

FLAVONOIDS OF *STRIGA ASIATICA*

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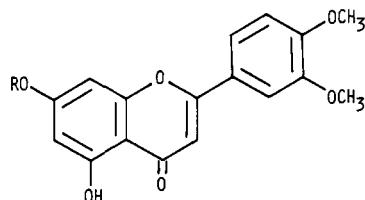
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Striga asiatica (L.) O. Kuntze (Scrophulariaceae), known as witch weed, grows in the South of China. The whole plant, a crude drug known as "Du-Jiao-Jin" in Chinese (Doku-kyaku-Kin in Japanese), has been used as a remedy for peevishness in unweaned infants and also for icterohepatitis in China. However, no chemical report on this plant has previously been made. In this paper, we describe the isolation and characterization of six known flavones, i.e., apigenin, acacetin, 5-hydroxy-7,4'-dimethoxyflavone (acacetin 7-methyl ether), chrysoeriol, 5,7-dihydroxy-3',4'-dimethoxyflavone (luteolin 3',4'-dimethyl ether) (**1**), and 5-hydroxy-7,3',4'-trimethoxyflavone (luteolin 7,3',4'-trimethyl ether) (**2**), from the whole plant.



- 1** R=H
2 R=CH₃

The fifth (**1**) and sixth (**2**) flavones isolated are both rare and are described in detail below; their structures (**1** and **2**) were confirmed by both physicochemical (mp, ms, uv, ¹H nmr, and nOe) and synthetic evidence. Synthetic **1** and **2** were prepared according to the following new route using an isopropyl ether as a protecting group (1). 2-Hydroxy-4,6-

diisopropoxyacetophenone (**1**) and veratraldehyde were condensed under alkaline conditions, and the resultant chalcone was oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give 5,7-diisopropoxy-3',4'-dimethoxyflavone, deisopropylation [with BCl₃ (**2**)] of which furnished **1**. Partial methylation of **1** gave **2**. This study provides the first synthetic proof for both these natural flavones and also the first synthesis of **2**.

Recently, natural **1** has been first isolated and characterized from three species (3-5), all in the family Compositae, and this report describes the fourth isolation and identification of **1** and the first from the family Scrophulariaceae. Prior to these reports on natural **1**, the uv (6,7) and ms (7) data of **1** probably originated from a synthetic material, were first published about ten years ago.

Natural **2**, although previously found in two *Piper* (Piperaceae) (8-10), two *Salvia* (Labiatae) (8, 11, 12), a *Turnera* (Turneraceae) (8, 13), a *Cistus* (Cistaceae) (14), and a *Lychnophora* (Compositae) (8, 15) species, is reported for the first time from Scrophulariaceae. To our knowledge, acacetin and acacetin 7-methyl ether are also characterized here for the first time from Scrophulariaceae.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Spectra were recorded with the following instruments and conditions; uv,

Shimadzu model UV 3000 in MeOH solution; ir, JEOL model A with KBr disks; ms, JEOL model DX-300 with in-beam method at 70 eV; ^1H nmr, JEOL model GX-400 (400 MHz) and/or Hitachi R-20B (60 MHz) with TMS as internal standard. Adsorbants for tlc and cc were from E. Merck.

PLANT MATERIAL.—*S. asiatica* was collected at Kwantung in China and imported via Hongkong in 1980. The plant was identified by one of us (K. Yoneda), and a voucher specimen is deposited in the herbarium of the Faculty of Pharmaceutical Sciences, Osaka University.

EXTRACTION AND ISOLATION.—The air-dried whole plant of *S. asiatica* (5 kg) was cut and extracted three times with MeOH for 2 h under reflux. Evaporation of the solvent in vacuo yielded an extract (291 g), a part (90 g) of which was partitioned between *n*-BuOH-EtOAc (1:1) and H_2O (1:1). The organic layer was evaporated to dryness to afford a residue (28 g), which was again partitioned between MeOH and *n*-hexane (1:1). The MeOH concentrate (16.6 g) was repeatedly chromatographed on silica gel columns (70-230 and 230-400 mesh), gradually eluting with CHCl_3 , CHCl_3 -MeOH (80:1), (40:1), (20:1), and (10:1). The two least polar compounds obtained from the above columns were further purified by preparative tlc respectively developed with C_6H_6 - Me_2CO (7:1) and (5:1). The six flavones in the following order from the silica gel columns were isolated all in a pure form: 5-hydroxy-7,4'-dimethoxyflavone (acacetin 7-methyl ether) (90 mg), 5-hydroxy-7,3',4'-trimethoxyflavone (luteolin 7,3',4'-trimethyl ether; 60 mg) (**2**), acacetin (80 mg), chrysoeriol (330 mg), apigenin (710 mg), and 5,7-dihydroxy-3',4'-dimethoxyflavone (luteolin 3',4'-dimethyl ether; 70 mg) (**1**).

