SYNTHESIS OF S-CONTAINING DERIVATIVES OF THE SESQUITERPENE LACTONE BRITANIN

N. P. Artemova,[1] L. E. Nikitina,[1] D. A. Yushkov,[1] O. G. Shigabutdinova,[1] V. V. Plemenkov,[1] V. V. Klochkov,[2] and B. I. Khairutdinov[2]

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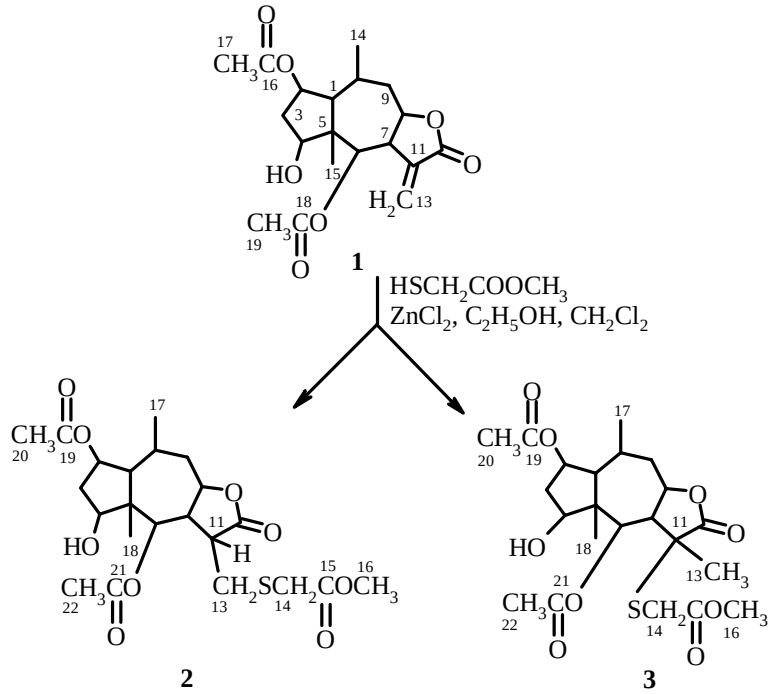
The optimal method for isolating the sesquiterpene lactone britanin from the aerial part of Inula britannica *L. (Asteraceae) was developed. Britanin was functionalized by reacting it with methyl mercaptoacetate.*

Key words: *Inula britannica*, britanin, sesquiterpene lactones and their S-containing derivatives.

Sesquiterpene lactones of *Inula britannica* L. (Asteraceae) have a variety of structures and pharmacological activities [1-3]. One of the principal lactones of this species is britanin pseudoguaianolide (**1**), which exhibits antiprotozoic, antibacterial, and antifungal activities [4]. Terpenoids containing a sulfide exhibit antitumor effects [5] and antimalarial activity [6, 7]. Therefore, chemical modification of britanin is certainly of practical interest.



1 **2** **3**

We investigated the aerial part of *I. britannica* growing in the Volzhsko-Kamsk region as a source of britanin. Three methods of processing the raw material were investigated in order to select the optimal method of extracting it. These were water extraction, treatment with hexane followed by water extraction, and chloroform extraction. The first two methods are more convenient for isolating britanin (the lactone crystallizes from the extract) and give the highest yields (0.125-0.15%). The

1) Kazan′ State Medical University, 420012, Kazan′, ul. Butlerova, 49, e-mail: nikit@mi.ru; 2) Kazan′ State University. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 37-38, January-February, 2005. Original article submitted August 2, 2004.

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last method typically has a lower yield (0.014%) due to unavoidable losses of the lactone during separation of the multicomponent (acccording to TLC) extract by column chromatography.

The yield of lactone from leaves and flowers (0.005 and 0.04%, respectively) is generally less than from the whole aerial part.

Therefore, britanin was extracted from the whole aerial part (herb) of *I. britannica* by water extraction with preliminary hexane treatment as the optimal method for isolating britanin.

Britanin (**1**) was identified by IR, PMR, and mass spectrometry and by comparison with the literature [1].

We studied the reaction of britanin with methyl mercaptoacetate because the functionalization of britanin by S-containing reagents has not been reported. The reaction of **1** with the S-containing reagent produced two products **2** and **3** via addition to the exocyclic double bond. The ratio of **2** and **3** in the reaction mixture was 3:1 according to GC.

The structure of **2** was established using PMR and ^{13}C NMR DEPT spectroscopy; the structure of **3**, using PMR spectroscopy.

The presence in the PMR spectrum of **2** of signals for only five methyls (0.92, 1.00, 2.00, 2.18, 2.23 ppm) indicates that the reaction proceeded against the Markovnikov rule. This was confirmed by ^{13}C NMR DEPT spectroscopy, which indicated the presence of signals for five methyls, four methylenes, and eight methines. The results agree with the pattern of electron-density distribution in britanin.

EXPERIMENTAL

The course of reactions and the purity of products (**1**-**3**) were monitored by TLC on Silufol UV-254 plates using petroleum ether:$CHCl_3$:ethylacetate (1:1:4) and alcoholic anisaldehyde (2%) and conc. H_2SO_4 developer.

