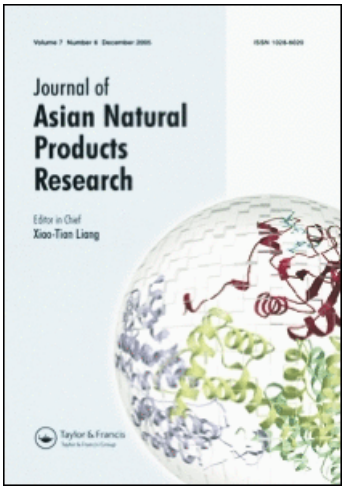

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NEW XANTHONE GLYCOSIDES FROM *SECURIDACA INAPPENDICULATA*

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Three new xanthone glycosides, securixanside A (**1**), securixanside B (**2**), and securixanside C (**3**) were isolated from the stems of *Securidaca inappendiculata*. These compounds were characterized by spectrometric and chemical methods, including FABMS and one- and two-dimensional NMR experiments.

Keywords: *Securidaca inappendiculata*; Polygalaceae; Xanthone glycoside; Securixanside A, B and C

INTRODUCTION

The genus *Securidaca* (Polygalaceae) consists of two species from tropical East Asia [1]. Chemical research on the gennus appears to be limited to an investigation of the flavonoids [2,3] and organic acids and its derivatives [4,5]. In our continuing search on activity metabolites for antidepressant and anti-Parkinson's disease, three new xanthone glycosides, securixanside A (**1**), securixanside B (**2**), and securixanside C (**3**), were isolated from the stems of *Securidaca inappendiculata* Hassk. We report here the isolation and structure determination of the new xanthones.

RESULTS AND DISCUSSION

Compound **1** was obtained as yellow amorphous solid, mp 278–280°C. Its HRFABMS showed a quasi-molecular ion peak at *m/z* 435.1291, corresponding to a molecular formula of $C_{21}H_{22}O_{10}$ (calcd. 435.1291), and a prominent fragment ion peak at *m/z* 273 $[M + H\text{-}162]^+$ due to the loss of hexose moiety. The ^1H, ^{13}C NMR spectra showed signals for a glucose unit, which was confirmed by TLC after acid hydrolysis of **1** [6]. The UV spectrum of **1** exhibited characteristic absorption bands of a xanthone (λ_{max} MeOH 232, 256, 312, 365 nm). The

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presence of a free hydroxyl group at C-6 or C-3 were excluded based on the lack of any change in the UV spectrum with NaOAc [7].

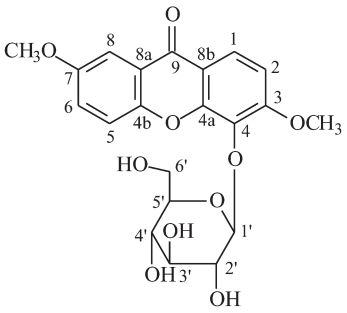
The ^{1}H NMR spectrum displayed signals of two aromatic methoxyls (δ 3.87, 3.88), an ABX system (δ 7.56, d. $J = 9.1$ Hz; δ 7.43, dd. $J = 9.1, 3.1$ Hz; δ 7.53, d. $J = 3.1$ Hz) and an AB system of two protons *ortho*-coupled (δ 7.35 and 7.70; $J = 9.4$ Hz), indicating that one aromatic ring of the xanthone nucleus was *mono*-substituted and the other was disubstituted. The ^{13}C NMR spectrum indicated that the aromatic methoxyl at δ 61.80 was di-*ortho*-substituted and there were no substituted groups at C-1 or C-8 position according to the carbonyl carbon shift (174.79) [8]. The signal of the anomeric proton of the glucose appeared at δ 4.91 (d, $J = 7.3$ Hz), indicating that the sugar moiety should be β-orientated. The ^{1}H and ^{13}C NMR data of **1** were assigned by the use of HMQC experiments.

Compound **1** was hydrolyzed with 1N HCl, and the products were partitioned between aqueous and organic solvents. The organic layer gave a xanthone compound (**1a**). Compared the spectral data of **1a** with 4-hydroxy-3,7-dimethoxyxanthone [9], the aglycone of **1** was determined as 4-hydroxy-3,7-dimethoxyxanthone and C-4 of **1** appeared at significantly lower field (3 ppm) suggested the β-glucose was connected at C-4 position.

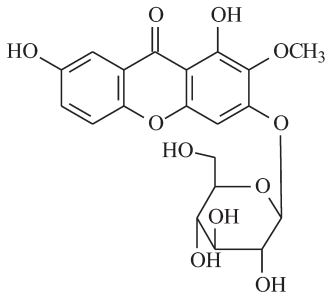
From these chemical and spectral evidences, the compound **1** was identified as 4-*O*-β-D-glucopyranosyl-3,7-dimethoxyxanthone, named securixanside A.

