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New Heterocyclic Derivatives of Usnic Acid †

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Abstract: New heterocyclic derivatives of usnic acid have been obtained by the reaction of bromousnic acid with CS_2-based nucleophiles. A series of compounds with dithiolane, 1,3,4-thiadiazine, and thiophene fragments has been synthesized.

Keywords: usnic acid; dithiolanes; 1,3,4-thiadiazine; thiophene

1. Introduction

Usnic acid **1** (Figure 1) is a well-known secondary lichen metabolite, the derivatives of which, like itself, show a wide spectrum of biological activity: antibacterial, analgesic, immunomodulatory, antitumor, etc. [1–3]. Studies carried out over the past decades indicate that derivatives of usnic acid containing a heterocyclic substituent in the A ring are promising pharmacological agents for the treatment of a number of serious diseases, such as cancer and tuberculosis [4,5].

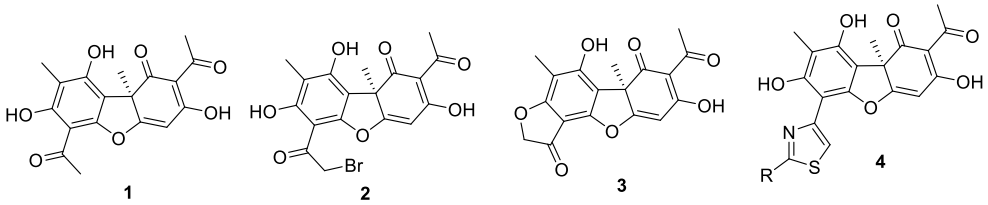


Figure 1. Usnic acid and its derivatives.

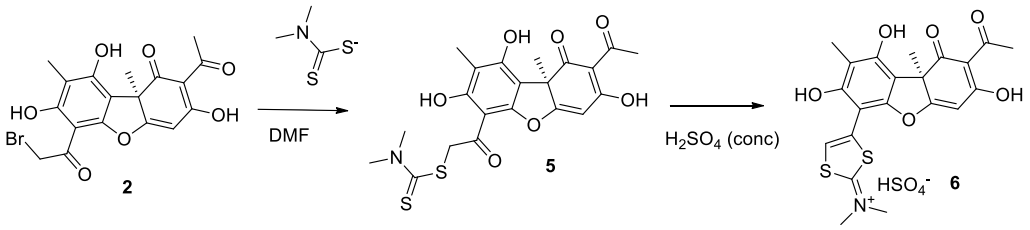
One of the most popular platforms for heterocycle substituent formation is bromine derivative of usnic acid **2** (Figure 1). Previously it was shown that the direction of the substitution reaction of the bromine atom varies with type of nucleophiles [6]. The reaction with N- and O-nucleophiles leads to an intramolecular nucleophilic substitution reaction with the formation of furanone **3** (Figure 1) [6], whereas reaction with 1,3-S,N-binucleophiles (thioureas, thioamides, thiosemicarbazones) leads to a desired substitution bromine atom with S followed by reaction of N-center with carbonyl group with formation of substituted thiazoles **4** (Figure 1) [4,5].

In this work, we have developed a technique for the synthesis of other then thiazole types of heterocyclic derivatives of usnic acid by the reaction compound 1 with CS2-based nucleophiles. A series of compounds with, dithiolane **5**, and thiophene **6** and **7** fragments has been synthesized.

