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Two new withanolides from the halophyte *Datura stramonium* L.

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Eight steroids, including five withanolides (**1**–**5**) and three other ergostane-type steroids (**6**–**8**), were isolated from the aerial parts of the halophyte *Datura stramonium* L., which were collected from the Yellow River Delta in China. Their structures were elucidated on the basis of extensive spectroscopic methods, especially 1D and 2D NMR techniques. Compounds **1** and **2** were new compounds and characterised as (22*R*)-27-hydroxy-7α-methoxy-1-oxowitha-3,5,24-trienolide and its 27-*O*-β-D-glucopyranoside. Compound **3** was a new natural product and identified as (22*R*)-27-hydroxy-1-oxowitha-2,5,24-trienolide and isolated from nature for the first time.

Keywords: *Datura stramonium*; halophyte; withanolides; steroids

1. Introduction

Withanolides are a group of naturally occurring steroidal compounds with an ergostane skeleton, in which C-26 with C-22, C-23 or C-28 are oxidised to form a δ- or γ-lactone. These compounds are structurally diverse and produced mainly by the genera *Withania*, *Physalis*, *Datura*, *Nicandra*, *Dunalia*, *Lycium*, *Tubocapsicum* and *Jaborosa* of the family Solanaceae (Glotter 1991; Chen et al. 2011). Many of these compounds often exhibit a variety of biological activities, such as antitumor, antimicrobial, anti-inflammatory, antioxidant, hepatoprotective, immuomodulatory, insect-antifeedant and insecticidal activities (Chen et al. 2011).

Datura stramonium L. is a common medical plant belonging to the family Solanaceae, and widely distributed in China. It has been used in Chinese folk medicine for the treatment of asthma, convulsions, pain and rheumatism for centuries (Editorial Board of Flora of China 1978). In the Yellow River Delta of China, *D. stramonium* L. is also one of the halophytic plants that can grow in salt marshes along the seashores, and plays an important role in protecting and maintaining local ecological stability (Duan et al. 2007). Due to our interest in the particular constituents of the halophytes, the aerial parts of *D. stramonium* L., which were collected from the Yellow River Delta have been investigated. Five withanolides including three new ones (**1**–**3**), together with three other known ergostane-type steroids (**6**–**8**) (Figure 1) have been isolated in this experiment. Herein, we report the isolation and structural elucidation of these compounds.

2. Results and discussion

Compound **1** was obtained as an amorphous powder with the molecular formula of $C_{29}H_{40}O_5$ as determined from its HR-EI-MS (*m/z* 468.2879 $[M]^+$, calculated for 468.2876) and NMR data. The UV absorption maximum at 223 nm and strong IR absorption at 3433 and 1705 cm^{-1}

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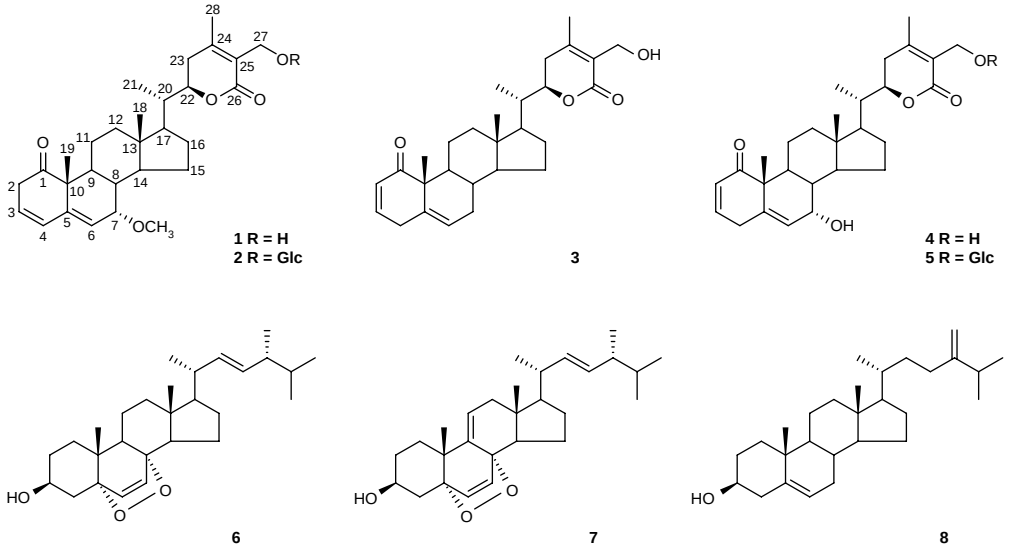

