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THE 4-ARYLTETRALONES OF *ARISTOLOCHIA CHILENSIS*

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ABSTRACT.—In addition to the previously reported (−)-aristotetralone [**1**], the roots of *Aristolochia chilensis* produce the 4-aryltetralones (−)-aristochilone [**2**], (−)-aristoligone [**3**], (−)-aristosynone [**4**], (−)-2-acetoxyaristotetralone [**5**], and (−)-2-hydroxyaristotetralone [**6**], as well as the 4-aryltetralol (−)-aristotetralol [**7**]. A negative specific rotation for a 4-aryltetralone is associated with the α orientation of the 4-aryl substituent.

The 4-aryltetralones are a small group of lignans only recently characterized. Prior to our studies on *Aristolochia chilensis* Miers (Aristolochiaceae) of Chilean origin, eight 4-aryltetralones had been obtained from *Virola sebifera* Aubl. (Myristicaceae) (1,2), and two had been found in *Schisandra* spp. (Schisandraceae) (3,4). In 1987, our initial results from a systematic study of the roots of *A. chilensis* were reported (5,6), and among the new natural products described was the 4-aryltetralone (−)-aristotetralone [**1**] (6).

We now wish to report on the more polar fractions of our *Aristolochia* root extracts. In addition to (−)-aristotetralone [**1**], these were found to contain five new 4-aryltetralones, namely (−)-aristochilone [**2**], (−)-aristoligone [**3**], (−)-aristosynone [**4**], (−)-2-acetoxyaristotetralone [**5**], and (−)-2-hydroxyaristotetralone [**6**]. Furthermore, the new alcohol (−)-aristotetralol [**7**] was also obtained.

(−)-Aristochilone [**2**], $C_{21}H_{24}O_5$, is an optically active, amorphous solid, $[\alpha]_D$ −134° (c = 1.62, $CHCl_3$); ν max ($CHCl_3$) 3550 (OH) and 1660 (C=O) cm^{-1}. Its mass spectrum shows the significant fragment m/z 300 $[M-56]^+$, a fission pattern diagnostic of several tetralin lignans (7).

The 360 MHz $CDCl_3$ nmr spectrum of (−)-aristochilone [**2**] is close to that for (−)-aristotetralone [**1**] and shows that the compound incorporates three methoxyl and, by extension, one hydroxyl groups. The positions of the aromatic substituents were settled through nmr nOe studies. In particular, nOe's were observed between the 7-methoxyl (δ 3.94) and H-8 (δ 7.57), between the 6-methoxyl (δ 3.81) and H-5 (δ 6.51), and between the 4′-methoxyl (δ 3.85) and H-5′ (δ 6.73) (see Experimental). The latter enhancement indicated that the phenolic hydroxyl must be located at C-3′.

Among the 4-aryltetralones, the nmr chemical shift of H-2 is diagnostic of the stereochemistry at C-2. Thus, H-2 in (−)-aristotetralone [**1**] appears at δ 2.42 and in (−)-aristochilone [**2**] at δ 2.44, so that these two 4-aryltetralones must incorporate the identical stereochemistry at C-2. Additionally, H-3 appears at δ 2.35 in (−)-aristotetralone [**1**] and at δ 2.34 in (−)-aristochilone [**2**], pointing to the identical stereochemistry for the two compounds.

(−)-Aristoligone [**3**] and its C-2 epimer, (−)-aristosynone [**4**], were obtained as a levorotatory 2:1 mixture that could not be separated even after several attempts at tlc.[2] The nmr spectrum, however, strongly suggested a mixture of two closely related 4-aryltetralones, each incorporating four methoxyl groups. In fact, the nmr signals for the major component, namely (−)-aristoligone [**3**], could be clearly differentiated from those of the minor component, (−)-aristosynone [**4**].

