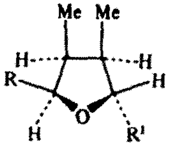
(−)-Zuonin-A (**19**) was obtained as a white crystalline solid, $C_{20}H_{20}O_5$, mp 119–121° (EtOH), $[\alpha]_D - 138.9°$ (*c* 1.00, $CHCl_3$). The melting point and spectroscopic properties (NMR, UV, mass) correspond with those for the known (+)-zuonin-A (**16**) [3], except that the rotation is of the opposite sign.

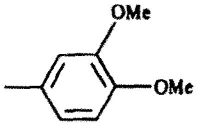
The phenolic (+)-aristolignin (**14**), $C_{21}H_{26}O_5$, was isolated as an oil, $[\alpha]_D + 24.3°$ (*c* 1.35, $CHCl_3$). The 360 MHz ($CDCl_3$) NMR spectrum is quoted around the structure shown in Fig. 1. *O*-Methylation of (+)-aristolignin (**14**) provided (+)-veraguesin (**10**), thus supplying additional support for the structure assignment.

The relative positions of the aromatic hydroxyl and methoxyl substituents, as well as the relative positions of the two aromatic rings in (+)-aristolignin (**14**) were settled through a complete NMR NOE study. Irradiation of the methoxyl singlet (δ3.92) led to a 17.1% enhancement of the H-2″ doublet (δ7.05). Irradiation of the H-2″ doublet (δ7.05) caused a 10.2% increase of the H-5 doublet (δ4.41) as well as a 16.4% increase of the methoxyl singlet (δ3.92). Additionally, irradiation of the H-5 doublet (δ4.41) resulted in a 7.2% enhancement of the H-2″ doublet (δ7.05) and a 7.2% enhancement of the H-6″ doublet of doublets (δ6.99).

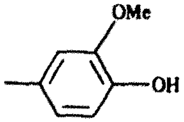
Turning now to the protons on or near the Ar′ ring, it was found that irradiation of the methoxyl singlets at δ3.88 and 3.86 effected a 19.7% increase of the H-5′ doublet (δ6.85) as well as of the H-2′ doublet (δ6.87). Finally, irradiation of the H-2 doublet (δ5.14) induced a 28.9% enhancement of the H-2′ doublet (δ6.87). These

Table 1. 2,5-Diaryl-3,4-dimethyltetrahydrofuranoid lignans

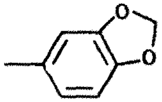
Group I	Group II and III	Group IV	Group V	Group VI
	 			
Galgravin (**1**) R = R^1 = Ar^1 (+)-Nectandrin-A (**2**) R = Ar^1, R^1 = Ar^2 Nectandrin-B (**3**) R = R^1 = Ar^2 Zuonin-B (**4**) R = R^1 = Ar^3	(−)-Galbacin (**5**) R = R^1 = Ar^3 (−)-Galbelgin (**6**) R = R^1 = Ar^1 (−)-Grandisin (**7**) R = R^1 = Ar^4 (+)-Galbacin (**8**) R = R^1 = Ar^3 (+)-Galbelgin (**9**) R = R^1 = Ar^1	(+)-Veraguesin (**10**) R = R^1 = Ar^1 (+)-Calopiptin (**11**) R = Ar^1, R^1 = Ar^3 (+)-Austrobailignan-7 (**12**) R = Ar^2, R^1 = Ar^3 (+)-Verrucosin (**13**) R = R^1 = Ar^2 (+)-Aristolignin (**14**) R = Ar^1, R^1 = Ar^2	(+)-Chicanin (**15**) R = Ar^2, R^1 = Ar^3 (+)-Zuonin-A (**16**) R = R^1 = Ar^3 (+)-Zuonin-C (**17**) R = Ar^1, R^1 = Ar^3 or R = Ar^3, R^1 = Ar^1	(−)-Machilusin (**18**) R = Ar^1, R^1 = Ar^3 or R = Ar^3, R^1 = Ar^1 (−)-Zuonin-A (**19**) R = R^1 = Ar^3



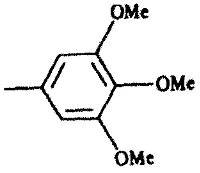
Ar^1



Ar^2



Ar^3



Ar^4

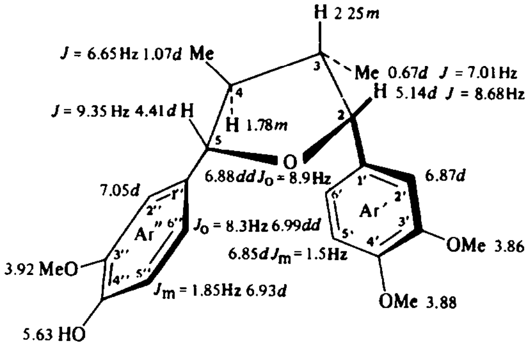


Fig. 1. ^{1}H NMR data for compound **14**.

and other significant NOEs have been summarized in the Experimental.