Figure 1. Structures of compounds **1**–**8**.

indicated the presence of hydroxyl and α,β-unsaturated δ-lactone groups. The NMR spectra of **1** showed patterns typical of common withanolides for rings A, B and the side chain. The ^{13}C NMR and DEPT spectra showed 29 carbon signals, including 4 methyls, 1 methoxyl, 7 methylenes, 10 methines and 7 quaternary carbons. The ^{1}H NMR spectrum of **1** showed the presence of five methyl groups, including three tertiary methyls at δ_H 0.75, 1.36 and 2.07 (each 3H, s, Me-18, Me-19 and Me-28, respectively), a secondary methyl at δ_H 1.05 (3H, d, $J = 6.7$ Hz, Me-21) and a methoxyl group (δ_H 3.33, 3H, s, 7-OCH_3). The Me-27 signal was absent in the ^{1}H NMR spectrum, but two more doublets at δ_H 4.42 (1H, d, $J = 12.6$ Hz) and 4.38 (1H, d, $J = 12.6$ Hz) suggesting that C-27 was substituted by a hydroxyl group. In addition, two oxymethine signals attributing to C-7 and C-22 and three olefinic protons were also observed in the lower field of the ^{1}H NMR spectrum. From the above information, we found that the NMR data of **1** were very similar to those of **4** (Kirson et al. 1971; Ma et al. 2006), except for the position of one double bond and one more methoxyl group in **1**. Three olefinic protons at δ_H 5.83 (1H, ddd, $J = 9.6$, 4.6, 3.0 Hz, H-3), 6.14 (1H, dd, $J = 9.9$, 2.1 Hz, H-4) and 5.98 (1H, d, $J = 5.1$ Hz, H-6) coupled with an unconjugated ketone carbonyl at δ_C 209.1 (s, C-1) and four olefinic carbons at δ_C 124.9 (d, C-3), 129.3 (d, C-4), 145.0 (s, C-5) and 124.5 (d, C-6) in the ^{13}C NMR spectrum indicated that a characteristic 3,5-dien-1-one system exist in rings A and B of **1** (Huang et al. 2009). Detailed comparison of the NMR spectral data of **1** with **4**, the upfield shift of H-7 from δ_H 4.01 to 3.46 in the ^{1}H NMR spectra and the downfield shift of C-7 from δ_C 63.5 to 72.5 in the ^{13}C NMR spectra, indicated that a hydroxyl group located at C-7 in **4** was replaced by a methoxyl group in **1**. Moreover, these assignments were further confirmed by ^{1}H, ^{1}H-COSY and HMBC experiments.

The relative stereochemistry of **1** was elucidated by the analysis of the NOESY spectrum and the coupling constant values. The NOESY correlations of H-7 (δ_H 3.46, 1H, t, $J = 4.6$ Hz) with H-6 and H-8 suggested that the 7-OCH_3 was α-oriented. Moreover, the smaller coupling of H-7 with H-8 which implied a pseudoequatorial position of H-7 further confirmed the α-orientation of 7-OCH_3. The configuration at C-22 was determined as *R* on the basis of the characteristic H-22 coupling constants at δ_H 4.49 (1H, dt, $J = 13.4$, 3.5 Hz) for the common related withanolides (Minguzzi et al. 2002; Ma et al. 2006). The rest of the configuration of **1** was

determined to be the same as that of **4** by comparing the NMR spectral data. Thus, the structure of **1** was identified as (22*R*)-27-hydroxy-7α-methoxy-1-oxowitha-3,5,24-trienolide.

