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GRAMINONE B, A NOVEL LIGNAN WITH VASODILATIVE ACTIVITY FROM *IMPERATA CYLINDRICA*

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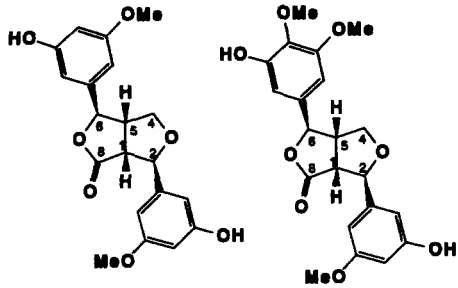
ABSTRACT.—Two novel lignans, graminones A [**1**] and B [**2**] have been isolated from *Imperata cylindrica* and their structures have been elucidated on the basis of their spectral data. Graminone B [**2**] showed inhibitory activity on the contraction of the rabbit aorta.

Numerous vasodilator drugs have been employed in therapeutic applications as well as for basic physiological research. During our investigation of pharmacologically active substances from medicinal plants (1,2), we have devoted our attention to the occurrence of natural products having vasodilative activity.

The rhizomes of *Imperata cylindrica* Beauvois (Gramineae) (Japanese name "Chigaya") have been used in Chinese medicine as a diuretic and anti-inflammatory agents (3–5). However, only a few studies concerning the constituents of this plant have been reported (6–9). In this communication, we wish to describe the isolation and structure determination of two new lignans, graminones A [**1**] and B [**2**], and the inhibitory activity of graminone B [**1**] on the contraction of the rabbit aorta.

The EtOAc solubles of the MeOH and H_2O extracts of rhizomes of *I. cylindrica* were repeatedly chromatographed over Si gel to afford graminones A [**1**] and B [**2**].

Graminone A [**1**] $[\alpha]^{25}D$ $-1.0°$ (c=0.10, $CHCl_3$), showed a molecular ion at m/z 372 in its eims. The ir spectrum of **1** displayed absorption bands at 1775 cm^{-1}, indicating the presence of a γ-lactone in the molecule. The detailed ^1H-^1H COSY and ^1H-^{13}C COSY nmr spectral analysis of **1** gave assignments of ^1H- and ^{13}C-nmr signals for the aliphatic portion



of the molecule as follows: δ 3.45 (1H, dd, J=9.2 and 4.6 Hz, H-1), 5.32 (1H, d, J=4.6 Hz, H-2), 4.02 (1H, dd, J=10.0 and 5.4 Hz, H-4), 4.31 (1H, dd, J=10.0 and 6.2 Hz, H-4), 3.23 (1H, m, H-5), 5.30 (1H, d, J=3.8 Hz, H-6); δ 53.4 (d, C-1), 83.5 (d, C-2), 72.7 (t, C-4), 50.0 (d, C-5), 84.9 (d, C-6), 177.4 (s, C-8). The results of a COLOC nmr spectrum of graminone A [**1**] are shown in Figure 1.

To determine the stereostructure of **1**, four diastereomers [**3–6**] must be considered. The stereochemical constraints posed by aryl substitution are indicated clearly in appropriate molecular models.

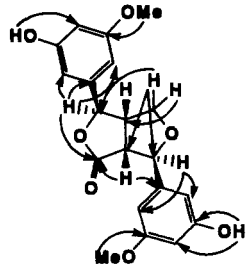


FIGURE 1. COLOC nmr interactions observed for **1**.

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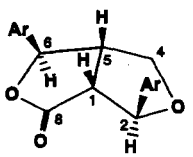

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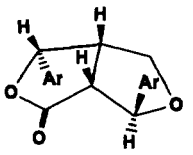

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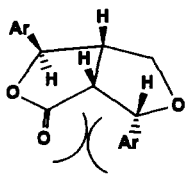

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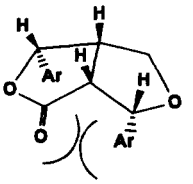

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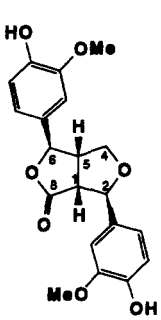
Severe crowding between the carbonyl at C-8 and the endo-aryl substituent at C-2 can not be eliminated in isomers **5** and **6**. Therefore, isomers **3** and **4** are more probable structures than **5** and **6**.

Since the ^{1}H-nmr chemical shift values and splitting patterns of **1** are nearly identical with those of **7**, from a comparison of the spectral data of the known compounds **7** and **8** (10), the stereostructure of graminone A was determined as **1**.

As evident from their spectral data, both **1** and **2** are structurally similar except that **2** has a third aromatic OMe group. The position of the third OMe group was assigned from the eims fragmentation pattern. Although the fragmentation patterns of **1** and **2** are similar, a fragment ion at *m/z* 193 in **2** can be accounted for via pathway [A], as shown in Figure 2, and is only possible when the third OMe group is in ring Ar-1. This



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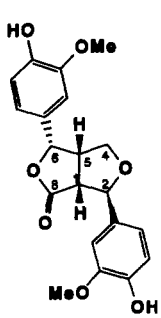

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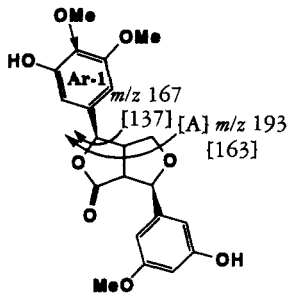

FIGURE 2. Mass spectral fragmentation pattern of **1** and **2** upon electron impact: values in brackets refer to **1**.

conclusion is supported by the presence of a peak at *m/z* 163 for **1**, but not for **2**, and by the presence of the peak at *m/z* 167 for **2**, but not for **1**.