The nmr spectrum of the mixture showed an absorption at δ 2.44 and a less intense

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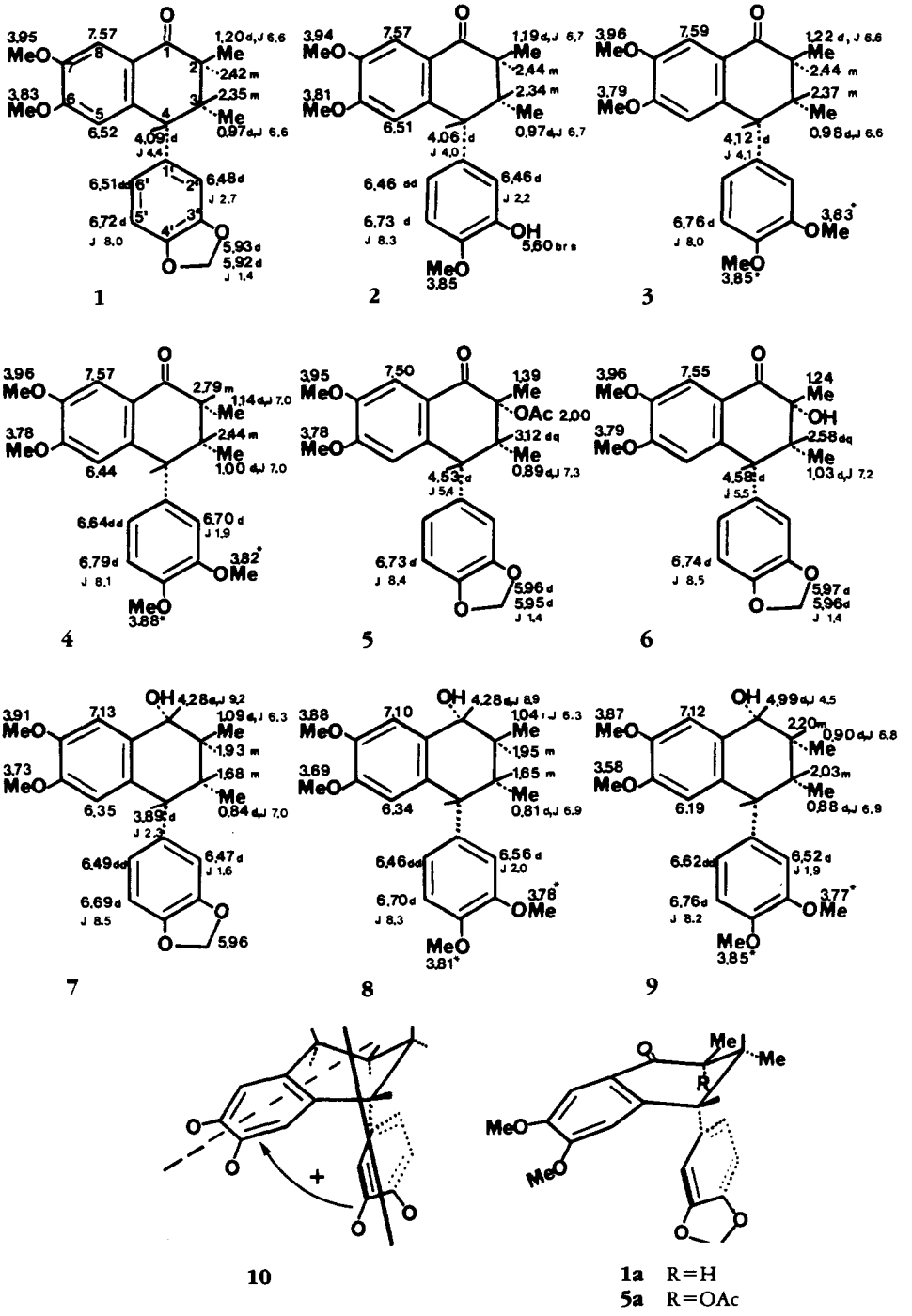
[2]It is suggested here that all future 4-aryltetralones bearing an overall *syn* relationship between the C-2, C-3, and C-4 substituents incorporate the term "*syn*" as an integral part of their trivial names.