Compound **2** was obtained as an amorphous powder, and its molecular formula was determined as $C_{35}H_{50}O_{10}$ by HR-EI-MS (*m/z* 630.3408 $[M]^+$, calculated for 630.3404) and ^{13}C NMR spectrum, which indicates 11 degrees of unsaturation. A careful comparison of the ^1H and ^{13}C NMR spectral data of **2** with those of **1** indicated that they were very similar, except for the presence of a β-glucopyranosyl moiety (anomeric proton: δ_H 5.06 [1H, d, $J = 7.8$ Hz, H-1′]; δ_C 104.7 [C-1′], 75.0 [C-2′], 78.4 [C-3′], 71.4 [C-4′], 78.3 [C-5′] and 62.6 [C-6′]) located at C-27 in **2**. This assignment was further confirmed by the downfield shift of C-27 from δ_C 57.6 to 63.3 in the ^{13}C NMR spectrum, and the HMBC correlation from the anomeric proton H-1′ to C-27 in **2**. It was obvious that compound **1** was the aglycone of **2**, and the stereochemistry of **2** was also same as that of **1** due to the similarities of the chemical shifts, the coupling constants and 2D NMR correlations between these two compounds. Accordingly, the structure of **2** was elucidated as (22*R*)-27-hydroxy-7α-methoxy-1-oxowitha-3,5,24-trienolide 27-*O*-β-D-glucopyranoside.

Compound **3** as a new natural product had been synthesised previously (Hirayama et al. 1982), and isolated from nature for the first time. The molecular formula of **3** was established as $C_{28}H_{38}O_4$ by means of a HR-EI-MS $[M]^+$ ion at *m/z* 438.2766 (calculated for 438.2770). The ^1H and ^{13}C NMR spectral data of **3** were closely related to those of **4** except for the absence of oxygenated methine signals (δ_H 3.85 [1H, br.s, H-7]; δ_C 64.3 [d, C-7]) in **3** (Kirson et al. 1971; Ma et al. 2006), indicating that no hydroxyl group was substituted at C-7 in the molecular formula of **3**. The other substitutions were in good agreement with that of **4**, and the full NMR spectral assignments for **3** were further confirmed by ^1H, ^1H-COSY, HSQC and HMBC experiments. Therefore, compound **3** was established as (22*R*)-27-hydroxy-1-oxowitha-2,5,24-trienolide.

In addition, two known withanolides, (22*R*)-7α,27-dihydroxy-1-oxowitha-2,5,24-trienolide (**4**) (Kirson et al. 1971; Ma et al. 2006) and daturataturin A (**5**) (Shingu et al. 1990; Ma et al. 2006), along with three other known ergostane-type steroids, namely (22*E*,24*R*)-5α,8α-epidioxy-ergosta-6,22-dien-3β-ol (**6**) (Kobori et al. 2006), (22*E*,24*R*)-5α,8α-epidioxy-ergosta-6,9(11),22-trien-3β-ol (**7**) (Kobori et al. 2006) and ergosta-5,24(28)-dien-3β-ol (24-methylenecholesterol, **8**) (Wu et al. 2011) were also isolated from *D. stramonium* L. in this study. The structures of these compounds were determined by MS, 1D NMR spectra and by comparison with the data of the literature reported.

3. Experimental

3.1 *General experimental procedures*

Optical rotations were determined on a Jasco P-1020 automatic digital polarimeter (Jasco, Japan). UV spectra were recorded on a Shimadzu UV-2401 PC spectrophotometer (Shimadzu, Japan). IR spectra were measured on a Jasco FT/IR-4100 spectrometer (Jasco, Japan) with KBr pellets. 1D and 2D NMR spectra were recorded on a Bruker Avance III 500 instruments (Bruker, Switzerland) with tetramethylsilane as an internal standard. ESI-MS were determined on a LCQ Fleet ion trap mass spectrometer (Thermo Fisher Scientific, San Jose, USA). HR-EI-MS were measured on AutoSpec Primier P776 mass spectrometer (Waters, Milford, USA). Column chromatography was performed over silica gel (200–300 mesh; Yantai Xinde Chemical Co. Ltd, Yantai, China), octadecyl silica (ODS) gel (YMC, Kyoto, Japan) and Sephadex LH-20 (Amersham Pharmacia Biotech, Uppsala, Sweden). Thin layer chromatography was performed on the silica gel plates (Yantai Xinde Chemical Co. Ltd, Yantai, China), and spots were visualised by spraying with 10% H_2SO_4 in EtOH followed by heating. Fractions were separated by preparative medium pressure liquid chromatography (MPLC) (Puriflash 450, Interchim

Company, France) on the flash chromatographic columns (Santai Technologies, Inc., Changzhou, China).