The results of our complete NMR NOE study of (+)-aristolignin (**14**) allowed a firm assignment of the positions of the aromatic substituents and also provided an insight into the preferred conformation of the molecule in solution. Ring Ar′ must be nearly in the same plane as H-2, as reflected by the high NOE values between H-2 and H-2′. In contrast, ring Ar″ occupies a site such that H-2″ and H-6″ are almost equidistant from H-5 as attested by rather similar NOE values between H-5 and H-6″, and H-5 and H-2″. Furthermore, H-3 (δ2.25) and H-5 (δ4.41) are quite close to each other, as reflected by the strong reciprocating NOEs between them (Experimental).

The present results and tabulation make it clear that all possible arrangements in terms of relative and absolute configurations are possible. Undoubtedly, new 2,5-diaryl-3,4-dimethyltetrahydrofuranoids will be isolated in the future, but the purification process is usually made difficult by the fact that several of these closely related species may co-occur within the same botanical source, while their chromatographic properties may be nearly identical.

EXPERIMENTAL

Isolation of constituents. A. chilensis (1.9 kg, dry roots) was collected in Lo Prado Pass, 6 miles from Santiago, in November 1984. Voucher specimens were deposited in the herbarium of the Natural History Museum in Santiago. The plant was dried, powdered and extracted with petrol at room temp. The petrol extracts (93 g) were concd and fractionated by CC over silica gel, using hexane gradually enriched with EtOAc. The fractions were monitored by TLC on silica gel glass plates, using the system $CHCl_3$–MeOH (98:2) and hexane–EtOAc (8:2), and spraying with 33% H_2SO_4. Final purification was by TLC using the systems C_6H_6–$CHCl_3$–EtOH (5:4:1) and C_6H_6–EtOH (9:1). Only 5 g of the crude extracts were actually fractionated.

Identification of (+)*-calopiptin* (**11**) *and* (+)*-austrobailignan-7* (**12**). These two known compounds (650 and 150 mg, respectively) were identified by comparison of mp, specific rotations and spectral characteristics with published data [8, 9].

(−)*-Zuonin-A* (**19**). 460 mg, mp 119–121° (EtOH); UV λ_{max}^{MeOH} nm: 236, 289 (log ε 3.99, 3.92); ^{1}H NMR (200 MHz, $CDCl_3$): δ6.93–6.79 (*m*, 6 Ar-H), 5.95 (*s*, 4H, 2O–CH_2–O), 5.41 (*d*, *J* = 4.3 Hz, 1H, H-2), 4.62 (*d*, *J* = 9.2 Hz, 1H, H-5), 2.41 (*m*, 2H, H-3 and H-4), 1.00 (*d*, *J* = 6.4 Hz, 3H, 4-Me), 0.63 (*d*, *J* = 7.0 Hz, 3H, 3-Me). MS *m/z* (rel. int.): 340 (M^+, 21), 190 (100), 178 (13), 175 (37), 162 (31).

(+)*-Aristolignin* (**14**). 200 mg, $[\alpha]_D + 24.3°$ (*c* 1.35, $CHCl_3$), UV λ_{max}^{MeOH} nm: 232, 280 (log ε 4.10, 3.77); MS *m/z* (rel. int.): 358 (M^+, 20), 206 (45), 192 (100), 177 (28), 165 (18), 151 (34). *O*-Methylation with ethereal diazomethane yielded (+)-veraguesin (**10**), identical with data reported [7]. ^{1}H NMR NOE: MeO-3″ to H-2″, 17.1%; H-2″ to Me-O-3″, 16.4%; H-2″ to H-5, 10.2%; H-5 to H-2″, 7.2%; H-6″ to H-5, 9.2%; H-5 to H-6″, 7.2%; H-5 to Me-4, 6.0%; Me-4 to H-5, 9.0%; H-5 to H-3, 10.0%; H-3 to H-5, 7.0%; M-4 to H-3, 7.0%; H-3 to Me-4, 5.0%; H-3 to H-2, 13.0%; H-2 to H-3, 14.0%; H-2 to H-2′, 28.9%; H-2′ to H-2, 16.4%; H-2′ to MeO-3′, 25.0%; MeO-3′ to H-2′, 19.7%; MeO-4′ to H-5′, 19.7%; H-5′ to MeO-4′, 25.0%.

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