Chemistry of Natural Compounds, Vol. 47, No. 2, May, 2011 [*Russian original No. 2, March-April, 2011*]

REDUCTION OF (+)-USNINIC ACID AND ITS PYRAZOLE DERIVATIVE BY SODIUM BOROHYDRIDE

D. N. Sokolov,* O. A. Luzina, M. P. Polovinka, and N. F. Salakhutdinov

UDC 547.992

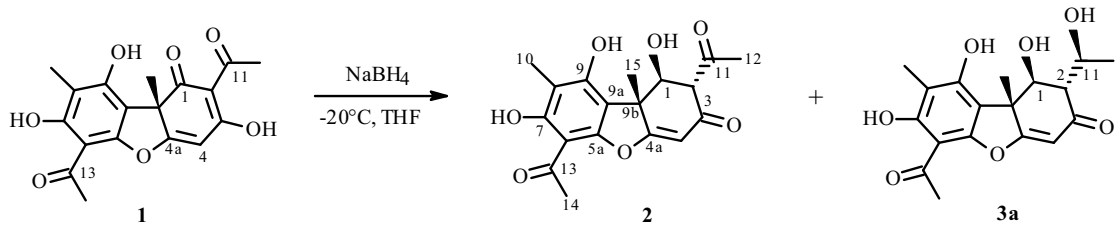
The reaction of (+)-usninic acid and its pyrazole derivative with sodium borohydride was studied. The reduction occurred stereoselectively at the endocyclic carbonyl group. Novel (+)-usninic acid derivatives that were reduction products of the carbonyls were obtained.

Keywords: (+)-usninic acid, reduction, sodium borohydride.

The isolation and synthetic transformation of plant metabolites in order to increase their biological activity and/or prepare new drugs is one of the leading areas in the chemistry of natural compounds. Usninic acid (**1**) is the principal secondary metabolite of several lichens and exhibits various types of biological activity [1]. The reduction of **1** by H_2/Pd, which quantitatively reduced the C_4–C_{4a} double bond, was reported previously [2]. However, there is practically no information on the reduction of the carbonyls of **1** by metal hydride complexes. An example of the reduction of **1** by $NaBH_4$ was described. A small amount of the carbonyl (C_{13}=O) reduction product was isolated from the product mixture [3].

Herein we present results for the preparation of (+)-usninic acid (**1**) derivatives reduced at the carbonyls in order to expand the repertoire of semi-synthetic natural dibenzofuran derivatives that hold promise of exhibiting high biological activity.

We reduced **1** with $NaBH_4$ under various conditions. The reaction occurred exceedingly nonselectively in alcohols (MeOH, EtOH, *i*-PrOH) at room temperature to form a multi-component product mixture (>20). The reaction did not occur if benzene or hexane was used as the solvent. The most acceptable solvent was THF. Reduction of **1** in THF occurred at low temperatures (–20°C). A mixture of products (~4:5) reduced at the C_1=O carbonyl (**2**) or two carbonyls (C_1=O and C_{11}=O) (**3**) formed during the two-hour reaction in overall yield 57%. In addition, the reaction mixture contained starting **1**. Increasing the reaction time in order to increase the conversion of substrate complicated the reaction mixture owing to increased amounts of minor products. Reduction of the C_1=O occurred stereoselectively. Compound **3** was apparently a mixture of stereoisomers with clear predominance of one of them. Thus, reduction of the C_{11}=O carbonyl occurred less selectively. We assumed the configuration of the C_1 center in both compounds based on literature data for the reaction mechanism of carbonyls with $NaBH_4$ [4]. The mutual axial–axial location of protons on C_1 and C_2 was established using the spin–spin coupling constant (SSCC) (10.5 Hz) and literature data for the SSCC in substituted cyclohexenones [5].

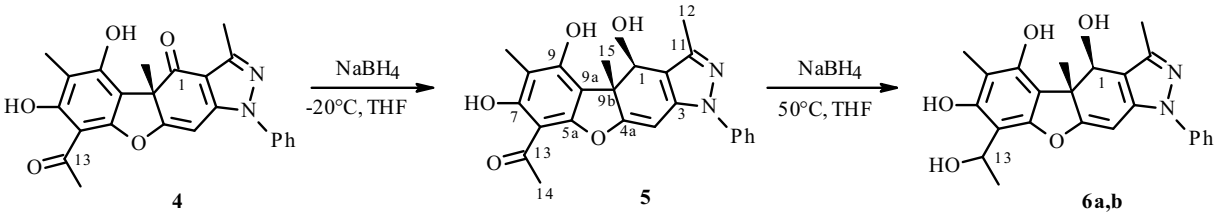


1 **2** **3a**

Reaction under analogous conditions of a pyrazole derivative of **1** (**4**) with $NaBH_4$ produced **5** by reduction of C_1=O. The reaction occurred stereoselectively in excellent (96%) yield at temperatures from –40 to 0°C. The yield of **5** decreased slightly with the temperature increased to ambient. Increasing the temperature further to 50°C caused **5** to react with the

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, 630090, Novosibirsk, e-mail: dsokolov@nioch.nsc.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 188–190, March–April, 2011. Original article submitted July 19, 2010.

excess of $NaBH_4$ to give the product from reduction of the C_{13}=O carbonyl (**6**) (a mixture of stereoisomers at the C_{13} center, ~2:3 according to PMR data).