3.2. *Plant material*

The aerial parts of *D. stramonium* L. were collected from the seashores of the Yellow River Delta, Binzhou of Shandong Province, China, in September 2011, and identified by Prof Dongli Shi, Binzhou University. The voucher specimen (No. 20110903-1) was deposited at the Key Laboratory of Coastal Biology and Biological Resources Utilization, Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences.

3.3. *Extraction and isolation*

The air-dried aerial parts (2.4 kg) of *D. stramonium* were extracted with MeOH at room temperature (4 × 10 L). The extracts were combined and concentrated, and the residue (319 g) was suspended in H_2O, and then successively partitioned with petroleum ether (PE), EtOAc, and *n*-BuOH, respectively. The PE-soluble extract (96.8 g) was subjected to silica gel column chromatography (PE:acetone, 1:0 to 1:5, v/v) on preparative MPLC to afford 10 fractions (A1–A10). Fraction A2 (7.6 g) was subjected to Sephadex LH-20 using $CHCl_3$:MeOH (1:1, v/v) and ODS column with gradient eluting (MeOH:H_2O, 50:50 to 100:0, v/v), and then further purified on silica gel chromatography column (PE:acetone, 4:1 and 5:1) to afford a mixture of **6** and **7** (12.0 mg) and **8** (4.6 mg). Fraction A6 (3.6 g) was also performed on Sephadex LH-20 and ODS columns, and finally purified on silica gel columns with PE:acetone (4:1) and $CHCl_3$:acetone (20:1) to yield **1** (23.5 mg) and **3** (15.7 mg), respectively. The EtOAc-soluble fraction (24.5 g) was subjected to silica gel column on preparative MPLC using PE/acetone system with gradient eluting to get 11 fractions (B1–B11). Fraction B5 was subjected to Sephadex LH-20 and repeated column chromatography over silica gel to obtain **4** (28.0 mg). Fraction B6 was purified on silica gel column ($CHCl_3$:MeOH, 10:1) and an ODS column (MeOH:H_2O, 45:55) to get **2** (11.4 mg). Compound **5** (146 mg) was obtained from fraction B8 after purification by a silica gel column using $CHCl_3$:MeOH (10:1) system.