Chemical shifts with identical superscripts are interchangeable. For compounds **4**, **8**, and **9**, the H-4 resonances are obscured by the methoxyl absorptions. For each of compounds **3**, **5**, and **6**, H-5 overlaps with H-2′ and H-6′ around δ 6.53.

one further downfield at δ 2.79. The former could be assigned to H-2 of (−)-aristoligone [**3**], which possesses the same stereochemistry as (−)-aristotetralone [**1**] and (−)-aristochilone [**2**]; the latter could be due to H-2 of (−)-aristosynone [**4**], which is epimeric with compounds **1–3** at C-2.

At this stage, we were intent upon obtaining each of the components of our binary mixture in a pure state, so as to characterize our compounds fully. To this purpose, (−)-aristochilone [**2**] was treated with ethereal CH_2N_2. Work-up provided amorphous (−)-aristoligone [**3**], $C_{22}H_{26}O_5$, $[\alpha]_D$ −190° (c=0.78, $CHCl_3$), ν max ($CHCl_3$) 1660 cm^{-1}. The mass spectrum displayed a characteristic strong ion m/z 314 $[M-56]^+$.

The generation of pure (−)-aristosynone [**4**], the minor component of our binary mixture, followed a somewhat more complex path. $NaBH_4$ reduction of the natural mixture of **3** and **4** proceeded in stereospecific fashion to provide an easily separable mixture of quasi-equatorial alcohols, (−)-aristoligol [**8**] and (−)-aristosynol [**9**], each analyzing for $C_{22}H_{28}O_5$. The two alcohols were obtained in a 2:1 ratio, so that (−)-aristoligol [**8**] must be derived from the major component **3**, while (−)-aristosynol [**9**] is related to the minor component **4**.

For the major alcohol (−)-aristoligol [**8**], $[\alpha]_D$ −167° (c=2.21, $CHCl_3$), the nmr absorption for H-1 is as a doublet at δ 4.28, $J_{1,2}$=8.9 Hz, denoting a *trans* relationship between H-1 and H-2. On the other hand, the minor alcohol (−)-aristosynol [**9**], $[\alpha]_D$ −35° (c=1.14, $CHCl_3$), displays an H-1 absorption at δ 4.99 with a relatively small $J_{1,2}$=4.5 Hz due to the *cis* stereochemistry between H-1 and H-2.

MnO_2 oxidation of (−)-aristosynol [**9**] then supplied the desired (−)-aristosynone [**4**], $C_{22}H_{26}O_5$, as an amorphous solid, $[\alpha]_D$ −32° (c=0.35, $CHCl_3$), ν max ($CHCl_3$) 1660 cm^{-1}. As expected of a 4-aryltetralone, the mass spectrum included ion m/z 314 $[M-56]^+$.

The nmr spectrum of a 2:1 mixture of our semisynthetic (−)-aristoligone [**3**] and (−)-aristosynone [**4**] corresponded to the spectrum of our natural mixture of **3** and **4**, thus confirming the identity of our compounds.

Whereas (−)-aristotetralone [**1**], (−)-aristochilone [**2**], (−)-aristoligone [**3**], and (−)-aristosynone [**4**] are the major 4-aryltetralones in *A. chilensis*, two analogues found in much smaller amounts were (−)-2-acetoxyaristotetralone [**5**] and (−)-2-hydroxyaristotetralone [**6**], both probably formed in nature through in vivo oxidation of **1**.

(−)-2-Acetoxyaristotetralone [**5**], $C_{23}H_{24}O_7$, is an optically active, amorphous material, $[\alpha]_D$ −62° (c=0.58, $CHCl_3$), ν max ($CHCl_3$) 1740 and 1680 cm^{-1}. The mass spectrum includes base peak m/z 352 $[M-60]^+$ due to loss of HOAc from the molecular ion.