Compound **2** was obtained as yellow amorphous solid, mp 256–258°C. The FABMS displayed a quasi-molecular ion peak at *m/z* 437 $[M + H]^+$ and a prominent fragment ion peak at *m/z* 275 $[M + H\text{-}162]^+$ due to the loss of sugar moiety. In combination with the NMR data, the molecular formula of **2** was determined to be $C_{20}H_{20}O_{11}$. The ^{1}H, ^{13}C NMR spectra of **2** showed signals for a glucose unit, which was confirmed by TLC after acid hydrolysis. It was suggested the presence of a xanthone skeleton from UV (MeOH) absorption at λ_{max} 234, 256, 294, 374 nm and IR (KBr) absorption bands at ν_{max} 3440, 1660, 1600 and 1580 cm^{-1}. The signal at δ 12.73 ppm in ^{1}H NMR spectrum of **1** (DMSO-d_6) indicated that a hydroxyl was chelated to a carbonyl group [10]. The ^{1}H NMR spectrum also exhibited one aromatic proton at δ 6.85 ppm (s), and three coupled aromatic protons at δ 7.33 (dd, $J = 9.0, 3.0$ Hz), δ 7.50 (d, $J = 9.0$ Hz) and δ 7.45 (d, $J = 3.0$ Hz), indicating that one aromatic ring of the xanthone nucleus was monosubstituted and the other was trisubstituted. The signals of the anomeric proton of the glucose appeared at δ 5.14 (d, $J = 7.1$ Hz) in the ^{1}H NMR spectrum, indicating that the sugar moiety should be β-orientated. Coupling constants and chemical shifts of the aromatic signals were in accord with data reported for 1,3,7-trihydroxy-2-methoxyxanthone [11], with the exception of C-3 appeared at higher field (0.9 ppm), and H-4, MeO-3 at significantly lower field (0.1–0.4 ppm). Comparison of the EIMS spectral data of the two compounds showed they have same cleavage pattern and main cleavage ions except the molecular and glucose cleavage ions of **2**. These data suggested the aglycone of **2** was 1,3,7-trihydroxy-2-methoxyxanthone and β-glucose was connected at C-3 position. Therefore, **2** was identified as 3-*O*-β-D-glucopyranosyl-1,7-dihydroxy-2-methoxyxanthone, named securixanside B.

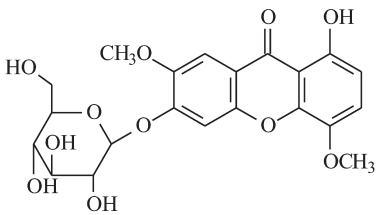
Compound **3** was obtained as yellow amorphous solid, mp 276–278°C. Its HRFABMS showed a quasi-molecular ion peak at *m/z* 451.1241 $[M + H]^+$, indicating the molecular formula of $C_{21}H_{22}O_{11}$ (calcd. 451.1241). In addition, the FABMS displayed a prominent fragment ion peak at *m/z* 289 $[M + H\text{-}162]^+$ due to the loss of hexose moiety. The ^{1}H, ^{13}C NMR spectra of **3** showed signals for a glucose unit, which was confirmed by TLC after acid hydrolysis. The UV spectrum of **3** exhibited characteristic absorption bands of a xanthone chromophore (λ_{max} MeOH 226, 266, 310, 378 nm). The presence of a free hydroxyl group at C-6 or C-3 were excluded based on the lack of any change in the UV spectrum with NaOAc. The ^{1}H NMR spectrum displayed signals of two aromatic methoxyl (δ 3.84, 3.89), an AB system of two protons *ortho*-coupled (δ 7.51 and 7.03; $J = 9.0$ Hz) and two singlets (δ 7.51,



1



2



3

FIGURE 1 Structures of compounds **1**, **2** and **3**.

7.31), indicating that one aromatic ring of the xanthone nucleus was 2,3-*ortho*-disubstituted and the other was 1,4-*para*-disubstituted. The signal at δ 12.87 ppm in ^{1}H NMR spectrum of **3** indicated that a hydroxyl was chelated to a carbonyl group. The presence of 6-*O*-β-D-glucopyranosyl-7-methoxyl and 1-hydroxy-4-methoxyl aromatic ring moiety in **3** was supported by comparison of the ^{13}C and ^{1}H NMR spectrum of **3** with known compounds, 6-*O*-β-D-glucopyranosyl-1-hydroxy-7-methoxyxanthone (**4**) [12] and 1,7-dihydroxy-4-methoxy-xanthone (**5**) [13]. The shifts of corresponding carbons in the ^{13}C NMR spectrum of **3**, **4** and **5** are essentially same. The signals of the anomeric proton of the glucose appeared at δ 5.05 (d, $J = 6.0$ Hz) in the ^{1}H NMR spectrum, indicating that the sugar moiety should be β-orientated.