3.3.1 *(22R)-27-hydroxy-7α-methoxy-1-oxowitha-3,5,24-trienolide (**1**)*

An amorphous powder; $[\alpha]_D^{16.3}$ −4.3 (c = 0.11, MeOH); UV (MeOH) λ_{max} (log ε) nm: 223 (3.39); IR (KBr) ν_{max} (cm^{-1}): 3433, 2939, 1705, 1454, 1396, 1188, 1126, 1084; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.14 (dd, J = 9.9, 2.1 Hz, H-4), 5.98 (d, J = 5.1 Hz, H-6), 5.83 (ddd, J = 9.6, 4.6, 3.0 Hz, H-3), 4.49 (1H, dt, J = 13.4, 3.5 Hz, H-22), 4.42 (1H, d, J = 12.6 Hz, H-27a), 4.38 (1H, d, J = 12.6 Hz, H-27b), 3.46 (1H, t, J = 4.6 Hz, H-7), 3.33 (3H, s, 7-OCH_3), 3.31 (1H, m, H-2a), 2.81 (1H, dd, J = 20.5, 4.5 Hz, H-2b), 2.53 (1H, m, H-23a), 2.19 (1H, m, H-9), 2.07 (3H, s, H-28), 2.06 (1H, m, H-23b), 2.04 (1H, m, H-20), 1.96 (1H, m, H-12a), 1.88 (1H, m, H-11a), 1.73 (1H, m, H-16a), 1.72 (1H, m, H-15a), 1.63 (1H, m, H-14), 1.55 (1H, m, H-8), 1.39 (1H, m, H-16b), 1.37 (1H, m, H-11b), 1.36 (3H, s, H-19), 1.36 (1H, m, H-12b), 1.24 (1H, m, H-17), 1.21 (1H, m, H-15b), 1.05 (3H, d, J = 6.7 Hz, H-21), 0.75 (3H, s, H-18). ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.1 (C-1), 167.1 (C-26), 153.0 (C-24), 145.0 (C-5), 129.3 (C-4), 125.6 (C-25), 124.9 (C-3), 124.5 (C-6), 78.9 (C-22), 72.5 (C-7), 57.6 (C-27), 56.5 (7-OCH_3), 52.8 (C-10), 51.9 (C-17), 49.1 (C-14), 42.7 (C-13), 39.6 (C-2), 39.1 (C-12), 38.9 (C-20), 36.8 (C-8), 34.4 (C-9), 29.8 (C-23), 27.3 (C-16), 24.0 (C-15), 22.3 (C-11), 20.0 (C-28), 19.6 (C-19), 13.3 (C-21), 11.6 (C-18). Positive ESI-MS: *m/z* 491 $[M + Na]^+$; HR-EI-MS: *m/z* 468.2879 $[M]^+$ (calculated for $C_{29}H_{40}O_5$, 468.2876).

3.3.2 *(22R)-27-hydroxy-7α-methoxy-1-oxowitha-3,5,24-trienolide 27-O-β-D-glucopyranoside (**2**)*

An amorphous powder; $[\alpha]_D^{16.3}$ −16.4 ($c = 0.09$, MeOH); UV (MeOH) λ_{max} (log ε) nm: 215 (3.19); IR (KBr) ν_{max} (cm^{-1}): 3413, 2935, 1701, 1454, 1396, 1192, 1076, 1045; ^{1}H NMR (500 MHz, C_5D_5N): δ 6.19 (1H, br.d, $J = 9.9$ Hz, H-4), 6.08 (1H, d, $J = 5.1$ Hz, H-6), 5.78 (1H, ddd, $J = 9.7$, 4. 6, 3.0 Hz, H-3), 5.07 (1H, d, $J = 10.9$ Hz, H-27a), 5.06 (1H, d, $J = 7.8$ Hz, H-1′), 4.85 (1H, d, $J = 10.9$ Hz, H-27b), 4.59 (1H, dd, $J = 11.8$, 2.4 Hz, H-6′a), 4.43 (1H, dd, $J = 11.8$, 5.3 Hz, H-6′b), 4.36 (1H, dt, $J = 13.2$, 3.4 Hz, H-22), 4.28 (1H, m, H-3′), 4.28 (1H, m, H-4′), 4.08 (1H, m, H-2′), 4.00 (1H, m, H-5′), 3.44 (1H, t, $J = 4.5$ Hz, H-7), 3.38 (1H, dt, $J = 20.5$, 2.9 Hz, H-2a), 3.32 (3H, s, 7-OCH_3), 2.81 (1H, dd, $J = 20.5$, 4.4 Hz, H-2b), 2.51 (1H, td, $J = 12.2$, 4.5 Hz, H-9), 2.27 (1H, m, H-23a), 2.16 (3H, s, H-28), 2.01 (1H, m, H-11a), 1.96 (1H, m, H-23b), 1.91 (1H, m, H-20), 1.86 (1H, m, H-12a), 1.73 (1H, m, H-14), 1.68 (1H, m, H-15a), 1.53 (1H, m, H-16a), 1.51 (1H, m, H-8), 1.37 (1H, m, H-11b), 1.35 (3H, s, H-19), 1.22 (1H, m, H-12b), 1.17 (1H, m, H-16b), 1.14 (1H, m, H-15b), 1.01 (1H, m, H-17), 0.96 (3H, d, $J = 6.6$ Hz, H-21), 0.63 (3H, s, H-18). ^{13}C NMR (125 MHz, C_5D_5N): δ 208.9 (C-1), 165.7 (C-26), 156.8 (C-24), 145.0 (C-5), 129.3 (C-4), 126.5 (C-3), 125.1 (C-6), 122.8 (C-25), 104.7 (C-1′), 78.4 (C-3′), 78.3 (C-5′), 78.0 (C-22), 75.0 (C-2′), 72.5 (C-7), 71.4 (C-4′), 63.3 (C-27), 62.6 (C-6′), 56.0 (7-OCH_3), 53.0 (C-10), 51.8 (C-17), 49.0 (C-14), 42.5 (C-13), 39.7 (C-2), 39.2 (C-12), 38.9 (C-20), 36.7 (C-8), 34.6 (C-9), 29.6 (C-23), 26.9 (C-16), 24.0 (C-15), 22.4 (C-11), 20.3 (C-19), 19.4 (C-28), 13.2 (C-21), 11.4 (C-18). Positive ESI-MS: *m/z* 653 $[M + Na]^+$; HR-EI-MS: *m/z* 630.3408 $[M]^+$ (calculated for $C_{35}H_{50}O_{10}$, 630.3404).

