TWO NEW BENZOFURAN DERIVATIVES, CORYLIFONOL AND ISOCORYLIFONOL FROM THE SEEDS OF *PSORALEA CORYLIFOLIA*

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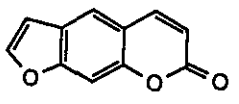
Abstract----------The seeds of *Psolalea corylifolia* were extracted with ether and 60% EtOH, successively. The latter extract was found to contain the known constituents psoralen, angelicin, corylifolinin, bukuchiol, *p*-hydroxybenzoic acid, and astragalin, together with two new benzofuran derivatives, *corylifonol and isocorylifonol*. Their structures have been elucidated by spectral evidence and chemical transformation.

The seeds of *Psoralea corylifolia* have been used as Chinese medicine for the treatment of uterine hemorrhage,[1] skin-photosensitizing activity, [2] coronary vasodilatory and inhibitory effect of Hella cell.[3] The studies of the chemical constituents of this seed are extensive and interesting components including coumarins,[4] flavonoids, [3,5] and terpenoids,[6] were observed. Above mentioned components are all isolated from ether or chloroform extract of the seed of *P.corylifolia* after defat. The polar fraction has not yet been investigated. In connection with our interests in coumarins and flavonoids and the seed of this plant as an important chinese medicine, we have investigated the polar portion of this seed. psoralen (**1**),[3] angelicin (**2**),[3] corylifolinin,[5c] bukuchiol,[6] *p*-hydroxybenzoic acid, [7] and astragalin,[8] together with two new benzofuran derivative, corylifonol (**3a**) and isocorylifonol (**4a**), were isolated. The identification of known compounds was based on comparison of physical data with those reported in the literature and structural elucidation of corylifonol and isocorylifonol were based on the following evidence.



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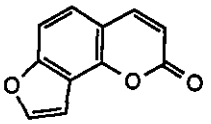

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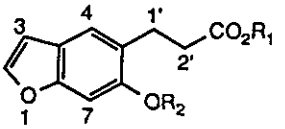

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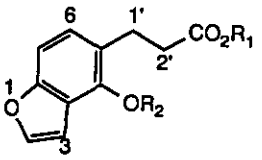
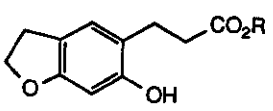
b R_1=Et, R_2=Ac



4a R_1=Et, R_2=H **c** R_1=Me, R_2=H

b R_1=Et, R_2=Ac



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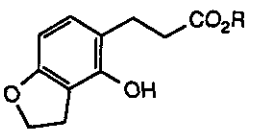

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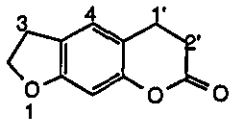
b R=Me



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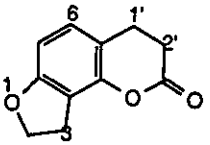

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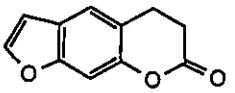

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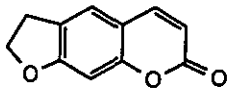

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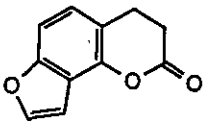

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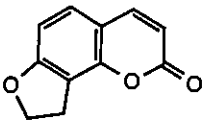

