[Chem. Pharm. Bull.
34(7)2743—2746(1986)]

Hongconin, a New Naphthalene Derivative from Hong-Cong, the Rhizome of *Eleutherine americana* MERR. *et* HEYNE (Iridaceae)

CHEN ZHENGXIONG (MASAO CHIN),*,[a] HUANG HUIZHU,[b] WANG CHENGRUI,[b]
LI YUHUI,[b] DING JIANMI,[b] USHIO SANKAWA,[c] HIROSHI NOGUCHI[c]
and YOICHI IITAKA[c]

Tsumura Laboratory,[a] 3586 Yoshiwara Ami-cho, Inashiki-gun, Ibaraki 300–11, Japan,
Shanghai Institute of Materia Medica, Academia Sinica,[b] Shanghai, China and
Faculty of Pharmaceutical Sciences, University of Tokyo,[c]
7-3-1, Hongo, Bunkyo-ku, Tokyo 113 Japan

(Received December 13, 1985)

A new naphthalene derivative, hongconin, was isolated from the rhizome of *Eleutherine americana* MERR. *et* HEYNE (Iridaceae), together with three known naphthalene derivatives (**1**—**3**). The structure of hongconin was elucidated as **4** on the basis of chemical and spectral studies, and X-ray analysis.

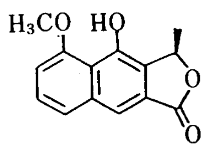
Keywords——*Eleutherine americana*; Iridaceae; naphthalene derivative; hongconin; increasing coronary flow

Eleutherine americana MERR. *et* HEYNE (Iridaceae) is a herbal plant cultivated in Hainan Island, South China. The rhizome of this plant (Hong-Cong in Chinese) is used as a folk medicine for the treatment of coronary disorders.1) The biological activity of Hong-Cong was confirmed by Pharmacological tests using isolated guinea pig heart, and Hong-Cong was also shown to be effective against angina pectoris in a preliminary clinical trial.2)

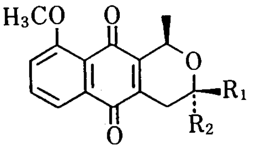
In a previous paper,3) we reported the isolation of three known naphthalene derivatives, eleutherol (**1**), eleutherin (**2**) and isoeleutherin (**3**), and a new naphthalene derivative named hongconin.4) We also reported that these four naphthalene derivatives had the effect of increasing coronary flow in an isolated guinea pig heart. Recently we briefly reported the structural determination of hongconin (**4**).5) This paper presents full details of the isolation of these naphthalene derivatives and the structural determination of hongconin (**4**).

When the alcoholic extract was concentrated to a small volume under reduced pressure, eleutherol (**1**) precipitated. The filtrate was subjected to silica gel column chromatography using dichloromethane as an eluent to give three main fractions (A, B and C) containing naphthalene derivatives. Fraction A was recrystallized from ethanol to give eleutherol (**1**). The mother liquor was rechromatographed using petroleum ether–dichloromethane (5 : 2) as an eluent to afford hongconin (**4**). Fraction B was recrystallized from acetone to give eleutherin (**2**) and fraction C yielded isoeleutherin (**3**) upon recrystallization from acetone. These crystalline products (**1**, **2** and **3**) were identified as eleutherol, eleutherin and isoeleutherin, respectively, on the basis of spectral analysis as well as comparisons of spectral data with those reported in the literature.4)

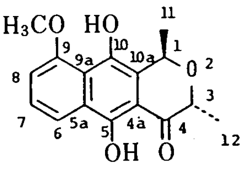
Hongconin (**4**) was obtained as yellow needles upon recrystallization from hexane–ether, but it turned brownish yellow when it was kept for a long time in the air. The infrared (IR) spectrum of hongconin (**4**) revealed the presence of hydroxyl groups, aromatic rings and an ether linkage. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum was more informative and revealed the presence of two hydroxyl group, three aromatic protons, one



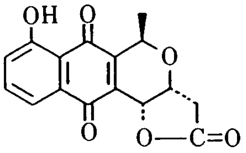
1



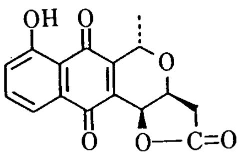
2 : $R_1=CH_3$, $R_2=H$
3 : $R_1=H$, $R_2=CH_3$