Graminone B [**2**] at 10^{-4} M gave a 50% inhibition of the contractile response of the rabbit isolated aorta to KCl (30 mM) without affecting norepinephrine (10^{-7} M)-induced contractions. Detailed pharmacological activities and structure-activity relationships are now under investigation.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Optical rotations were measured on a Jasco DIP-360 digital polarimeter. Uv spectra were taken on a Hitachi U-2000 spectrometer. Ir spectra were taken on a Shimadzu IR-408 spectrometer. Eims spectra were obtained on a JEOL JMS DX-500 spectrometer. ^{1}H- and ^{13}C-nmr spectra were recorded on a JEOL JNM GX-500 spectrometer using TMS as internal standard.

PLANT MATERIAL.—The rhizomes of *I. cylindrica* were supplied by Nippon Hunmatsu Yakuhin, Ltd., Osaka, Japan. A voucher specimen has been deposited in the herbarium department of the Pharmaceutical Institute, Tohoku University.

EXTRACTION AND ISOLATION.—The rhizomes of *I. cylindrica* (2 kg) were cut and extracted with 5 liters of boiling MeOH and H_2O. The residues from the MeOH and H_2O extracts (280 g and 70 g) were combined, then partitioned between EtOAc and H_2O. The EtOAc extract (35 g) was subjected to Si gel cc and tlc using the solvent systems $CHCl_3$-MeOH (100:1), EtOAc-MeOH (60:1), hexane-Me_2CO (3:2), and C_6H_6-EtOAc (1:1) as eluates to afford **1** and **2** as 0.04% and 0.02% of the extract, respectively. These newly isolated compounds were obtained as colorless oils.

Graminone A [**1**].—$[\alpha]^{25}D$ −1.0° (*c*=0.10, $CHCl_3$); uv λ max (MeOH) 232 (ε 13392), 280 (ε 4960) nm; ir ν max (film) 1775, 1675 cm^{-1}; hrms *m/z* found 372.1197, calcd for $C_{20}H_{20}O_7$, 372.1209; ^1H nmr (500 MHz, $CDCl_3$) δ 3.23 (1H, m, H-5), 3.45 (1H, dd, *J*=9.2 and 4.6 Hz, H-1), 3.87 (6H, s, 2×OMe), 4.02 (1H, dd, *J*=10.0 and 5.4 Hz, H-4), 4.31 (1H, dd, *J*=10.0 and 6.2 Hz, H-4), 5.30 (1H, d, *J*=3.8 Hz, H-6), 5.32 (1H, d, *J*=4.6 Hz, H-2), 5.69 (1H, s, OH), 5.77 (1H, s, OH), 6.76 (2H, br s, Ar-H), 6.85 (2H, br s, Ar-H), 6.88 (2H, br s, Ar-H); ^{13}C nmr (125 MHz, $CDCl_3$) δ 50.0 (d), 53.4 (d), 56.1 (2×q), 72.7 (t), 83.5 (d), 84.9 (d), 108 (d), 108.3 (d), 114.5 (d), 115 (d), 118.3 (d), 118.7 (d), 131.3 (s), 132.3 (s), 145.6 (s), 146.3 (s), 147.0 (s), 147.3 (s), 177.4 (s).

Graminone B [**2**].—$[\alpha]^{25}D$ −4.0° (*c*=0.10, $CHCl_3$); uv λ max (MeOH) 232 (ε 14472), 285 (ε 5360) nm; ir ν max (film) 1775, 1675 cm^{-1}; hrms *m/z* found 402.1319, calcd for $C_{21}H_{22}O_8$, 402.1315; ^1H nmr (500 MHz, $CDCl_3$) δ 3.22 (1H, m, H-5), 3.44 (1H, dd, *J*=9.2 and 3.7 Hz, H-1), 3.88 (6H, s, 2×OMe), 3.89 (3H, s, OMe), 4.03 (1H, dd, *J*=9.8 and 4.3 Hz, H-4), 4.33 (1H, dd, *J*=9.8 and 6.7 Hz, H-4), 5.30 (1H, d, *J*=3.7 Hz, H-6), 5.33 (1H, d, *J*=3.7 Hz, H-2), 5.55 (1H, br s, OH), 5.60 (1H, br s, OH), 6.48 (1H, s, Ar-H), 6.90–6.95 (4H, complex, Ar-H); ^{13}C nmr (125 MHz, $CDCl_3$) δ 50.3 (d), 53.3 (d), 56.1 (q), 56.6 (2×q), 72.8 (t), 83.5 (d), 84.8 (d), 102.1 (2×d), 108.3 (d), 114.5 (d), 118.2 (d), 130.5 (s), 132.5 (s), 135.2 (s), 145.5 (s), 146.8 (s), 147.5 (2×s), 177 (s).

BIOASSAYS.—A bioassay using the rabbit aorta was performed as described previously (11). On sacrifice of each animal, the aorta was isolated, cut helically, and mounted vertically in a tissue bath containing 10 ml Krebs-Ringer bicarbonate solution of the following composition (in mM): HEPES, 20; NaCl, 120; KCl, 4.8; $MgSO_4$, 1.3; $CaCl_2$, 1.2; $NaHCO_3$, 25.2; and glucose, 5.8; pH was adjusted at 7.4. Through the solution was bubbled a gas mixture consisting of O_2-CO_2 (95:5) during which time the solution was maintained at 37°. A resting tension of 1 g was applied to each strip. The contraction induced by 30 mM KCl or 10^{-7} M norepinephrine was measured by the force-displacement transducer and recorded on the thermal array recorder.

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