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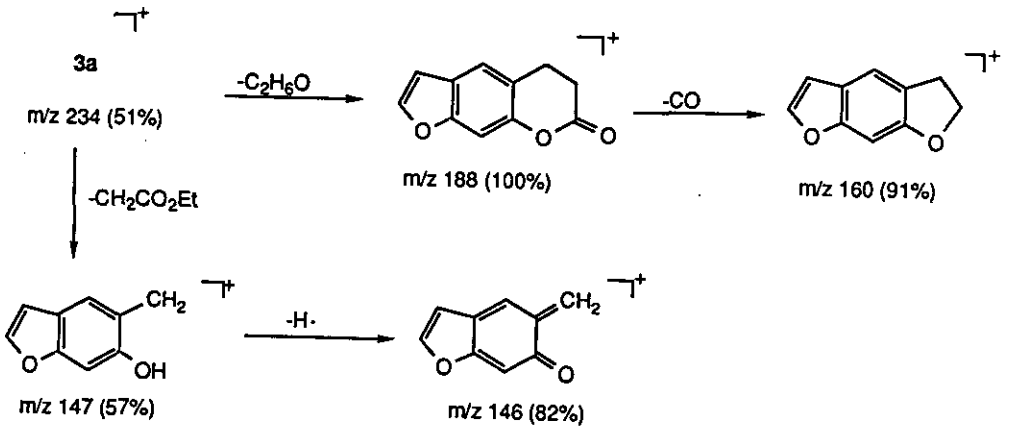

Figure 1

Corylifonol (**3a**) [an amorphous; uv λ_{max}^{MeOH} (log ε) :206 (3.40), 244 (3.38), 251 (3.33), and 289 (3.12) nm] has the molecular formula $C_{13}H_{14}O_4$ on the basis of elemental analysis and mass spectrum (M^+ at m/z 234) and its ir spectrum revealed the presence of hydroxy (3360 cm^{-1}), ester (1730, 1705, 1175, and 1075 cm^{-1}), and aromatic (1620, 1530, and 1510 cm^{-1}) groups. The ^1H nmr spectrum (Table 1) of corylifonol (**3a**) exhibited signals for ethyl ester [δ 1.20 (3H, t, J=6.9 Hz) and 4.13 (2H, q, J=6.9 Hz)], two methylene groups [δ 2.71 and 2.97 (each 2H, t, J=6.6 Hz)], two phenyl protons [δ 7.01 and 7.25 (each 1H, s)], and two furyl protons [δ 6.60 and 7.45 (each 1H, d, J=2.3 Hz)]. Acetylation of (**3a**) with Ac_2O-pyridine yielded a monoacetate (**3b**) [an amorphous; $\upsilon_{cm^{-1}}$ 1760; δ 2.30 (3H, s)]. Hydrogenation of (**3a**) with H_2 / Pd-C in methanol gave dihydrocorylifonol (**5a**) [an amorphous; $\upsilon_{cm^{-1}}$ 3280, 1715; δ 3.07 and 4.50 (each 2H, t, J=8.4 Hz)]

Table 1 ^1H nmr data (δ-value) for (**3a**), (**4a**), (**5a**), and (**6a**) (300 MHz, $CDCl_3$, TMS as internal standard)

H	3a	4a	5a	6a
2	7.45 d (2.3)*	7.48 d (2.2)	4.50 t (8.4)	4.55 t (8.6)
3	6.60 d (2.3)	6.86 d (2.2)	3.07 t (8.4)	3.15 t (8.6)
4	7.25 s		6.85 s	
6		6.96 d (8.4)		6.80 d (8.0)
7	7.01 s	7.02 d (8.4)	6.34 s	6.32 d (8.0)
1'	2.97 t (6.6)	2.94 t (6.4)	2.79 t (6.5)	2.78 m
2'	2.71 t (6.6)	2.72 t (6.4)	2.63 t (6.5)	2.66 m
$C\underline{H_3}CH_2O$-	1.20 t (6.9)	1.20 t (7.2)	1.21 t (7.2)	1.23 t (6.9)
$CH_3C\underline{H_2}O$-	4.13 q (6.9)	4.13 q (7.2)	4.12 q (7.2)	4.17 q (6.9)

*Figures in parentheses are coupling constants in Hz.