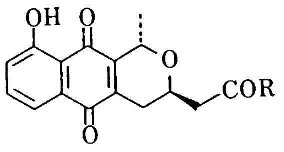
4



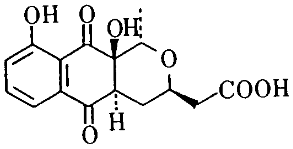
5



6



7 : R=OH
8 : $R=NH_2$



9

Chart 1

Table I. Fractional Atomic Coordinates and Anisotropic Thermal Parameters for Non-hydrogen Atoms, $\times 10^4$

No.	Atom	X	Y	Z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
1	C(1)	2514 (6)	2355 (4)	−1390 (22)	44 (4)	20 (2)	436 (57)	0 (3)	10 (16)	12 (11)
2	C(3)	2199 (7)	3462 (4)	429 (26)	61 (5)	21 (2)	528 (69)	−2 (3)	28 (19)	−29 (12)
3	C(4)	1374 (6)	3227 (4)	1849 (25)	45 (4)	22 (2)	536 (65)	4 (3)	−31 (17)	−10 (13)
4	C(4A)	1214 (5)	2527 (4)	1871 (23)	33 (4)	23 (2)	460 (55)	5 (2)	−28 (14)	0 (12)
5	C(5)	527 (5)	2276 (5)	3445 (26)	33 (4)	32 (3)	495 (66)	3 (3)	−27 (15)	−16 (13)
6	C(5A)	367 (6)	1575 (5)	3501 (27)	36 (4)	28 (3)	546 (71)	−2 (3)	−25 (15)	−4 (13)
7	C(6)	−361 (6)	1330 (5)	4971 (33)	36 (4)	40 (3)	691 (85)	−9 (3)	−11 (18)	−1 (17)
8	C(7)	−533 (7)	646 (5)	4993 (35)	50 (5)	37 (3)	850 (96)	−6 (4)	−29 (22)	29 (19)
9	C(8)	6 (7)	205 (5)	3374 (31)	50 (5)	37 (3)	755 (97)	−7 (4)	−18 (23)	25 (17)
10	C(9)	715 (6)	448 (5)	1984 (29)	53 (5)	25 (3)	625 (76)	0 (3)	−36 (19)	12 (14)
11	C(9A)	930 (6)	1134 (4)	1932 (25)	39 (4)	25 (2)	445 (59)	1 (3)	−20 (15)	−6 (12)
12	C(10)	1640 (5)	1412 (5)	409 (26)	35 (4)	28 (3)	551 (68)	5 (3)	−16 (16)	−2 (13)
13	C(10A)	1783 (5)	2084 (4)	343 (23)	34 (4)	21 (2)	396 (53)	−3 (2)	−16 (14)	4 (11)
14	C(11)	3352 (5)	2276 (5)	291 (28)	32 (4)	35 (3)	599 (69)	4 (3)	−8 (16)	34 (15)
15	C(12)	2144 (8)	4203 (5)	−749 (32)	92 (7)	21 (3)	814 (97)	−1 (4)	−2 (26)	10 (15)
16	C(13)	1076 (8)	−668 (5)	50 (36)	82 (7)	17 (2)	1038 (101)	−6 (3)	−43 (28)	−21 (16)
17	O(2)	2377 (4)	3047 (3)	−2159 (16)	59 (3)	26 (2)	441 (40)	−2 (2)	−2 (12)	3 (9)
18	O(4)	884 (4)	3644 (3)	3040 (21)	55 (3)	29 (2)	795 (60)	11 (2)	−14 (14)	−27 (10)
19	O(5)	−6 (4)	2676 (3)	4950 (21)	40 (3)	37 (2)	780 (53)	11 (2)	8 (13)	−49 (12)
20	O(9)	2204 (4)	1011 (3)	−1114 (19)	49 (3)	25 (2)	750 (57)	4 (2)	31 (13)	−19 (9)
21	O(10)	1267 (5)	38 (3)	417 (24)	64 (4)	27 (2)	1016 (71)	−1 (2)	−4 (17)	−10 (11)

