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New Dibenzofuran Compounds Obtained by Dihydrousnic Acid Hydrogenation †

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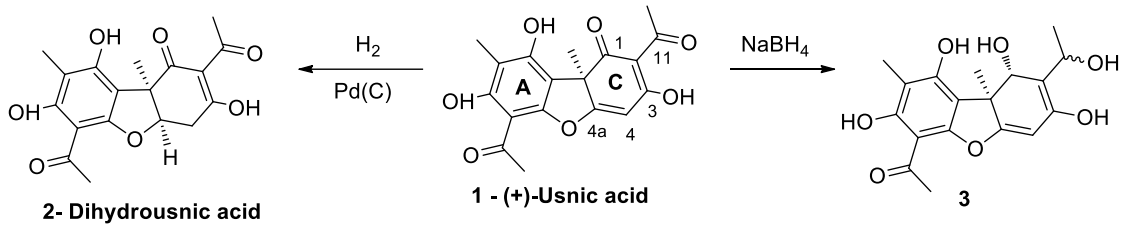
Abstract: It has been found that usnic acid carbonyl groups can be hydrogenated by the action the action of H2/Pd(C). The two new dibenzofuran derivatives have been synthysized.

Keywords: usnic acid; hydrogenation

1. Introduction

(+)-Usnic acid (1) is a commercially available lichen metabolite. Its biological activity is diverse: from antibacterial and anticancer to immunomodulating [1]. Its biological properties, as well as broad occurrence in various lichen species and high optical purity of the isolated product make it promising as a base for developing novel pharmaceuticals.

Earlier it was shown that the interaction of (+)-usnic acid 1 with reducing agents occurs along the C ring of the dibenzofuran core. The reaction proceeds under the action of H2/Pd(C) through the reduction of the C4-C4a double bond with the formation of dihydrousnic acid 2, or under the action of sodium borohydride through the reduction of C1=O and C11=O carbonyl groups to hydroxyl ones with the formation of mixture of diastereomeric compounds 3 [2].



Scheme 1. Hydrogenation of usnic acid by different reagents.

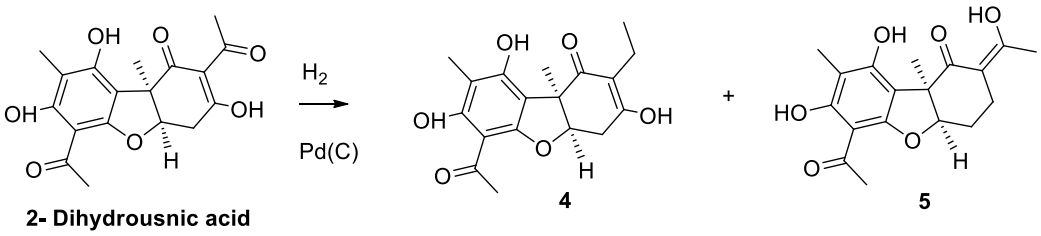
We found that further hydrogenation of dihydrousnic acid in H2/Pd (C) led to the two new products.

2. Results and Discussion

The hydrogenation was carried out in THF at room temperature and atmospheric pressure. Based on the ^{13}C and ^{1}H NMR spectra, the reaction proceeds in ring C, since the signals related to the atoms of ring A remain unchanged. Also, the position of the signals in the ^{1}H and ^{13}C spectra for CH(4a) also remained unchanged, which indicates that the furan cycle remains closed. Consequently, the carbonyl groups of ring C were subjected to reduction. For each of the products, reduction of only one of the three carbonyl groups of ring C was observed. Hydrogenation of β-diketone systems under

similar conditions is known in the literature [3,4]. The reduction of carbonyl groups in this case occurs with the formation of methylene groups.

In the first product spectra characteristic signals for the ethyl fragment were found, which indicates that the reduction in this case occurred at the exocyclic carbonyl group. In the second product spectra a shift of the C4 signal of the methylene group towards the strong field and an increase in the multiplicity of this signal due to the appearance of another methylene group nearby was observed. Therefore, the reduction of the C3=O carbonyl group took place.



Scheme 2. Hydrogenation of dihydrousnic acid.

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. Dihydrousnic acid **2** was obtained by hydrogenation as described

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 $CDCl_3$ 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 $CDCl_3$). 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. Hydrogenation of Dihydrousnic acid

Dihydrousnic acid (2 g) were added to 25 mL of THF. After the substance dissolved, a catalyst was added to the mixture. A three-way crane was placed on the flask. One output is connected to hydrogen, the other to a vacuum pump. The air from the flask was removed by vacuum. Then the system was filled with hydrogen and was stirred for 5 min. The procedure was repeated once. The obtained mixture was stirred in the hydrogen atmosphere overnight. After that, the mixture was filtered out and the solvent was removed. The products were isolated after column chromatography.

(2R,7R)-10-acetyl-4-ethyl-5,11,13-trihydroxy-2,12-dimethyl-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(13), 4,9,11-tetraen-3-one (4): Yellow amorphous powder. Yeld: 36%. δ_H ($CDCl_3$, J Hz): 0.95 (3H, t, J = 7.5), 1.59 (3H, s), 2.01 (3H, s), 2.27 (1H, dq, J_1 = 7.5, J_2 = 7.0), 2.33 (1H, dq, J_1 = 7.5, J_2 = 7.0), 2.55 (3H, s), 2.89 (1H, dd, J_1 = 6.0, J_2 = 17.6) and 2.99 (1H, dd, J_1 = 6.0, J_2 = 17.6) (AB-system), 4.83 (1H, dd, J_1 = 6.0, J_2 = 6.0), 9.63 (1H, ss), 13.35 (1H, s). δc ($CDCl_3$): 7.14, 12.77, 15.44, 23.89, 31.11, 31.90, 51.77, 84.75, 101.67, 105.84, 106.05, 116.92, 159.19, 159.70, 162.95, 170.0, 198.3, 201.89.

(2R,4E,7R)-10-acetyl-11,13-dihydroxy-4-(1-hydroxyethylidene)-2,12-dimethyl-8-oxatricyclo [7.4.0.0^{2,7}] trideca-1(13),9,11-trien-3-one (5): Yellow amorphous powder. Yeld: 15%. δ_H ($CDCl_3$, J Hz): 1.59 (3H, s), 1.99 (3H, s), 1.99–2.07 (2H, m), 2.28–2.40 (1H, m), 2.34 (1H, ddd, J_1 = 4.8, J_2 = 7.0, J_3 = 15.0) and 2.48 (1H, ddd, J_1 = 4.8, J_2 = 7.0, J_3 = 15.0) (AB-system), 2.55 (3H, s), 4.69 (1H, dd, J_1 = 4.6, J_2 = 6.9), 9.38 (1H, s), 13.42 (1H, s), 16.47 (1H, s). δc ($CDCl_3$): 8.05, 20.2, 22.90, 25.20, 27.05, 32.24, 52.67, 89.89, 102.62, 106.42, 106.64, 106.70, 160.02, 160.07, 164.04, 191.74, 195.06, 202.47.

4. Conclusions

Thus, two new compounds based on the usnic acid were obtained. The triketone system of the C ring in the new compounds is destroyed, which should contribute to the loss of protonophore properties responsible for the toxicity of the native compound. This feature allows the synthesized compounds to be considered as promising platforms for creating new biologically active compounds with increased safety.

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

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