(Table 1). An additional proof for the structure of corylifonol (**3a**) is the cleavage patterns of EI ms of (**3a**) (Figure 1). The second compound, isocorylifonol (**4a**) [an amorphous; uv λ_{max}^{MeOH} (log ε) 212 (4.04), 246 (3.65), 252 (3.64), and 284 (3.32) nm] has the molecuar formula $C_{13}H_{14}O_4$ on the basis of elemental analysis and mass spectrum (M^+ at m/z 234). The ir absorption bands express it contains hydroxy (3350 cm^{-1}), ester (1730, 1705, 1215, and 1050 cm^{-1}), and aromatic (1615, 1600, and 1480 cm^{-1}) group. The ^1H nmr spectrum (Table 1) of isocorylifonol (**4a**) expresses similarity to that of corylifonol (**3a**) except AB system signals [δ 6.96 and 7.02 (each 1H, d, J=8.4 Hz)] of phenyl protons instead of two singlets. A monoacetate (**4b**) [an amorphous; $\upsilon_{cm^{-1}}$1755; δ 2.29 (3H, s)] was obtained from (**4a**) by acetylation with the condition as above mentioned. Dihydroisocorylifonol (**6a**) [$\upsilon_{cm^{-1}}$ 3270 and 1720; δ 3.15 and 4.55 (each 2H, t, J=8.6 Hz)] (Table 1) was obtained from (**4a**) by catalytic hydrogenation (with Pd-C in methanol). Ascribing to above evidence, the structure of isocorylifonol (**4a**) can be assigned as shown formula, an isomer of (**3a**). The Elms of (**4a**) exhibited the M^+ peak at m/z 234 (52%) and fragment ion peaks at m/z 188 (83%), 160 (46%), 147 (48%), and 146 (100%). [The fragments are similar to (**3a**) as in Figure 1]. It is an additional proof for the structure of isocorylifonol.

The chemical correlations between psoralen (**1**) and corylifonol (**3a**) and between angelicin (**2**) and isocorylifonol (**4a**) were shown as follows. The hydrogenation of psoralen (**1**) was carried out under the condition of PtO_2 in ethyl acetate, overnight. Tetrahydropsoralen (**7**) (mp150-152°C) was yielded quantitatively. No olefinic proton was observed in the ^1H nmr spectra of **7** instead of mutual coupling of two pair methylene groups (see Table 2). The ester absorption band of **7** shows higher wave number at 1750 cm^{-1}. Tetrahydropsoralen (**7**) and sodium ethoxide were dissolved in dry ethanol, which was allowed to stir at room temperature for 4 h under nitrogen atmosphere. It gave a product which was identical with **5a**. When the hydrogenation of psoralen (**1**) was achieved under the conditions of Pd-C in methanol, **7** was not observed but the methyl ester (**5b**) was yielded. The reaction of **7** with sodium methoxide in

dry methanol gave same product (**5b**) [$\upsilon_{cm^{-1}}$ 3255 and 1710; δ 3.66 (3H,s)] (Table 2). The result manifests the methanolysis reaction occurred simultaneously in hydrogenation. Tetrahydropsoralen (**7**) readily afforded compounds (**5a**) and (**5b**) by stirring in ethanol and methanol only, respectively. Angelicin (**2**) was readily transformed to tetrahydroangelicin (**8**) [$\upsilon_{cm^{-1}}$ 1750 ; δ 2.72 and 2.92 (each 2H, t, J=7.6 Hz), and 3.22 and 4.60 (each 2H, t, J=8.7 Hz)] by catalytic hydrogenation with PtO_2 in ethyl acetate. Sodium ethoxide and (**8**) were stirred in dry ethanol at room temperature under nitrogen atmosphere to yield compound (**6a**). When catalytic hydrogenation was performed with Pd-C in methanol, angelicin (**2**) also gave methanolysis product (**6b**) [$\upsilon_{cm^{-1}}$ 3440 and 1710; δ 3.68 (3H, s) (Table 2)] which was identical with the product from reaction of sodium methoxide with compound (**8**). Without any catalyst, compound (**8**) can readily be transformed to **6a** and **6b** by stirring in ethanol and methanol, respectively, at room temperature.