3.3.3 *(22R)-27-hydroxy-1-oxowitha-2,5,24-trienolide (**3**)*

An amorphous powder; $[\alpha]_D^{16.4}$ + 40.3 ($c = 0.06$, MeOH); UV (MeOH) λ_{max} (log ε) nm: 214 (3.34); IR (KBr) ν_{max} (cm^{-1}): 3429, 2931, 1697, 1458, 1392, 1188, 1130, 1026; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (1H, ddd, $J = 10.0$, 5.0, 2.5 Hz, H-3), 5.90 (1H, ddd, $J = 10.0$, 3.1, 1.1 Hz, H-2), 5.59 (1H, br.d, $J = 6.1$ Hz, H-6), 4.47 (1H, dt, $J = 13.3$, 3.5 Hz, H-22), 4.43 (1H, d, $J = 12.6$ Hz, H-27a), 4.38 (1H, d, $J = 12.6$ Hz, H-27b), 3.31 (1H, br.d, $J = 21.3$ Hz, H-4a), 2.85 (1H, dd, $J = 21.3$, 4.9 Hz, H-4b), 2.54 (1H, dd, $J = 17.6$, 13.8 Hz, H-23a), 2.24 (1H, m, H-11a), 2.07 (3H, s, H-28), 2.04 (1H, m, H-23b), 2.04 (1H, m, H-20), 2.02 (1H, m, H-12a), 1.97 (1H, m, H-7a), 1.70 (1H, m, H-16a), 1.69 (1H, m, H-9), 1.66 (1H, m, H-15a), 1.58 (1H, m, H-7b), 1.52 (1H, m, H-11b), 1.45 (1H, m, H-8), 1.38 (1H, m, H-16b), 1.37 (1H, m, H-12b), 1.26 (3H, s, H-19), 1.18 (1H, m, H-15b), 1.16 (1H, m, H-17), 1.13 (1H, m, H-14), 1.06 (3H, d, $J = 6.7$ Hz, H-21), 0.77 (3H, s, H-18). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.5 (C-1), 167.1 (C-26), 152.9 (C-24), 145.2 (C-3), 136.0 (C-5), 128.0 (C-2), 125.7 (C-25), 124.7 (C-6), 78.9 (C-22), 57.5 (C-27), 56.2 (C-14), 52.1 (C-17), 50.6 (C-10), 42.9 (C-9), 42.7 (C-13), 39.7 (C-12), 38.9 (C-20), 33.5 (C-4), 33.2 (C-8), 30.8 (C-7), 29.8 (C-23), 27.3 (C-16), 24.3 (C-15), 23.6 (C-11), 20.0 (C-28), 19.0 (C-19), 13.3 (C-21), 11.9 (C-18). Positive ESI-MS: *m/z* 461 $[M + Na]^+$; HR-EI-MS: *m/z* 438.2766 $[M]^+$ (calculated for $C_{28}H_{38}O_4$, 438.2770).

Supplementary material

Supplementary material relating to this article is available online, alongside Figures S1–S18.

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