Temperature factor, T, is the form of $T=\exp(-(\beta_{11}hh+\beta_{22}kk+\beta_{33}ll+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl))$.

methoxyl group and two O–CH–CH_3 groups. Irradiation of a triplet signal at δ 7.28 collapsed the doublets at δ 8.00 and 6.95 into two singlets. When the doublet signal at δ 8.00 was irradiated, the triplet at δ 7.28 and doublet at δ 6.85 changed to an AB-type quartet. Thus the three aromatic signals are assignable to aromatic protons (C-6, C-7 and C-8) with the same substitution pattern as those of **1**—**3**. When a quartet signal at δ 5.41 was irradiated, the doublet signal of the methyl group at δ 1.58 collapsed to a singlet. The doublet signal of a methyl group at δ 1.48 also changed to a singlet upon irradiation of a quartet methine signal at δ 4.63. Acetylation of hongconin (**4**) with acetic anhydride and concentrated sulfuric acid yielded a diacetate, which showed absorption of a carbonyl group adjacent to aromatic ring at an unusually high wave number of 1702 cm^{-1}, besides two acetate absorptions at 1775 and 1770 cm^{-1}. This indicated the presence of acetoxyl group at the peri-position to the carbonyl group. Hongconin was then formulated as **4** on the basis of the chemical and spectral data, and also the presumed biosynthetic relation among the naphthalenic compounds obtained from the same plant.

In order to exclude possible tautomeric structures, the structure of hongconin (**4**) was finally determined by X-ray analysis. Crystals obtained from hexane–ether were found suitable for single crystal X-ray analysis. The crystal is orthorhombic with space group $P2_12_12_1$. It contains four molecules in a cell with dimensions of $a=16.037$ (**8**), $b=20.092$ (**10**), $c=4.315$ (**2**) Å, D_x (Calcd) $=1.32\,g\cdot cm^{-3}$, $V=1390.4\,Å^3$. A total of 1194 reflections were recorded using a Philips PW 1100 diffractometer with CuK_α radiation. The structure was solved by the direct method (MULTAN) and refined by the block-diagonal least-squares method (HBLS). The reduced R value was 0.094 including anisotropic temperature factors for all 21 atoms. The formula of hongconin is **4** or its enantiomer.

The structures of naphthalene congeners produced by *Eleuterine* plants clearly indicate that they are biogenetically related to antibiotics such as kalafungin (**5**),[7] and nanaomycins D (**6**),[8] A (**7**), C (**8**) and B (**9**).[9] The parent carbon skeleton of the compounds derived from the higher plants has apparently undergone decarboxylation.

Recently it was reported that tablets of a mixture of naphthalene derivatives named Hong-Cong-Su-Pian are effective against angina pectoris, and the effect was approximately equal to that of Persantine (Dipyridamol) in a clinical trial.[6]

Experimental

General Procedure——NMR spectra were taken on a JEOL PS-100 spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded with a Unicam SP-100. Thin layer chromatography (TLC) was carried out on Merck plates precoated with Kieselgel 60 F_{254} using CH_2Cl_2 (solvent system 1) and hexane–$CHCl_3$–MeOH (20 : 50 : 1) (solvent system 2) as developing solvents. All melting points were determined on a Kofler apparatus and are uncorrected. High-resolution mass spectra (high-MS) were taken on a JEOL JMS DX-300 spectrometer.

Separation of Naphthalene Derivatives——The dried rhizoma of *Eleutherine americana* (3 kg) was extracted three times with ethanol at room temperature. The combined ethanol solution was concentrated under reduced pressure to a small volume to give eleutherol (**1**) as a precipitate (5.1 g). The filtrate was subjected to column chromatography on silica gel (500 g), developing with CH_2Cl_2 to give three main fractions—fr. A, fr. B and fr. C. Fraction A was concentrated to dryness *in vacuo* and the residue was recrystallized from ethanol to give eleutherol (**1**) (0.9 g). The total yield of **1** was (6 g, 0.2%). The mother liquor was rechromatographed on silica gel (40 g) with hexane–CH_2Cl_2 (5 : 2), and the first eluate was concentrated *in vacuo*. The residue was recrystallized from hexane–ether to afford hongconin (**4**) (0.06 g, 0.002%). Fraction B was concentrated to dryness *in vacuo* and the residue was recrystallized from acetone to give eleutherin (**2**) (5.1 g, 0.17%). Fraction C was concentrated to dryness *in vacuo* and the residue was recrystallized from acetone to give isoeleutherin (**3**) (2.4 g, 0.08%).

