New Pyrrole Alkaloids from *Solanum sodomaeum*

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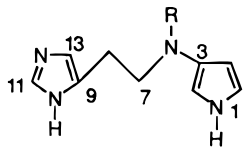
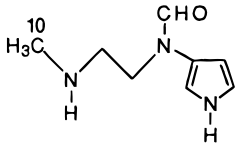
Two new pyrrole alkaloids, solsodomine A and B, were isolated from the fresh berries of *Solanum sodomaeum* L., collected from the Libyan desert. The structures of these compounds were established by 2D-NMR, including ^{15}N NMR spectroscopy and chemical degradation. Solsodomine A (**1**) shows activity against *Mycobacterium intracellulare*. This is the first report of pyrrole alkaloids from the genus *Solanum*.

Solanum is one of the largest genera in the plant kingdom. It includes about 1400 species widely distributed throughout the world.[1,2] *Solanum* has been extensively studied for its steroidal alkaloids, nitrogen-containing compounds, and isoprenoids.[3] *Solanum* alkaloids exhibit an interesting range of bioactivity. Solapartine, solapalmitine, and solapalmitenine show tumor inhibitory activity against human nasopharynx carcinoma (KB).[4] Solamargine possesses potent cytotoxic activity to human hepatocyte (Hep3B) and normal skin fibroblasts.[5] Other *Solanum* alkaloids show significant antifungal and antihepatotoxic activities.[6,7] *Solanum sodomaeum* L. (Solanaceae) is an annual herb, wildly distributed in the Libyan desert.[8] A topical formulation containing purified glycoalkaloids from *S. sodomaeum* L. has proven effective in the treatment of malignant human skin tumors; basal cell carcinomas, squamous cell carcinomas, and the benign tumors; keratoses, and keratoacanthomas.[9] Another study of the mixture of glycoalkaloids extracted from the title plant indicated its antineoplastic activity against Sarcoma 180 in mice.[10] This paper represents the first study of the less polar nonsteroidal alkaloids from *S. sodomaeum* and the first report for pyrrole alkaloids from the genus *Solanum*.

The alkaloid-containing extract of fresh berries of *S. sodomaeum* L. was fractionated into the less polar ($CHCl_3$) and the more polar (EtOAc) fractions. Unlike the EtOAc fraction, the $CHCl_3$ fraction did not give positive Lieberman−Burchard, Salkowski, or Molish's tests, indicating the absence of steroidal glycosides.[11] TLC screening of the $CHCl_3$ fraction indicated the presence of alkaloids by a positive Dragendorff's test.[11] Fractionation of the $CHCl_3$ extract on silica gel 60 afforded two new pyrrole alkaloids, named solsodomine A (**1**) and B (**2**). The FTIR spectra of **1** showed absorptions at 3465 and 1657 cm^{-1}, suggesting the presence of NH and *N*-formyl functionalities. The CIMS spectra of **1** displayed a molecular ion peak at *m*/*z* 204, consistent with the molecular formula $C_{10}H_{12}ON_4$ and the presence of seven degrees of unsaturation. The proton singlet at δ 9.40 is correlated to a methine carbon resonating at δ 179.1, indicating the presence of an *N*-formyl group (Table 1). The downfield methylene triplet (δ 4.44) is correlated by the HMQC experiment to the nitrogenated methylene carbon at δ 48.6 (C-7). The C-7 methylene group displayed COSY coupling to another methylene triplet (δ 2.93), which is correlated in the HMQC spectrum to the methylene carbon at δ 28.6 (C-8). The presence of the pyrrole functionality was indicated from the two COSY-coupled doublet of doublets resonating at δ 6.05 and 6.87, correlating to the two methine carbons at δ 109.3 and 125.3 (C-4 and C-5, respectively). Both protons (δ 6.05 and 6.87) show long-range COSY couplings to a broad proton singlet resonating at δ 6.75, correlated to the methine carbon at δ 131.9 (C-2). The imidazole moiety was suggested from the two long-range COSY-coupled singlets resonating at δ 7.47 and 6.57, which are correlated to the methine carbons absorbing at δ 134.2 and 116.6 (C-11 and C-13 respectively). Analysis of the HMBC data of **1** further supported the proposed structure (Figure 1). The ^3J-HMBC correlations of H-14 with C-3 and C-7 supported its location on N-6. The ^3J-HMBC correlations of H-2 with C-4 and C-5 further supported the pyrrole ring entity. The same proved true for the imidazole ring with ^3J-HMBC correlations between H-11, C-9, and C-13. Additional confirmation was obtained from the analysis of ^{1}H−^{15}N HMBC data (Figure 1, Table 1). The downfield nitrogen resonating at δ 225.2 (N-10) show ^3J-HMBC correlations to H-8 and H-13, in addition to a ^2J-HMBC correlation to H-11. The nitrogen resonating at δ 190.8 (N-12) shows ^2J-HMBC correlations to H-11 and H-13. The nitrogen (N-1) resonating at δ