From all above mentioned, the compound **3** was identified as 6-*O*-β-D-glucopyranosyl-1-hydroxy-4,7-dimethoxyxanthone, named securixanside C (Fig. 1).

EXPERIMENTAL SECTION

General Experimental Procedures

Melting points were determined using a Fisher Johns apparatus and are uncorrected. UV spectra were measured on a philips PYE Unican Pu8800 spectrophotometer. IR spectra were obtained in KBr disks on a Perkin–Elmer 983G spectrophotometer. One- and two-dimensional NMR spectra were recorded on a Bruker ARX 400 spectrometer. The FABMS (positive mode) were recorded in a Zabspec E mass spectrometer. EIMS were obtained on a VG ZAB-2f mass spectrometer. TLC and HPTLC employed precoated Silica gel plates

(Qingdao Haiyang) and polyamide plates (Zhejiang Huangyan). For column chromatography, Silica gel (Qingdao Haiyang) and Sephadex LH 20 (Pharmacia) were used. The MPLC (medium pressure liquid chromatography) were performed on a system equipped with a Büchi pump B-688, Büchi B-684 Fraction collector, UVILOG-5IIIA UV-Detector, Büchi columns and precolumns, with the stationary phase Silica gel 60 (15–40 μm, Qingdao Haiyang) and polyamide (>200 mesh, Hunan Lixian Yizhong).

Plant Material

The stems of *S. inappendiculata* were collected in Yunnan province of China and identified by Prof. Wen-Yan Lian (our Institute) and Prof. Hong Wang (Menglun Botanical Garden). A voucher specimen (YS-9801) was deposited in the New Drug Research and Development Center of our Institute.

Extraction and Isolation

The dried ground stems (10 kg) of the plant material were extracted with 95% EtOH (30 l × 3, 2 h each) under reflux. The EtOH extract (750 g) was fractionized by solvent reflux in a Soxhlet apparatus (silica gel as absorbent) into $CHCl_3$, EtOAc, Me_2CO and MeOH parts. The EtOAc part (31 g) was chromatographed on MPLC (silica gel, 200–300 mesh) and eluted with a gradient of Me_2CO in $CHCl_3$ (100:0–40:60) to give 36 fractions. Fractions 1–3 (100:0–96:4) were purified by polyamide column chromatography eluted with $CHCl_3$–MeOH (1:0–0:1, gradient) and Sephadex LH-20 to give compound **1** (18 mg). The Me_2CO part (322 g) was chromatographed on silica gel column chromatography (100–200 mesh) and eluted with a gradient of Me_2CO in $CHCl_3$ (100:0–50:50) to give 13 fractions. Fraction 4 was purified by polyamide column chromatography eluted with $CHCl_3$–MeOH (1:0–0:1, gradient) and Sephadex LH-20 to give compound **2** (7 mg) [fraction 4–6 (60:40)]; Fraction 5 was chromatographed on MPLC (silica gel H) and eluted with a gradient of MeOH in $CHCl_3$ (100:0–40:60) to give thirteen parts. Part 10 (60:40) was purified by Sephadex LH-20 to give compound **3** (10 mg).

Securixanside A (**1**), obtained as yellow, amorphous powder from MeOH, mp 278–280°C; showed positive reaction with Molish reagent, negative reaction with Mg–HCl, dark purple fluorescence under UV light (on polyamide film) and dark green color with $FeCl_3$; UV (MeOH) λ_{max} 232, 256, 312, 365 nm; IR(KBr) ν_{max} 3480, 1645, 1620, 1490, 1480 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.70 (1H, d, J = 9.4 Hz, H-1), 7.56 (1H, d, J = 9.1 Hz, H-5), 7.53 (1H, d, J = 3.1 Hz, H-8), 7.43 (1H, dd, J = 9.1, 3.1 Hz, H-6), 7.35 (1H, d, J = 9.4 Hz, H-2), 4.91 (1H, d, J = 7.31 Hz, Anomeric-H), 3.88, 3.87 (each 3H, s, MeO-3,7); ^{13}C NMR (DMSO-d_6) δ 124.4 (C-1), 113.2 (C-2), 151.4 (C-3), 148.2 (C-4), 146.6 (C-4a), 149.3 (C-4b), 119.1 (C-5), 124.0 (C-6), 155.5 (C-7), 105.9 (C-8), 121.9 (C-8a), 115.7 (C-8b), 174.8 (C-9), 61.2 (MeO-3), 55.6 (MeO-7), 101.5 (C-1′), 73.3 (C-2′), 76.7 (C-3′), 69.7 (C-4′), 77.1 (C-5′), 60.7 (C-6′); FABMS m/z 434.9 ($[M + H]^+$, 100), 456.8 ($[M + Na]^+$, 10), 273 ([aglycon + H]$^+$, 50); EIMS m/z 272 ([aglycon]$^+$, 100), 254 (95), 225 (25); HRFABMS m/z [M^+ + 1] 435.1291 (calcd. for $C_{21}H_{22}O_{11}$ +1, 435.1291).