Eleutherol (1)——Crude eleutherol was obtained as slightly yellow needles. Crude eleutherol was recrystallized repeatedly from ethanol or ethyl acetate to give colorless needles. Colorless needles, mp 203 °C. *Anal.* Calcd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 69.03; H, 5.22. $[\alpha]_D^{23}$ +83° ($c=0.373$, $CHCl_3$). TLC *Rf* value: 0.60 (solvent system 1); 0.36 (solvent system 2), violet under UV 365 nm. ^{1}H-NMR (in $CDCl_3$)δ: 1.66 (3H, d, $J=6.5$ Hz, $C\underline{H}_3$–CH–O), 4.04 (3H, s, $OC\underline{H}_3$), 5.63 (1H, q, $J=6.5$ Hz, CH_3–$C\underline{H}$–O), 6.83 (1H, d, $J=7$ Hz, H-8), 7.33 (1H, t, $J=7$ Hz, H-7), 7.47 (1H, d, $J=7$ Hz, H-6), 7.76 (1H, s, H-4), 9.52 (1H, s, OH).

Eleutherin (2)——Yellow needles from acetone, mp 173—175 °C. *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.22; H, 6.02. $[\alpha]_D^{34}$ +345.6° ($c=1.855$, $CHCl_3$). TLC *Rf* value: 0.36 (solvent system 1); 0.29 (solvent system 2), dark brown under UV 365 nm. ^{1}H-NMR (in $CDCl_3$) δ: 1.31 (3H, d, $J=6.5$ Hz, $C\underline{H}_3$–CH–O), 1.50 (3H, d, $J=6.5$ Hz, $C\underline{H}_3$–CH–O), 2.15 and 2.70 (each 1H, m, CH_2), 3.51 (1H, m, CH_3–$C\underline{H}$–O), 3.96 (3H, s, OCH_3), 4.80 (1H, m, CH_3–$C\underline{H}$–O), 7.18—7.72 (2H, aromatic H).

Isoeleutherin (3)——Yellow needles from acetone, mp 174—175 °C. *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92.

Found: C, 70.24; H, 6.01. $[\alpha]_D^{23}$ $-51.8°$ ($c=0.965$, $CHCl_3$). TLC *Rf* value: 0.27 (solvent system 1); 0.23 (solvent system 2), dark brown under UV 365 nm. ^{1}H-NMR (in $CDCl_3$) δ: 1.28 (3H, d, $J=6.5$ Hz, $C\underline{H}_3$–CH–O), 1.47 (3H, d, $J=6.5$ Hz, $C\underline{H}_3$–CH–O), 2.13 (1H, m) and 2.68 (each 1H, m, CH_2), 3.94 (3H, s, OCH_3), 3.99 (1H, m, CH_3–$C\underline{H}$–O), 4.90 (1H, m, CH_3–$C\underline{H}$–O), 7.16—7.68 (3H, aromatic H).

Hongconin (4)——Yellow needles from hexane–ether, mp 135 °C. The needles gradually turned brownish yellow on standing for a long time in air. High-MS *m*/*z*: Calcd for $C_{16}H_{16}O_5$: 288.09880. Obs. 288.10050. $[\alpha]_D^{20}$ $-26°$ ($c=1.94$, $CHCl_3$). TLC *Rf* value: 0.76 (solvent system 1), 0.60 (solvent system 2), orange under UV 365 nm. ^{1}H-NMR (in $CDCl_3$) δ: 1.48 (3H, d, $J=7$ Hz, $C\underline{H}_3$–CH–O), 1.58 (3H, d, $J=7$ Hz, $C\underline{H}_3$–CH–O), 4.02 (3H, s, OCH_3), 463 (1H, q, $J=7$ Hz, CH_3–$C\underline{H}$–O), 5.41 (1H, q, $J=7$ Hz, CH_3–$C\underline{H}$–O), 6.95 (1H, d, $J=7$ Hz, H-8), 7.28 (1H, t, $J=7$ Hz, H-7), 8.00 (1H, d, $J=7$ Hz, H-6), 8.87 (1H, s, OH), 12.72 (1H, s, OH). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 3060, 3024, 3000 (aromatic C–H), 1650 (C=O), 1640 (C=C), 1614, 1586 (aromatic skeleton), 1242 (ether), 1110 (ether), 800, 772, 762 (1,2,3-substituted benzene). UV λ_{max}^{EtOH} nm (log ε): 221 (3.487), 267 (3.480), 430 (2.633).

