Cylindrene, a Novel Sesquiterpenoid from Imperata clylindrica with Inhibitory Activity on Contractions of Vascular Smooth Muscle

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CYLINDRENE, A NOVEL SESQUITERPENOID FROM *IMPERATA CYLINDRICA* WITH INHIBITORY ACTIVITY ON CONTRACTIONS OF VASCULAR SMOOTH MUSCLE

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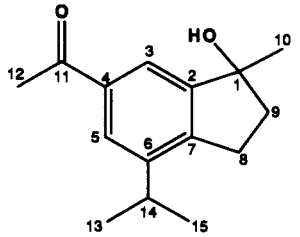
ABSTRACT.—Cylindrene [**1**], a novel substance with inhibitory activity on rabbit vascular smooth muscle has been isolated from *Imperata cylindrica* and its structure has been elucidated on the basis of its spectral data.

Vasodilator drugs have been employed not only in basic research but also in therapy for a variety of cardiovascular diseases. In the course of our screening program for vasoactive substances from medicinal plants, cylindrene [**1**] has been isolated as an active substance from *Imperata cylindrica*. In this communication, we report on the isolation and structure elucidation of cylindrene [**1**], and its inhibitory activity on the vascular smooth muscle.

The rhizomes of *Imperata cylindrica* Beauvois (Gramineae) (Japanese name "Chigaya") have been used in Chinese medicine as diuretic and anti-inflammatory agents (1–3). However, only a few studies concerning the constituents of this plant have been reported (4–7).

The rhizomes of *I. cylindrica* were cut, extracted with boiling MeOH, and then with boiling H_2O. These extracts were concentrated, combined, and partitioned between EtOAc and H_2O. The EtOAc solubles were repeatedly chromatographed on a Si gel column to afford a fraction that was further separated using prep. tlc to afford cylindrene [**1**].

Cylindrene [**1**], obtained as a colorless oil, showed a molecular ion at *m/z* 232 in the eims. The ^{1}H-nmr spectrum displayed two aryl protons at δ 6.93 and



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δ 6.99, and in the ^{13}C-nmr spectrum there were six aryl carbon signals. These ^{1}H- and ^{13}C-nmr spectral features are characteristic for a tetrasubstituted phenyl ring. A planar structure was accorded to cylindrene [**1**] as shown from further detailed analysis of its ^{1}H-^{13}C COSY and COLOC nmr spectra. The results of the COLOC spectrum are summarized in Figure 1. No correlation for H-8 was detected in the COLOC spectrum, but the coupling between H-8 and H-9 was measured in a ^{1}H decoupling experiment. On the basis of these spectral data, the structure of cylindrene was elucidated as **1**.

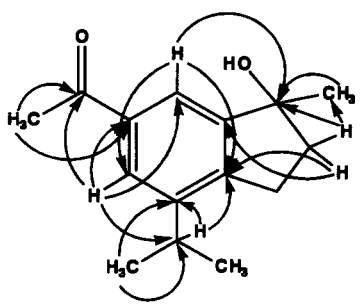

FIGURE 1. Correlations observed in the COLOC nmr spectrum of cylindrene [**1**].

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Cylindrene at 3×10^{-4} M inhibited by 40% the contractile response of a rabbit isolated aorta preparation to norepinephrine at 1×10^{-7} M without affecting 30 mM KCl-induced contractions. Detailed biological activities of **1** and its structure-activity relationship are now under investigation.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The optical rotation was measured on a Jasco DIP-360 digital polarimeter. The uv spectrum was taken on a Hitachi U-2000 spectrometer, and the ir spectrum was run on a Shimadzu IR-408 spectrometer. Eims 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 commercial rhizomes of *I. cylindrica* (2 kg) were supplied by Tochimoto-Tenkaido.

EXTRACTION AND ISOLATION.—Rhizomes of *I. cylindrica* were cut, extracted with 5 liters of boiling MeOH and 5 liters of boiling H_2O. The residues (280 g and 70 g) from the MeOH and H_2O extracts were combined, then partitioned between EtOAc and H_2O. The EtOAc extract was concentrated *in vacuo*. The EtOAc extract (35 g) was directly chromatographed on Si gel. After elution of fatty acids and their esters with $CHCl_3$-MeOH (100:1), a pale yellow oil (110 mg) was eluted, which was repeatedly chromatographed by Si gel tlc using solutions of $CHCl_3$-MeOH (15:1), EtOAc-MeOH (60:1), and hexane-Me_2CO (2:1) as eluates to afford cylindrene [**1**] in 0.02% yield based on the weight of the EtOAc extract.

Cylindrene [**1**] was obtained as colorless oil: $[\alpha]^{25}D$ −29.5° (c=0.1, $CHCl_3$); uv (MeOH) λ max (log ε) 243 (4.15), 320 (3.49) nm; ir (film) ν max 3360, 1725 cm^{-1}; ^{1}H nmr ($CDCl_3$, 500 MHz) δ 1.19 (6H, d, J=5.6 Hz, H-13, -15), 1.43 (3H, s, H-10), 1.98 (1H, m, H-9), 2.13 (1H, m, H-9), 2.17 (3H, s, H-12), 2.71 (1H, m, H-8), 2.72 (1H, q, J=5.6 Hz, H-14), 2.91 (1H, m, H-8), 6.93 (1H, br s, H-5), 6.99 (1H, br s, H-3); ^{13}C nmr ($CDCl_3$, 125 MHz) δ 17.9 (q, C-12), 23.0 (q, C-13), 23.1 (q, C-15), 28.3 (q, C-10), 31.5 (t, C-8), 38.1 (d, C-14), 39.3 (t, C-9), 81.8 (s, C-1), 127.3 (d, C-3), 135.5 (d, C-5), 146.9 (s, C-4), 149.1 (s, C-7), 155.8 (s, C-2), 156.0 (s, C-6), 186.1 (s, C-11); eims (70 eV) m/z [M]$^+$ 232 (25), 189 (100), 147 (18), 43 (18); hreims found 232.1467 (calcd for $C_{15}H_{20}O_2$ 232.1464).

Bioassay.—The bioassay for inhibitory activity of the contractile response of the rabbit aorta was performed as below (8). Rabbits were sacrified by bleeding. The aorta was isolated and cut into helical strips. This prepared aorta was mounted vertically in 10 ml of a tissue bath containing 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 was measured by the force-displacement transducer and recorded on the thermal array recorder.

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