PMR and ^{13}C NMR spectra of **1**-**3** in $CDCl_3$ were measured on a Varian UNITY spectrometer (working frequency 300 and 75.43 MHz) with TMS internal standard; IR spectra, in mineral oil on a Specord-75 IR spectrometer. Mass spectra of **1** were obtained in an Incos-50B mass spectrometer in combination with a Varian-3400 GC with a capillary column, SE-30 phase, 0.25 mm diameter, ionizing-electron energy 70 eV, injector temperature 250°C, and ion-source temperature 150°C.

Isolation of Britanin (1). Raw material (herb, leaves, flowers of *I. britannica* L.) was collected during the start of flowering under natural habitat conditions near Kazan′ in July-August 2000-2002. **1** was isolated using ground (10 mm) and air-dried raw material.

Water Extraction. Raw material was extracted three times with hot water (80°C) in a 1:5 ratio. The water extract was treated with $CHCl_3$. Crystallizing resins were obtained after the $CHCl_3$ was removed from the extracts of the aerial part (herb) and flowers and were treated with diethylether. Four recrystallizations from ethanol isolated **1** as colorless crystals from the aerial part (0.25 g, 0.125%) and flowers (0.06 g, 0.04%). Crystallization was not observed in the extract from leaves. Therefore, the resin was chromatographed over a silica-gel column with elution by C_6H_{14}:$CHCl_3$ mixtures and $CHCl_3$ to afford **1** (0.01 g, 0.005%), R_f 0.52 (petroleum ether:$CHCl_3$:ethylacetate, 1:1:4), mp 189-190°C, $[M]^+$ 365.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.00 (3H, d, H-14), 1.05 (3H, s, H-15), 2.07, 2.28 (6H, s, s, H-17, H-19), 3.05 (1H, m, H-7), 4.15 (1H, dd, J = 8, J = 11, H-4), 4.56 (1H, m, H-8), 4.92 (1H, m, H-2), 5.10 (1H, d, J = 8, H-6), 5.40, 6.20 (2H, AB centers, J = 3, H-13).

IR spectrum (ν, cm^{-1}): 3540 (OH), 1760 (γ-lactone carbonyl), 1730, 1250 (OCO), 1680 (C=C).

Mass spectrum (*m*/*z*, I_{rel}, %): 365 (0.7) $[M - 1]^+$, 362 (66.5), 319 (20.5), 291 (100), 279 (64.0), 259 (31.9), 225 (30.7), 219 (63.5), 213 (10.5), 175 (11.0), 159 (11.6), 145 (22.5), 131 (12.9), 128 (16.0), 115 (23.2), 91 (21.7), 82 (16.8), 67 (16.5), 55 (32.6).

Hexane Treatment Followed by Water Extraction. The aerial part of the plant (200 g) was treated hexane in a 1:5 ratio at room temperature. The extract with the lipophilic components was removed. Then the process was performed as described above to afford **1** (0.30 g, 0.15%).

$CHCl_3$ Extraction. The aerial part of the plant (200 g) was exhaustively extracted with $CHCl_3$. The combined $CHCl_3$ extracts were evaporated and treated with ethanol (60%). Then compounds were extracted from the aqueous alcohol solution by $CHCl_3$. The resulting resin was chromatographed over a silica-gel column with elution by C_6H_{14}:$CHCl_3$ mixtures and $CHCl_3$ to afford **1** (0.028 g, 0.014%).

Synthesis of S-containing Derivatives of 1 (2, 3). A solution of **1** (0.82 mmol) in CH_2Cl_2 was stirred and treated at room temperature with methyl mercaptoacetate (1.07 mmol) and $ZnCl_2$ (0.055 g) dissolved in ethanol (2 mL), treated with water (200 mL) after 24 h, extracted with CH_2Cl_2, and dried over $MgSO_4$. Solvents were removed. Products were isolated by column chromatography over silica gel (petroleum ether:$CHCl_3$:ethylacetate with increasing polarity) as oily liquids.

Methyl Ester of 2α,6α-Diacetoxy-4β-hydroxy-7α(H),8,10β(H)-pseudoguai-8,12-olidylmethylenethioacetic Acid (2). R_f 0.26 (petroleum ether:$CHCl_3$:ethylacetate, 1:1:4).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.92 (3H, d, H-17), 1.00 (3H, s, H-18), 2.00, 2.18, 2.23 (9H, s, s, s, H-16, H-20, H-22), 2.78 (1H, m, H-11), 3.27, 3.40 (2H, AB centers, J = 15.6, H-13), 3.70 (2H, s, H-14).

^{13}C NMR DEPT spectrum (75.43 MHz, $CDCl_3$): 16.6, 19.9 (C-17, C-18), 17 (C-5), 21.4 (C-20, C-22), 29.6 (C-11), 31.1, 35.2 (C-3, C-9), 36.1 (C-13), 43.1 (C-14), 47.9, 49.4, 50.9 (C-1, C-7, C-10), 52.6 (C-16), 73.0, 75.1, 77.2, 77.3 (C-2, C-4, C-6, C-8), 170.4, 170.9, 171.9 (C-15, C-19, C-21), 175.5 (C-12).

Methyl Ester of 2α,6α-Diacetoxy-4β-hydroxy-7α(H),8,10β(H),13-methylpseudoguai-8,12-olidylthioacetic Acid (3). R_f 0.12 (petroleum ether:$CHCl_3$:ethylacetate, 1:1:4).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 0.85 (3H, d, H-17), 0.95 (3H, s, H-18), 2.00, 2.20, 2.27, 2.30 (12H, s, s, s, s, H-13, H-16, H-20, H-22), 3.75 (2H, s, H-14).

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