Acetylation of 4——A solution of **4** (15 mg) in acetic anhydride (1.5 ml) and conc. sulfuric acid (0.05 ml) was allowed to stand at room temperature for 2 h. The reaction mixture was poured into ice-water. The precipitate was collected and washed with cold water and then recrystallized from ethanol to give pale yellow needles (10 mg), mp 194—196 °C. High-MS *m*/*z*: Calcd for $C_{20}H_{20}O_7$: 372.12089. Obs. 372.12199. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775 (acetate C=O), 1770 (acetate C=O), 1702 (C=O). ^{1}H-NMR (in $CDCl_3$) δ: 1.40 (3H, d, $J=7$ Hz, $C\underline{H}_3$–CH–O), 1.56 (3H, d, $J=7$ Hz, $C\underline{H}_3$–CH–O), 2.30 (3H, s, $COC\underline{H}_3$), 2.46 (3H, s, $COC\underline{H}_3$), 3.82 (3H, s, $OC\underline{H}_3$), 4.50 (1H, q, $J=7$ Hz, CH_3–$C\underline{H}$–O), 5.25 (1H, m, CH_3–$C\underline{H}$–O), 6.90 (1H, d, $J=7$ Hz, H-8), 7.40 (1H, t, $J=7$ Hz, H-7), 7.60 (1H, d, $J=7$ Hz, H-6).

Acknowledgement We wish to thank the Analytical Department of Shanghai Institute of Materia Medica, Academia Sinica, for CH analyses, IR, UV and NMR measurements. Thanks are also due to Dr. M. Kubo at Tsumura Laboratory for high-resolution MS measurement.

References

1) Hainan-Renmin Hospital Guanxinbin-Keyan-Xiaozu, *Hainan-Weisheng* (海南衛生), No. 2, 43 (1977).
2) Xinhua Section Hospital, Changning District, Shanghai, unpublished.
3) Z. Chen, H. Huang, C. Wang, Y. Li, and J. Ding, *Zhongcaoyao* (中草薬), **12**, 484 (1981).
4) H. Schmid, Th. M. Meijer, and A. Ebnöther, *Helv. Chim. Acta*, **33**, 595 (1950); H. Schmid, A. Ebnöther, and Th. M. Meijer, *ibid.*, **33**, 1751 (1950); H. Schmid and A. Ebnöther, *ibid.*, **34**, 561, 1041 (1951).
5) Z. Chen (M. Chin), H. Huang, C. Wang, Y. Li, J. Ding, U. Sankawa, H. Noguchi, and Y. Iitaka, *Heterocycles*, **22**, 691 (1984).
6) J. Ding and H. Huang, *Zhongcaoyao* (中草薬), **13**, 499 (1982).
7) M. E. Bergy, *J. Antibiotics*, **21**, 454 (1968); A. Zeeck, H. Zährer, and M. Mardin, *Justus Liebigs Ann. Chem.*, **1974**, 1101.
8) S. Omura, H. Tanaka, Y. Okada, and H. Maruyama, *J. Chem. Soc., Chem. Commun.*, **1976**, 320.
9) S. Omura, H. Tanaka, Y. Koyama, R. Oiwa, J. Awaya, T. Nagai, and H. Tata, *J. Antibiotics*, **27**, 263 (1974); H. Tanaka, Y. Koyama, J. Awaya, H. Marumo, R. Oiwa, M. Katagiri, T. Nagai, and S. Omura, *ibid.*, **28**, 860 (1975); H. Tanaka, Y. Koyama, T. Nagai, H. Maruma, and S. Omura, *ibid.*, **28**, 868 (1975).