IDENTIFICATION OF FLAVONES.—Apigenin, acacetin, and chrysoeriol were identified by mp, uv (6,7), ms (7), ^1H nmr (400 MHz), nOe, and authentic natural sample comparison (mixed mp, ir, uv, and co-tlc). Acacetin 7-methyl ether was also identified by the physicochemical evidence [mp, uv, ms, ^1H nmr (400 MHz), and nOe experiment] (8,9,16-18) and by direct comparison with a synthetic standard (mixed mp, ir, uv, and co-tlc), which was prepared by us from 2-hydroxy-4,6-diisopropoxyacetophenone (see below) and anisaldehyde (commercially available) according to a synthetic route similar to that for flavones **1** and **2**.

Luteolin 3',4'-dimethyl ether (**1**), mp 276-278° (from MeOH) [lit. (5) mp 289°]; ir ν max (KBr) 3100 (br, hydrogen bonded OH), 1650, 1610, 1580, 1500, 1250, 1160, 1015, 840, 800, and 765 cm^{-1} [cf. lit. (5) ν max (nujol)]; uv λ (MeOH) and +NaOMe, essentially same to lit. (3,5-7): + AlCl_3 261, 276, 295, 359, 387 nm

[cf. lit. (3,7); ms m/z (%) 314 (M^+ for $\text{C}_{17}\text{H}_{14}\text{O}_6$, 100), 300 (8), 284 (13), 270 (12), 228 (4), 162 (32), 153 (46), 152 (24), 147 (21), 118 (11), 91 (15), and 69 (17) [cf. lit. (3,7)]; ^1H nmr [400 MHz; CDCl_3 -MeOH- d_4 (1:1)] δ 3.97, 3.99 (3H each, both s, 3'- and 4'-OMe), 6.29 (1H, d, $J=2.2$ Hz, 6-H), 6.48 (1H, d, $J=2.2$ Hz, 8-H), 6.60 (1H, s, 3-H), 7.06 (1H, d, $J=8.5$ Hz, 5'-H), 7.42 (1H, d, $J=2.2$ Hz, 2'-H), and 7.59 (1H, dd, $J=8.5$ and 2.2 Hz, 6'-H) [cf. lit. (5) 100 MHz; Py- d_5]; nOe: Irradiation of both 3'- and 4'-methoxys caused enhancements of 2'- and 5'-protons. All these data were consistent with structure **1**.

Luteolin 7,3',4'-trimethyl ether (**2**), mp 163-165° (from MeOH) [lit. (9,13) 163°; lit. (11) 164°]; ir ν max (KBr) essentially same as lit. (13) [also cf. lit. (9,12)]; uv λ max (MeOH) essentially same to lit. (9); +NaOMe 287, 310sh, 365sh; + AlCl_3 262, 278, 296sh, 359, 387 nm [cf. (9,12)]; ms m/z (%) 328 (M^+ for $\text{C}_{18}\text{H}_{16}\text{O}_6$, 100), 299 (22), 285 (6), 242 (2), 167 (20), 166 (2), 162 (9), 147 (6), 91 (5), and 57 (14) [cf. lit. (9,13)]; ^1H nmr (400 MHz; CDCl_3) δ 3.89, 3.97, 3.98 (3H each, all s, 7-, 3'-, and 4'-OMe), 6.38 (1H, d, $J=2.2$ Hz, 6-H), 6.50 (1H, d, $J=2.2$ Hz, 8-H), 6.59 (1H, s, 3-H), 6.99 (1H, d, $J=8.5$ Hz, 5'-H), 7.34 (1H, d, $J=2.2$ Hz, 2'-H), 7.52 (1H, dd, $J=8.5$ and 2.2 Hz, 6'-H), and 12.79 (1H, s, 5-OH) [cf. lit. (9) 100 MHz; lit. (11-13) 60 MHz]. This is the first fully analyzed and fully assigned data of **2**; nOe experiment: Irradiation of all methoxy methyls caused enhancements of 6-, 8-, 2'-, and 5'-protons. All data described above were in good agreement with structure **2**.