Securixanside B (**2**), obtained as yellow, amorphous powder from MeOH, mp 256–258°C; showed positive reaction with Molish reagent, negative reaction with Mg–HCl, dark purple fluorescence under UV light (on polyamide film) and dark green color with $FeCl_3$; UV (MeOH) λ_{max} 234, 256, 294, 374 nm; IR(KBr) ν_{max} 3440, 1660, 1600, 1580, 1475 cm^{-1}; ^1H NMR (DMSO-d_6) δ12.73 (1H, s, HO-1), 9.85 (1H, s, HO-7), 7.50 (1H, d, J = 9.0 Hz, H-5), 7.45 (1H, d, J = 3.0 Hz, H-8), 7.33 (1H, dd, J = 9.0, 3.0 Hz, H-6) 6.85 (1H, s, H-4), 3.87 (3H, s, MeO-2), 5.14 (1H, d, J = 7.1 Hz, Anomeric-H); ^{13}C NMR (DMSO-d_6) δ 153.3 (C-1),

131.5 (C-2), 153.5 (C-3), 93.7 (C-4),152.2(C-4a), 149.1 (C-4b), 118.7 (C-5), 124.7 (C-6), 153.8 (C-7), 107.7 (C-8), 119.8 (C-8a), 103.5 (C-8b), 180.5 (C-9), 60.2 (MeO), 100.1 (C-1′), 73.1 (C-2′), 76.5 (C-3′), 69.6 (C-4′), 77.1 (C-5′), 60.6 (C-6′); FABMS *m/z* 437 ($[M + H]^+$, 65), 275 ($[aglycon + H]^+$, 75); EIMS *m/z* 274 ($[aglycon]^+$, 75), 259 (60), 244 (10), 231 (100).

Securixanside C (**3**), obtained as yellow, amorphous powder from MeOH, mp 276–278°C; showed positive reaction with Molish reagent, negative reaction with Mg–HCl, dark purple fluorescence under UV light (on polyamide film) and dark green color with $FeCl_3$; UV (MeOH) λ_{max} 226, 266, 310, 378 nm, +NaAc + H_3BO_3 unchanged; IR(KBr) ν_{max} 3440, 1650, 1610, 1585, 1480 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.87 (1H, s, HO-1), 7.51 (1H, s, H-8), 7.51 (1H, d, $J = 9.0$ Hz, H-3), 7.31 (1H, s, H-5), 7.03 (1H, d, $J = 9.0$ Hz, H-2), 5.05 (1H, d, $J = 6.0$ Hz, Anomeric-H), 3.89 (3H, s, MeO-7), 3.84 (3H, s, MeO-4); ^{13}C NMR (DMSO-d_6) δ 154.0 (C-1), 105.6 (C-2), 121.4 (C-3), 142.1 (C-4), 149.7 (C-4a), 149.4 (C-4b), 103.1 (C-5), 152.2 (C-6), 146.8 (C-7), 104.7 (C-8), 122.8 (C-8a), 108.1 (C-8b), 180.9 (C-9), 56.8 (MeO-7), 56.0 (MeO-4), 99.7 (C-1′), 73.1 (C-2′), 76.7 (C-3′), 69.6 (C-4′), 77.2 (C-5′), 60.7 (C-6′); FABMS *m/z* 451 ($[M + H]^+$, 15), 289 ($[aglycon + H]^+$, 50); EIMS *m/z* 288 ($[aglycon]^+$, 100), 273 (55), 259 (20), 245 (65), 230 (25); HRFABMS *m/z* [$M^+ + 1$] 451.1241 (calcd. for $C_{21}H_{22}O_{11} + 1$, 451.1240).

TLC acid hydrolysis of **1**–**3**. Compounds **1**, **2** and **3** were spotted on a TLC plate together with sugar references. The plate was exposed in HCl vapor, and then developed with the lower layer of chloroform–methanol–water (30:12:4)-glacial acetic acid (9:1), and sprayed with 10% H_2SO_4, heated at 120°C. From compound **1**–**3** only glucose was detected [6].

Acid hydrolysis of compound **1**. Compound **1** (10 mg) was dissolved in 4 ml of MeOH and refluxed with 1N HCl (4 ml) at 80°C for 1 h. the reaction mixture was diluted with H_2O (20 ml) and extracted with EtOAc (20 ml). The EtOAc layer was evaporated to dry under reduced pressure. The residue was chromatographed over Si gel and eluted with increasing polarities of *n*-hexane/EtOAc to yield **1a**.

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