R — **2**

1 CHO

3 H

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Table 1. ^{13}C and ^{1}H NMR Spectral Data of Compounds **1** and **2**[a]

	1			2	
position	δ_C	δ_H	δ_N	δ_C	δ_H
1		5.86, br s	165.8		5.87, br s
2	131.9, d	6.75, br s		132.9, d	7.03, br s
3	130.4, s			132.8, s	
4	109.3, d	6.05 dd (4.0, 2.5)		109.8, d	6.22 dd (4.1, 2.5)
5	125.3, d	6.87 dd (4.0, 2.4)		125.7, d	6.96 dd (4.1, 2.4)
6			165.6		
7	48.6, t	4.44 t (7.2)		51.1, t	4.42 t (7.1)
8	28.6, t	2.93 t (7.3)		50.3, t	3.84 t (7.2)
9	133.5, s				u
10		5.86, br s	225.2	31.8, q	3.41, s
11	134.2, d	7.47, s			
12			190.8		
13	116.6, d	6.57, s			
N_6−formyl	179.1, d	9.40, s		179.8, d	9.42, s

[a] In $CDCl_3$, at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 50 MHz for ^{15}N. Carbon multiplicities were determined by the DEPT 135° experiment; s = quaternary, d = methine, t = methylene, q = methyl carbons, u = unobserved; coupling constants (*J*) are in Hz.

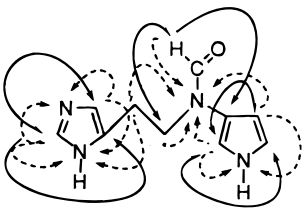

Figure 1. Important $^{1}H-^{13}C$ (solid lines) and $^{1}H-^{15}N$ (dashed lines) HMBC correlations of **1**.

165.8 shows ^{2}J-HMBC correlations to H-2 and H-5, as well as a ^{3}J-HMBC correlation to H-4. Similarly, the nitrogen (N-6) absorbing at δ 165.6 showed ^{2}J-HMBC correlations to H-7 and the downfield *N*-formyl proton singlet, in addition to ^{3}J-HMBC correlations to H-2, H-4, and H-8. The downfield shifting of the aliphatic N-6 is attributed to the deshielding effect of the *N*-formyl moiety. Acid hydrolysis of **1** afforded **3** which has similar ^{1}H NMR spectral data except for the absence of the *N*-formyl signal.

The CIMS spectra of solsodomine B (**2**) displayed a molecular ion peak at *m*/*z* 168 $[M + H]^+$, consistent with the molecular formula $C_8H_{13}ON_3$ and the presence of four degrees of unsaturation. The FTIR and ^{1}H and ^{13}C NMR spectra (Table 1) of **2** showed distinct similarity to those of **1** except for the lack of the imidazole moiety and the emergence of a new *N*-methyl group. The proton singlet resonating at δ 3.41 correlated to the methyl carbon at δ 31.8 (C-10). The downfield shift of the methylene proton triplet resonating at δ 3.84 and correlated to the methylene carbon at δ 50.3 is attributed to the nitrogenated C-8.

Solsodomine A (**1**) shows moderate activity against *Mycobacterium intracellulare* with an MIC of 10 μg/mL. Compounds **1** and **2** did not show *in vitro* antimalarial activity against *Plasmodium falciparum* W2 and D6 clones, cytotoxic activity to Vero cells, or antifungal activity against *Cryptococcus neoformans* and *Candida albicans*.