SYNTHESIS OF 1 AND 2.—Condensation of 2-hydroxy-4,6-diisopropoxyacetophenone (1.5 g; 6 mmol) [prepared from commercial phloroacetophenone and diisopropyl bromide according to lit. (1)] and veratraldehyde (0.99 g; 6 mmol) (commercially available) in 10% ethanolic KOH (70 ml) gave 2'-hydroxy-4',6'-diisopropoxy-3,4-dimethoxychalcone (1.8 g), yellow needles of mp 105-107° (from MeOH), ^1H nmr (60 MHz; CDCl_3) δ 1.33 (6H, d, $J=6.0$ Hz, gem. dimethyl), 1.43 (6H, d, $J=6.0$ Hz, gem. dimethyl), 3.84 (6H, s, 2 \times OMe), 4.32-4.80 (2H, m, 2 \times methine H of isoPr), 5.81 (1H, d, $J=2.1$ Hz, 5'-H), 5.96 (1H, d, $J=2.1$ Hz, 3'-H), 6.77 (1H, d, $J=8.8$ Hz, 5-H), 7.02 (1H, d, $J=2.0$ Hz, 2-H), 7.07 (1H, dd, $J=8.8$ and 2.0 Hz, 6-H), 7.55 (1H, d, $J=15.0$ Hz, β -H), 7.86 (1H, d, $J=15.0$ Hz, α -H), and 14.15 (1H, s, OH).

A mixture solution of the chalcone (1 g; 2.5 mmol) obtained above and DDQ (1.1 g; 5 mmol) in dry dioxane (30 ml) was heated under reflux for 7 h and then cooled. The precipitate (the hydroquinone derived from DDQ) was filtered off, and the filtrate was purified on silica gel column (C_6H_6 as eluent) to afford the corresponding

flavone derivative (650 mg), a brown oil, ^1H nmr (60 MHz; CCl_4) δ 1.39 (12H, d, $J=6.0$ Hz, $2\times$ gem. dimethyl), 3.77, 3.80 (3H each, both s, $2\times\text{OMe}$), 4.10-4.70 (2H, m, $2\times$ methine H of isoPr), 6.15 (1H, d, $J=2.3$ Hz, 6-H), 6.32 (1H, s, 3-H), 6.34 (1H, d, $J=2.3$ Hz, 8-H), and 6.61-7.32 (3H, m, 2'-, 5'-, and 6'-Hs).

To a solution of the flavone isopropyl ether (650 mg) in CH_2Cl_2 , BCl_3 (0.5 ml) was added at -70° (2). The mixture solution was left at room temperature for 1 h and poured into H_2O . Extraction with EtOAc and subsequent recrystallization furnished synthetic **1** (220 mg), mp $275-276^\circ$, ^1H nmr (60 MHz; $\text{DMSO}-d_6$) δ 3.81, 3.82 (3H each, both s, $2\times\text{OMe}$), 6.10 (1H, d, $J=2.0$ Hz, 6-H), 6.37 (1H, d, $J=2.0$ Hz, 8-H), 6.75 (1H, s, 3-H), 6.96 (1H, d, $J=8.1$ Hz, 5'-H), 7.41 (1H, d, $J=1.9$ Hz, 2'-H), and 7.52 (1H, dd, $J=8.1$ and 1.9 Hz, 6'-H) (*Anal.* calcd for $\text{C}_{17}\text{H}_{14}\text{O}_6$: C, 64.96; H, 4.49. Found: C, 64.92; H, 4.50%), which was identical to natural **1** in all respects (mixed mp, ir, uv, ms, and co-tlc).

Synthetic flavone **1** (80 mg) was methylated with CH_3I (2 ml) and K_2CO_3 (1.5 g) in Me_2CO to yield the trimethoxyflavone (**2**) as pale yellow needles, mp $160-161^\circ$ (MeOH), which was consistent with natural **2** by mixed mp, ir, uv, ^1H nmr, and co-tlc.

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