The relative stereochemistry at C-2, C-3, and C-4 was settled through nmr decoupling studies, supplemented by nOe data. The molecule exists primarily in conformation **5a** in which ring B is a twisted envelope. Upon signal saturation, enhancements could be observed between 2-Me (δ 1.39) and H-3 (δ 3.12), and also between H-3 and H-4 (δ 4.53), pointing to a *syn* relationship between 2-Me, H-3, and H-4. Additionally, the coupling constant between H-3 and H-4 is small, 5.4 Hz, because the H-3(4) dihedral angle is about 45°. The signals for H-2′, H-5, and H-6′ overlapped around δ 6.5 and could not be resolved.

It is interesting to note that (−)-2-acetoxyaristotetralone [**5**] possesses the same overall relative stereochemistry as (−)-aristotetralone [**1**] and that (−)-aristotetralone also exists in the corresponding conformation **1a** (6).

The second of our minor products, (−)-2-hydroxyaristotetralone [**6**], $C_{21}H_{22}O_6$, also amorphous, exhibited $[\alpha]_D$ −62° (c=0.23, $CHCl_3$), ν max ($CHCl_3$) 3500 and 1670 cm^{-1}. The mass spectrum incorporated the base peak m/z 352 $[M-18]^+$ due to facile loss of H_2O and a strong peak m/z 298 $[M-72]^+$ representing loss of 2-butanone from the molecular ion.

The nmr spectrum bore some similarities to that of acetate **5**. In particular, H-4 appeared at δ 4.58, which compares very well with the value of δ 4.53 recorded for the

corresponding hydrogen in compound **5**. Additionally, $J_{3,4}=5.5$ Hz, which is very close to the corresponding value for **5**. These data indicate a similar relative stereochemistry for the two compounds.

The cd spectra of alcohols **7–9** display a positive Cotton effect, with a maximum between 280 and 290 nm, denoting that the 4-aryl substituent is in the α configuration, i.e., below the mean plane of the molecule (8). We find that this conclusion is also supported by the aromatic chirality rule (9), inasmuch as the positive Cotton effect requires a positive twist as indicated in expression **10**.

A generalization that may safely be drawn at this stage, based on the present data as well as on previously reported results (3,4), is that the negative specific rotation for a 4-aryltetralone lignan is to be associated with the α orientation of the 4-aryl substituent, regardless of the configuration at C-2 and C-3.

Although the specific rotations of our compounds are consistently negative, it should be remarked that in the case of compounds **4**, **5**, **6**, and **9**, the magnitude of the rotation is smaller (−32° to −62°) than in the other instances (−133° to −190°). These four compounds are also those that have a C-2 α pseudo-axial substituent.

Finally, yet another minor product we found in *A. chilensis* roots was the alcohol (−)-aristotetralol [**7**], $C_{21}H_{24}O_5$, $[\alpha]_D$ −149° ($c=1.49$, $CHCl_3$). This amorphous natural product was identical with material generated by $NaBH_4$ reduction of (−)-aristotetralone [**1**]. The nmr spectrum of **7** revealed an H-1 doublet absorption at δ 4.28. Significantly, $J_{1,2}=9.2$ Hz, indicating a *trans* relationship between the two hydrogens in question.

EXPERIMENTAL

PLANT COLLECTION, EXTRACTION, AND ISOLATION.—*A. chilensis* (1.9 kg, dry roots) was collected in Lo Prado Pass, 10 km west of 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 successively with petroleum ether and EtOH at room temperature. The EtOH extracts were concentrated, leaving a residue (79 g). This was fractionated by cc over Si gel, using hexane gradually enriched with EtOAc. The fractions were monitored by tlc on Si gel, using the systems hexane-EtOAc (4:1) or $CHCl_3$ and spraying with 33% H_2SO_4. Final purification was on Si gel tlc, using $CHCl_3$ and $CHCl_3$ with 1% MeOH. All nmr spectra were obtained at 360 MHz in $CDCl_3$ solution.

(−)-ARISTOTETRALONE [**1**].—Wt 590 mg, spectrally and chromatographically identical with material previously reported (6).