This is the first report for pyrrole alkaloids in the genus *Solanum*; however, they have been previously reported in the family Solanaceae from *Nicotiana bigelovii* and *Nicotiana setchellii* .[2]

Experimental Section

General Experimental Procedures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. UV spectra were acquired on a Perkin-Elmer Lambda 3B UV/vis spectrophotometer. The IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 spectrometer. The ^{15}N NMR was recorded on a Bruker DRX-500 spectrometer. The LRCIMS spectra were obtained at the University of Kansas on a Fisons/VG Autospec Q mass spectrometer. TLC analysis was carried out on precoated silica gel G_{254} (Merck) or aluminum oxide ALOX-100 UV_{254} (Macherey-Nagel) plates. For column chromatography, Baker silica gel 60, 40 μm was used.

Plant Material. Fresh *S. sodomaeum* L. berries were collected near Tripoli during spring 1994. The plant was identified by Dr. A. El-Gadi, Department of Botany, Al Faateh University, Tripoli, Libya. A voucher specimen (94Trip-3) was deposited at Pharmacognosy Department, Mansoura University, Egypt.

Extraction and Isolations. Fresh *S. sodomaeum* L. berries (4.5 kg) were minced, and the formed paste was extracted twice each with 2 L of 95% hot ethanol and concentrated under reduced pressure. The semi-solid ethanolic extract (750 g) was treated with 1 L of 5% aqueous tartaric acid and filtered. The filtrate was extracted twice, each with 1 L of $CHCl_3$. The acid-soluble fraction was alkalinized to pH 9, using concentrated NH_4OH, and then extracted with $CHCl_3$ (1 L × 3) followed by EtOAc (1 L × 3). The chloroform fraction was subjected to repeated column chromatography on silica gel 60 using *n*-hexane and gradient elution with EtOAc. The alkaloid-containing fractions were further subjected to preparative TLC on Al_2O_3, using cyclohexanes−EtOAc (2:1) to afford compounds **1** (85.5 mg, R_f 0.45) and **2** (2.2 mg, R_f 0.71).

Solsodomine A (1): yellow needles from EtOH; mp 118−119 °C; UV λ_{max} (log ϵ) (MeOH) 280 (3.08), 320 (3.06), 348 (2.93) nm; IR υ_{max} ($CHCl_3$) 3465, (NH), 3006−2931, 1657 (N−CH=O) cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; LR-CIMS *m*/*z* (fragment) 204.0 (M^+, 15) (calcd for $C_{10}H_{12}ON_4$, 204.10), 190.0 (95), 176 (25), 162 (65), 94 (55), 81 (30), 69 (20).

Acid Hydrolysis of 1. Forty mg of **1** was dissolved in 1 mL of EtOH, and 5 mL of 6 N HCl was added. The reaction mixture was heated for 120 min at 80 °C. The pH was adjusted to 7, using dilute NH_4OH, and then the reaction mixture was extracted with $CHCl_3$ (15 mL × 2). The $CHCl_3$ solution was evaporated and subjected to preparative TLC on silica gel G_{254} using $CHCl_3$−MeOH (9:1) to afford compound **3** (3.8 mg, R_f 0.32).

Solsodomine B (2): colorless needles from EtOH; mp 112−113 °C; UV λ_{max} (logϵ) (MeOH) 271 (3.10), 317 (3.01), 342 (2.03) nm; IR υ_{max} ($CHCl_3$) 3455, (NH), 2995−2930, 1655 (N−CH=O) cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; LR-CIMS *m*/*z* (fragment) 168.0 $[(M + H), 10]^+$ (calcd for $C_8H_{14}ON_3$, 168.11), 124.0 (100), 79 (15), 43 (50).

Compound 3: yellow needles from EtOH; mp 122−123 °C; UV λ_{max} (log ϵ) (MeOH) 266 (2.99), 319 (3.11),

341 (2.71) nm; IR υ_{max} ($CHCl_3$) 3455, (NH), 3010−2950 cm^{-1}; ^1H NMR data (400 MHz, $CDCl_3$) δ 6.42 (1H, brs, H-2), 6.10 (1H, dd (4.0, 2.1), H-4), 6.53 (1H, dd (4.0, 2.2), H-5), 3.97 (2H, t (7.1), H7), 2.96 (2H, t (7.1), H-8), 7.43 (1H, s, H-11), 6.56 (1H, s, H-13).

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