2. Results and Discussion

Dithiolane **6** was prepared by the reaction of bromoderivative **2** with 1,3-S,S-binuclephile sodium N,N-dimethyldithiocarbamate (Scheme 1). The reaction was carried out in DMF, the substitution product for the bromine atom 10 was precipitated with water. The reaction of the second

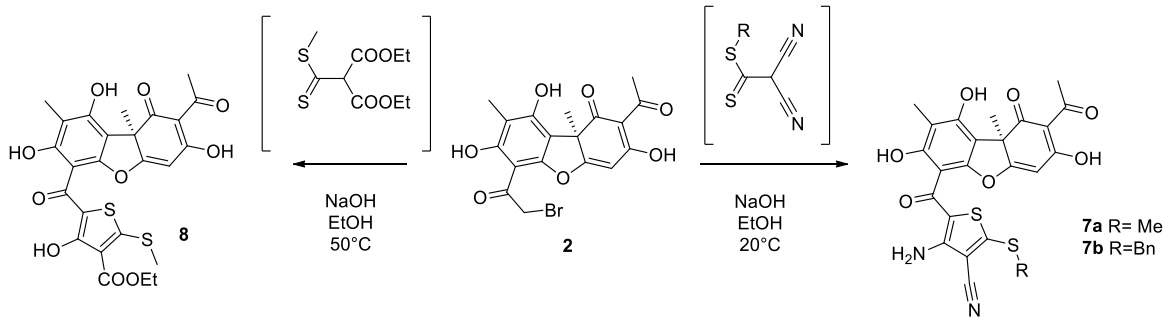
nucleophilic center with the carbonyl group proceeds in the presence of concentrated sulfuric acid and leads to the formation of the dithiolan ring. The yield of compound **6** in two stages was 67%.



Scheme 1. Synthesis of Usnic acid dithiolanic derivative.

In the absence of a reactive second nucleophilic center, the reaction of bromusnic acid **2** with the S-nucleophile proceeds without the involvement of the carbonyl group C13=O, the thiophene ring is formed on the adjacent methylene carbon atom. Thus, we have obtained heterocyclic derivatives of usnic acid **7** and **8** containing a thiophene substituent.

Alkylated (by methyl iodide or benzyl bromide action) dicyanodithioacetates **10a,b** and a dithioacetic acid derivative **11** were synthesized in situ by the reaction of carbon disulfide with malonodinitrile or diethyl malonate, respectively, in the presence of alkylating agents and potassium hydroxide (Scheme 3). To the resulting mixture was added the bromoderivative of usnic acid **2** and left to stir for 3 h at room temperature (for **7a**,**b**) and with heating (for **8**), the reaction products, the **7a**,**b** and **8** compounds precipitate upon addition of water and acidification with aqueous hydrochloric acid. (Scheme 3). Compounds **7a**,**b** and **8** were isolated in 90%, 50% and 90% yields, respectively.



Scheme 2. Synthesis of Usnic acid thiophene derivative.

3. Materials and Methods

3.1. Methods

Reagent-grade solvents were redistilled prior to use. Synthetic starting materials, reagents, and solvents were purchased from Sigma-Aldrich, Acros Organics, and AlfaAesar. Usnic acid bromine derivative was obtained by bromination of usnic acid as described in the paper [4].

The analytical and spectral studies were conducted at the Chemical Service Center for the collective use of Siberian Branch of the Russian Academy of Science.

The ^{1}H and ^{13}C-NMR spectra for solutions of the compounds in CDCl3 were recorded on a Bruker AV-400 spectrometer (400.13 and 100.61 MHz, respectively). The residual signals of the solvent were used as references (δ_H 2.48, δ_C 39.52 for DMSO-d_6 and δ_H 7.27, δ_C 77.1 for $CDCl_3$). The mass spectra (70 eV) were recorded on a DFS Thermo Scientific high-resolution mass spectrometer. The melting points were measured using a Kofler heating stage. Merck silica gel (63–200 μ) was used for the column chromatography. Thin-layer chromatography was performed on TLC Silica gel 60F254 (Merck KGaA, Darmstadt, Germany).

3.1.1. Synthesis of Usnic Acid Dithiolanic Derivative (6)

(a) The Usnic acid bromine derivative (2) (100 mg, 0.24 mmol) and sodium N,N-dimethyldithiocarbamate (38 mg, 0.24 mmol) were placed in a flask with 12 mL DMF. The reaction mixture was stirred for one hour at room temperature. Then, the solution was diluted with water and acidified (1 M HCI) until precipitation. The obtained precipitate was filtered, washed with water and dried in the air.