Table 2 ^{1}H nmr data (δ-value) for (**5b**), (**6b**), (**7**), and (**8**) (300 MHz, $CDCl_3$, TMS as internal standard)

H	**5b**	**6b**	**7**	**8**
2	4.50 t (8.5)*	4.55 t (8.6)	4.52 t (8.5)	4.60 t (8.7)
3	3.07 t (8.5)	3.15 t (8.6)	3.10 t (8.5)	3.22 t (8.7)
4	6.85 s		6.92 s	
6		6.80 d (8.0)		6.90 d (7.9)
7	6.39 s	6.33 d (8.0)	6.41 s	6.51 d (7.9)
1'	2.80 t (6.4)	2.79 m	2.82 t (7.6)	2.92 t (7.6)
2'	2.64 t (6.4)	2.67 m	2.67 t (7.6)	2.72 t (7.6)
CH_3O-	3.66 s	3.68 s		

* Figures in parentheses are coupling constants in Hz.

Partial catalytic hydrogenation of psoralen (**1**) and angelicin (**2**) was achieved as follows. Psoralen (**1**) or angelicin (**2**) was dissolved in ethyl acetate and 10% Pd-C was used as catalyst. The partial hydrogenation reaction ceased as the starting material was not detected by thin layer chromatography. After purification on silica gel chromatography, psoralen (**1**) gave **7**, **9**, and **10** and angelicin (**2**) yielded **8**, **11** and **12** . Compound (**9**) dissolved in ethanol and methanol was stirred at room temperature and afforded corylifonol (**3a**) and (**3c**) , respectively. On the same way, isocorylifonol (**4a**) and (**4c**) were obtained from ethanolysis and methanolysis of compound (**11**), respectively.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^1H and ^{13}C nmr spectra run on a Bruker AM 300 at 300 MHz in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ-values and coupling constants (J) are given in hertz (Hz). Elms and uv spectra were taken on a JEOL-JMS-100 spectrometer and Hitachi U-3200 spectrophotometer, respectively.

Extraction and Isolation

The seeds of *Psoralea corylifolia* (12 kg) was extracted with ether (4 l) three times (2 h for every time) at room temperature. The residue (253 g) was subsequently extracted with 60% EtOH (1 l) four times (4 h for every time) at 60°C. After removal of the solvent it yielded a viscous mass (105 g) which was subjected to partition with ether (2 l) and H_2O (1 l). The water was removed from lower layer under *vacuo* to leave a black viscous mass (76 g) which was followed to column chromato-graphy over Diaion HP-20 (H_2O-MeOH gradient). The 60-80% aqueous methanol eluent was repeatedly chromatographed over Sephadex LH-20 and silica gel column, and then astragalin (26mg), *p*-hydroxybenzoic acid (15 mg), corylifolinin (21 mg), bukuchiol (14 mg),

psoralen (**1**) (9.5 g), angelicin (**2**) (6.8 g) corylifonol (**3a**) (25 mg), and isocorylifonol (**4a**) (18 mg) were isolated. Corylifonol (**3a**); ir (KBr) (υ_{cm-1}) 3360, 3000, 1730, 1705, 1620, 1600, 1530, 1510, 1175, 1075; Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.67; H, 5.98. Found C, 66.70; H, 5.96. ^{1}H nmr: Table 1. Isocorylifonol (**4a**); ir (KBr) (υ_{cm-1}) 3350, 3000, 1730, 1705, 1615, 1600, 1480, 1215, 1050; Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.67; H, 5.98. Found C, 66.80; H, 5.92. ^{1}H nmr ($CDCl_3$): Table 1.