(−)-ARISTOCHILONE [**2**].—Wt 105 mg; uv λ max (MeOH) 233, 278, 314 nm (log ε 4.32, 4.08, 3.77); eims *m/z* $[M]^+$ 356 (100), 341 (20), 327 (8), 300 (63), 285 (26), 269 (31), 257 (19), 165 (11), 149 (6); ^1H nmr nOe H-8 to MeO-7, 16%; MeO-7 to H-8, 55%; H-5 to MeO-6, 13%; MeO-6 to H-5, 33%; H-5′ to MeO-4′, 15%; MeO-4′ to H-5′, 29%.

(−)-ARISTOLIGONE [**3**].—Treatment of **2** (20 mg) with ethereal CH_2N_2 gave after purification by tlc **3** (10 mg); uv λ max (MeOH) 232, 276, 313 nm (log ε 4.35, 4.06, 3.74); eims *m/z* $[M]^+$ 370 (100), 355 (18), 314 (60), 283 (25), 271 (17), 255 (7), 232 (20), 165 (12), 157 (15). The natural mixture of **3** and **4** weighed 400 mg.

(−)-ARISTOSYNONE [**4**].—Treatment of **9** (9 mg) with MnO_2 in hexane at room temperature overnight supplied, after tlc, ketone **4** (5 mg); uv λ max (MeOH) 231, 279 nm (log ε 4.27, 3.97); eims *m/z* $[M]^+$ 370 (100), 355 (21), 314 (75), 283 (33), 271 (22), 255 (14), 232 (30), 165 (7), 157 (20).

(−)-2-ACETOXYARISTOTETRALONE [**5**].—Wt 7 mg; uv λ max (MeOH) 235, 280, 315 nm (log ε 4.24, 398, 370); eims *m/z* $[M]^+$ 412 (0.06), 352 (100), 337 (28), 321 (11), 309 (6), 298 (6), 297 (12), 192 (26), 165 (13), 149 (12); ^1H nmr nOe H-4 to H-3, 23%; H-3 to H-4, 20%; H-3 to Me-3, 7%; Me-3 to H-3, 16%; H-3 to Me-2, 5%; Me-2 to H-3, 5%; Me-2 to Me-3, 7%; Me-3 to Me-2, 8%.

(−)-2-HYDROXYARISTOTETRALONE [**6**].—Wt 3 mg; uv λ max (MeOH) 236, 281, 314 nm (log ε 4.27, 4.05, 3.78); eims *m/z* $[M]^+$ 370 (22), 352 (100), 337 (26), 321 (10), 298 (33), 267 (8), 255 (12), 165 (12), 149 (11).

(−)-2-ARISTOTETRANOL [7].—Wt 8 mg; uv λ max (MeOH) 233, 285 nm (log ε 4.05, 3.80); eims *m/z* $[M]^+$ 356 (100), 338 (71), 323 (55), 299 (28), 298 (16), 283 (50), 178 (13), 165 (9), 150 (13), 135 (17); cd (MeOH) Δε (nm) +0.3 (287), 0 (282), −0.6 (270). The compound is identical with the semisynthetic material obtained by $NaBH_4$ reduction of **1**.

(−)-ARISTOLIGOL [**8**] AND (−)-ARISTOSYNOL [**9**].—$NaBH_4$ in MeOH reduction of the natural mixture of **3** and **4** (40 mg) gave rise to a mixture of **8** and **9**. Alcohol **8** 22 mg; uv λ max 234, 281 nm (log ε 4.35, 3.79); eims *m/z* $[M]^+$ 372 (100), 354 (19), 339 (16), 299 (38), 285 (42), 269 (15), 234 (9), 219 (17), 194 (15), 178 (30), 165 (29), 151 (40), 150 (26); cd (MeOH) Δε (nm) +0.1 (28), 0 (279), −0.2 (269). (−)-Aristosynol [**9**] 11 mg; uv λ max 232, 281 nm (log ε 4.26, 3.81); eims *m/z* $[M]^+$ 372 (50), 354 (75), 339 (65), 299 (25), 285 (23), 269 (16), 234 (100), 219 (95), 194 (13), 178 (19), 165 (28), 151 (34); cd (MeOH) Δε (nm) +0.3 (285), 0 (278), −0.5 (269).

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