(2R)-4-acetyl-10-{2-[(dimethylcarbomothiol)sulfanyl]acetyl}-5,11,13-trihydroxy-2,12-dimethyl-8-oxatricyclo [7.4.0.02,7]trideca-1(13),4,6,9,11-pentaen-3-on (5): Yellow amorphous powder. Yeld: 95%. M.p. = 133–135 °C. δ_H ($CDCl_3$): 1.77 (3H, s), 2.09 (3H, s), 2.64 (3H, s), 3.46 (3H, s), 3.53 (3H, s), 4.92 (2H, s), 6.01 (1H, s), 11.11 (1H, s), 12.80 (1H, ss), 18.83 (1H, s). δc ($CDCl_3$): 7.37, 27.67, 31.88, 41.52, 45.62, 47.90, 58.77, 98.45, 100.85, 104.06, 104.99, 109.27, 154.66, 157.69, 163.45, 178.79, 191.44, 194.52, 195.21, 197.75, 201.55. HRMS: Found: m/z 463.0752 $[M]^+$ $C_{21}H_{21}O_7NS_2$. Calculated: M = 463.0754.

(b) Compound 5 was placed in 5 mL of sulfuric acid. The obtained solution was stirred for 15 min without heating (TLC control). After that, the reaction mixture was poured into a glass with 30 mL of diethyl ether and the precipitate was filtered. The product was purified by column chromatography.

4-[(1R)-12-acetyl-3,5,11-trihydroxy-1,4-dimethyl-13-oxo-8-oxatricyclo[7.4.0.02,7]trideca-2,4,6,9,11-pentaen-6-yl]-N,N-dimethyl-2H-1,3-dithiol-2-iminium hydrosulfate (6): Dark-brown amorphous powder. Yeld: 70%. δ_H (DMSO-d_6): 1.75 (3H, s), 2.09 (3H, s), 2.60 (3H, s), 3.54 (3H, s), 3.55 (3H, s), 7.97 (1H, s), 6.17 (1H, s), 10.62 (1H, s), 10.60 (1H, ss). δc (DMSO-d_6): 8.95, 27.44, 31.34, 46.72, 47.12, 59.12, 97.77, 97.81, 105.20, 105.56, 108.82, 121.71, 129.79, 151.67, 152.37, 153.68, 179.55, 186.99, 191.28, 197.93, 201.05.

3.1.2. Synthesis of Usnic Acid Thiophene Derivatives (**7a,b** and **8**)

Carbon sulfide (2.2 mmol) of sulfur carbon and malononitrile or diethylmalonate (1 mmol) was added to DMF (2 mL). Prepared solution of sodium hydroxide 1.1 mmol in 1 mL of water was added to the obtained solution. The mixture was left to be stirred on an ice bath for an hour. After that methyliodide or benzylbromide (1 mmol) was added to the mixture. The resulting mixture was stirred for 30 min at room temperature. Bromine derivative 2 was added to the reaction mixture. Resulting mixture was stirred at room temperature for an hour. After that, the reaction mixture was diluted with water and and acidified (1M HCI). The obtained precipitate was filtered, washed with water and dried.

5-[(1R)-12-acetyl-3,5,11-trihydroxy-1,4-imethyl-13-oxo-8-oxatricyclo[7.4.0.02,7]trideca-2,4,6,9,11-pentaen-6-carbonyl]-4-amino-2-(methylsulfanyl)thiophene-3-carbonitrile (7a): Yellow amorphous powder. Yeld 90%. M.p. = 110–112 °C. δ_H ($CDCl_3$): 1.72 (3H, s), 2.11 (3H, s), 2.58 (3H, s), 2.65 (3H, s), 5.86 (1H, s), 6.84 (2H, ss), 10.21 (1H, s), 10.75 (1H, s), 18.82 (1H, s). δc ($CDCl_3$): 7.52, 16.99, 27.42, 31.35, 58.80, 97.22, 97.53, 101.98, 103.40, 104.93, 108.68, 109.40, 111.8, 150.43, 155.47, 156.91, 159.35, 162.37, 178.72, 182.68, 191.26, 197.51, 201.20. IR (cm^{-1}): 543, 619, 659, 667, 746, 788, 819, 840, 862, 929, 958, 1029, 1051, 1070, 1118, 1184, 1322, 1369, 1409, 1459, 1492, 1556, 1625, 1683, 2215, 2925, 3155, 3319, 3428. HRMS: Found: m/z 498.0554 $[M]^+$ $C_{23}H_{18}O_7N_2S_2$. Calculated: M = 498.0550.