Acetylation of **3a** and **4a** with Acetic Anhydride and Pyridine

Corylifonol (**3a**) (5 mg) and isocorylifonol (**4a**) (5 mg) were allowed to react with Ac_2O (1 ml) in pyridine (1 ml) at room temperature overnight, respectively. Usual work-up gave monoacetate (**3b**) [amorphous; ir (KBr) (υ_{cm-1}) 3000, 1760, 1710, 1610, 1600, 1500, 1200; ^{1}H nmr ($CDCl_3$) δ 1.20 (3H, t, J=6.9 Hz), 2.30 (3H, s), 2.61 and 2.93 (each 2H, t, J=6.6 Hz), 4.14 (2H, q, J=6.9 Hz), 6.67 and 7.43 (each 1H, d, J=2.3 Hz), and 7.11 and 7.40 (each 1H, s)] and (**4b**) [amorphous; ir (KBr) (υ_{cm-1}) 3000, 1755, 1710,1605, 1590, 1500, 1205; ^{1}H nmr ($CDCl_3$) δ 1.21 (3H, t, J=7.2 Hz), 2.29 (3H, s), 2.61 and 2.92 (each 2H, t, J=6.6 Hz), 4.15 (2H,q, J=6.9 Hz), 6.68 and 7.45 (each 1H, d, J=2.3 Hz), and 7.08 and 7.17 (each 1H, d, J=8.4 Hz)], respectively.

Hydrogenation of **3a** and **4a** with Pd-C

Compound (**3a**) (5 mg) was dissolved in 5 ml of MeOH, then 10 mg of 10% Pd-C suspended in 5 ml of MeOH were added and the mixture was saturated with H_2. After 2 h, the catalyst was removed by filtration and washed several times with MeOH. The combined filtrate yielded **5a**, (5 mg) [amorphous: ir (KBr) (υ_{cm-1}) 3280, 1715, 1610, 1530, 1220, 1050, 1030; ^{1}H nmr: Table 1]. Isocorylifonol (**4a**) (5 mg) was subjected to hydrogenation in the similar conditions as above and yielded **6a** (5 mg) [amorphous; ir (KBr) (υ_{cm-1}) 3270, 1720, 1610, 1490, 1220, 1140, and 1025; ^{1}H nmr: Table 1].

Preparation of Compounds (5a) and (6a) from Psoralen (1) and Angelicin (2), respectively

Psoralen (**1**) (20 mg) and angelicin (**2**) (20 mg) was subjected to hydrogenation under the conditions of PtO_2 (4 mg) in ethyl acetate (15 ml) for overnight , respectively. Tetrahydropsoralen (**7**) (20 mg) [mp 150-152 °C; ir(KBr) (υ_{cm-1}) 1750, 1630, 1600, 1485, 1140, and 1050; ^1H nmr: Table 2] and tetrahydroangelicin (**8**) (20 mg) [mp 79-80°C; ir (KBr) (υ_{cm-1}) 1750, 1630, 1605, 1490, 1150, and 1050; ^1H nmr: Table 2] were yielded quantitatively, respectively. Then **7** or **8** (each of 13 mg) and sodium ethoxide (15 mg, 0.22 mmol) were dissolved in dry ethanol (5 ml), each was allowed to stir at room temperature for 4 h under nitrogen atmosphere . Every reaction gave only a product which was identical with **5a** or **6a** (each 13 mg) after purification, respectively.

Preparations of 5b and 6b from Psoralen (1) and Angelicin (2), respectively

Psoralen (**1**) or angelicin (**2**) (each 10 mg) was carried out hydrogenation under the conditions of Pd-C (3 mg) in methanol (10 ml) in the similar condition as mentioned above, and gave methanolysis product (**5b**) (8 mg) [mp 87-88°C; ir (KBr)(υ_{cm-1}) 3255, 1750, 1715, 1620, 1500, 1150, 1070; ^1H nmr: Table 2] or (**6b**) (7 mg) [mp 89-90°C; ir (KBr) (υ_{cm-1}) 3440, 1710,1610, 1490, 1200, 1050; ^1H nmr: Table 2], respectively.

Preparation of 5a and 5b from Compound (7)

Compound (**7**) (10 mg) was stirred in ethanol (3 ml) or methanol (3 ml) at room temperature for 4 h. Compound (**5a**) (10 mg) or (**5b**) (10 mg) was quantitatively obtained after removing of solvent.

Partial Hydrogenation of Psoralen (1) and Angelicin (2)

Psoralen (**1**) (20 mg) or angelicin (**2**) (20 mg) was dissolved in ethyl acetate (10 ml) and 10% Pd-C(10 mg) was added. Then each reaction mixture was stirred for 4 h. After purification on silica gel column chromatography (hexane: ethyl acetate= 3 :1), psoralen (**1**) yielded **7** (12 mg), **9**

(3 mg) [mp 97-98°C, ir (KBr) (υ_{cm-1}) 3380, 1730 and 1710; ^{1}H nmr ($CDCl_3$) δ 2.73 and 2.97 (each 2H, t, J=6.5 Hz), 3.66 (3H, s), 6.60 and 7.49 (each 1H, d, J=2.1 Hz), 7.02 and 7.26 (each 1H, s), and 7.03 (1H, s, -OH)], and **10** (3 mg) [mp 195-196°C, ir (KBr) (υ_{cm-1}) 3030, 1715, 1630, and 1570; ^{1}H nmr ($CDCl_3$) δ 3.21 and 4.65 (each 2H, t, J=8.5 Hz), 6.15 and 7.56 (each 1H, d, J=9.3 Hz), and 6.67 and 7.20 (each 1H, s)], and angelicin (**2**) gave **8** (3 mg),**11** (12 mg) [mp 67-68°C; ir (KBr) (υ_{cm-1}) 3105, 1760, 1630, and 1600; ^{1}H nmr ($CDCl_3$) δ 2.81 and 3. 04 (each 2H, t, J=7.6 Hz), 6.86 and 7.55 (each 1H, d, t, J=2.1 Hz), and 7.04 and 7.20 (each 1H, d, J=7.2 Hz)], and **12** (1.5 mg) [amorphous; ir (KBr) (υ_{cm-1}) 3030, 1710, 1635, and 1555; ^{1}H nmr ($CDCl_3$) δ 3.36 and 4.72 (each 2H, t, J=8.8 Hz), 6.20 and 7.61 (each 1H, d, J=9.6 Hz), and 6.73 and 7.24 (each 1H, d, J=8.1 Hz)].

Preparation of Corylifonol (**3a**) and (**3c**) from Compound (**9**)

Compound (**9**) (8 mg), dissolved in ethanol (10 ml) and methanol (10 ml), was stirred at room temperature for 4 h, and quantitatively afforded corylifonol (**3a**) (7 mg) and (**3c**) (8 mg) [amorphous; ir (KBr) (υ_{cm-1}) 3380, 1730, 1710, 1615, 1600, 1530, 1505, 1175, and 1075; ^{1}H nmr ($CDCl_3$) δ 2.70 and 2.97 (each 2H, t, J=6.6 Hz), 3.66 (3H, s), 6.61 ands 7.45 (each 1H, d, J=2.2 Hz), 7.01 and 7.25 (each 1H, s), and 7.03 (1H, s , -OH)], respectively.

Preparation of Isocorylifonol (**4a**) and (**4c**) from Compound (**11**)

Compound (**11**) (6 mg) was subjectesd to ethanolysis and methanolysis in the same methods as mentioned above, and quantitatively gave isocorylifonol (**4a**) (5 mg) and (**4c**) (6 mg) [amorphous; ir (KBr) (υ_{cm-1}) 3380, 1730, 1710, 1610,1590, 1500, 1210, and 1050; ^{1}H nmr ($CDCl_3$) δ 2.72 and 2.95 (each 2H, t, J=6.4 Hz), 3.67 (3H, s), 6.95 and 7.02 (each 1H, d, J=8.4 Hz), 6.85 and 7.48 (each 1H, d, J=2.1 Hz), and 7.94 (1H, s, -OH)], respectively.

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