5-[(1R)-12-acetyl-3,5,11-trihydroxy-1,4-dimethyl-13-oxo-8-oxatricyclo[7.4.0.02,7]trideca-2,4,6,9,11-pentaen-6-carbonyl]-4-amino-2-(benzylsulfanyl)thiophene-3-carbonitrile (7b): Yellow amorphouspowder. Yeld 50%. M.p. = 104–105 °C δ_H ($CDCl_3$): 1.69 (3H, s), 2.11 (3H, s), 2.65 (3H, s), 4.22 (2H, s), 5.73 (1H, s), 6.79 (2H, ss), 7.28–7.30 (5H, m), 10.22 (1H, s), 10.76 (1H, s), 18.83 (1H, s). δc ($CDCl_3$): 7.46, 27.24, 31.32, 39.19, 58.54, 97.31, 99.26, 102.63, 103.19, 104.64, 108.87, 109.46, 111.74, 127.67, 128.11, 128.28, 133.68, 150.23, 154.66, 156.39, 158.11, 158.58, 178.72, 182.17, 191.00, 197.33, 200.93. IR (cm^{-1}): 459, 484, 509, 543, 561, 572, 617, 657, 669, 700, 730, 763, 777, 786, 817, 844, 900, 931, 958, 975, 1025, 1051, 1070, 1118, 1149, 1180, 1280, 1319, 1348, 1367, 1405, 1454, 1484, 1560, 1616, 1685, 2223, 2923, 2975, 3027, 3087, 3187, 3299, 3396. HRMS: Found: m/z 574.0860 $[M]^+$ $C_{29}H_{22}O_7N_2S_2$. Calculated: M = 574.0865.

Ethyl 5-[(1R)-12-acetyl-3,5,11-trihydroxy-1,4-dimethyl-13-oxo-8-oxatricyclo[7.4.0.02,7]trideca-2,4, 6,9,11-pentaen-6-carbonyl]-4-hydroxy-2-(methylsulfonyl)thiophene-3-carboxylate (8): Yellow amorphous

powder. Yeld: 90%. M.p. = 110–112 °C. δ_H ($CDCl_3$, J Hz): 1.36 (3H, t, *J* = 7.16), 1.67 (3H, s), 2.04 (3H, s), 2.58 (6H, s), 4.36 (2H, q, *J* = 7.16), 5.70 (1H, s), 10.83 (1H, s), 10.91 (1H, ss), 10.96 (1H, ss), 18.72 (1H, s). δ_C ($CDCl_3$): 7.33, 13.73, 16.56, 27.48, 31.55, 58.89, 61.66, 96.93, 101.71, 103.63, 104.74, 108.32, 112.66, 116.13, 153.61, 156.18, 160.33, 160.43, 162.12, 165.26, 178.72, 182.05, 191.26, 197.60, 201.17. HRMS: Found: m/z 546.0654 $[M]^+$ $C_{25}H_{22}O_{10}S_2$. Calculated: M = 546.0656.

4. Conclusions

Thus, we have developed a technique for the synthesis of new heterocyclic derivatives of usnic acid. The novel compounds can be considered as promising biologically active agents.

Author Contributions: Conceptualization, Data curation, Synthetic investigation, Writing—original draft, and review & editing, O.A.L. and A.S.F.; Supervision: N.F.S. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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