4 **5** **6a,b**

Thus, reduction of the carbonyls of **1** by $NaBH_4$ occurred sequentially. The endocyclic carbonyl (C_1=O) was most reactive. It was reduced stereoselectively. The C_{13}=O carbonyl was reduced only at elevated temperature and not stereoselectively. This was shown using the reaction of a pyrazole derivative of **1** (**4**) with $NaBH_4$ as an example.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer at operating frequency 500.13 MHz (^1H) and 125.76 (^{13}C); IR spectra, on a Vector 22 spectrometer; mass spectra (ionizing-electron energy 70 eV), in a DFS high-resolution mass spectrometer. Melting points were measured on a Kofler block. Compound **1** ($[\alpha]_D$ +478°, *c* 0.1, $CHCl_3$) was isolated from a mixture of lichens of the genus *Usnea* by the literature method [6]. Compound **4** was synthesized by the literature method [7]. We used commercially available $NaBH_4$. The reaction of **1** was monitored experimentally using PMR spectra. Column chromatography used Merck silica gel (60–200 μ). Atoms in the compounds were numbered based on the commonly accepted numbering of usninic acid structures and did not always agree with the numbering of the atoms according to the nomenclature name.

Reaction of 1 with $NaBH_4$. A solution of **1** (1 mmol) in THF (20 mL) was cooled to –20°C, treated with a suspension of $NaBH_4$ (50 mg) in THF (5 mL), stirred at that temperature for 2 h, treated with dilute HCl solution until the pH was ~5, brought to room temperature, treated with CH_2Cl_2 (30 mL), washed with H_2O (2×), and dried over calcined $MgSO_4$. The solvent was removed. The products were chromatographed over a column of silica gel (60–200 μ) with elution by $CHCl_3$ to isolate starting **1** (30%) and a mixture of **2** and **3a, b** in a 4:5 ratio according to PMR spectra in overall yield 57%. Compounds **2** and **3a, b** were separated by repeated chromatography over a column of silica gel (60–200 μ) with elution by CH_2Cl_2.

1,1′-{(1*S*,9b*R*)-1,7,9-Trihydroxy-8,9b-dimethyl-3-oxo-1,2,3,9b-tetrahydrodibenzo[b,d]furan-2,6-diyl}diethanone (2). Yield 12%, mp 97°C, $[\alpha]_D$ +346° (c 0.1, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1043, 1158, 1290, 1625, 1718, 3211, 3411.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.53 (3H, s, H-15), 2.04 (3H, s, H-10), 2.55 (3H, s, H-12), 2.65 (3H, s, H-14), 3.76 (1H, d, J = 10.5, H-2), 4.70 (1H, d, J = 10.5, H-1), 4.97 (1H, s, 1-OH), 5.79 (1H, s, H-4), 9.23 (1H, s, 9-OH), 13.29 (1H, s, 7-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 9.68 (C-10), 22.30 (C-15), 33.48 and 34.85 (C-12 and C-14), 51.37 (C-9b), 65.51 (C-1), 74.37 (C-2), 103.65 (C-6), 105.96 (C-4), 110.12 (C-8), 110.76 (C-9a), 157.53 (C-5a), 158.92 (C-9), 165.73 (C-7), 184.15 (C-4a), 192.83 (C-3), 202.91 (C-13), 208.83 (C-11).

Found: *m*/*z* 346.1050 $[M]^+$; $C_{18}H_{18}O_7$; calcd: MW = 346.1047.

(1*S*,9b*R*)-6-Acetyl-1,7,9-trihydroxy-2-(1-hydroxyethyl)-8,9b-dimethyl-1,2-dihydrodibenzo[b,d]furan-3(9b*H*)-one (3a, 3b) (**3a**:**3b** ratio ~10:1 according to PMR). Yield 12%, mp 92°C. IR spectrum (KBr, ν, cm^{-1}): 1046, 1157, 1289, 1625, 3204, 3400.

PMR spectrum of **3a** ($CDCl_3$, δ, ppm, J/Hz): 1.23 (3H, d, J = 6, H-12), 1.54 (3H, s, H-15), 2.07 (3H, s, H-10), 2.67 (3H, s, H-14), 3.05 (1H, dd, J = 4.5, 10.5, H-2), 4.56 (1H, d, J = 10.5, H-1), 4.98 (1H, dq, J = 4.5, 6, H-11), 5.75 (1H, s, H-4), 5.92 (1H, s, 1-OH), 9.48 (1H, s, 9-OH), 13.31 (1H, s, 7-OH).

The following resonances in the PMR spectrum of **3b** could be assigned: 1.26 (3H, d, J = 6, H-12), 1.53 (3H, s, H-15), 2.06 (3H, s, H-10), 2.68 (3H, s, H-14), 4.83 (1H, m), 5.85 (1H, s, H-4).

^{13}C NMR spectrum of **3a** ($CDCl_3$, δ, ppm): 7.02 (C-10), 18.57 and 19.70 (C-12 and C-15), 30.79 (C-14), 48.75 (C-9b), 51.85 (C-2), 69.30 (C-11), 71.74 (C-1), 100.93 (C-6), 103.48 (C-4), 108.04 and 108.14 (C-8 and C-9a), 154.96 (C-5a), 156.51 (C-9), 162.85 (C-7), 181.99 (C-4a), 194.84 (C-3), 200.33 (C-13).

Found: *m*/*z* 348.1210 $[M]^+$; $C_{18}H_{20}O_7$; calcd: MW = 348.1204.

Reaction of 4 with $NaBH_4$. A solution of **4** (1 mmol) in THF (20 mL) was cooled to –20°C, treated with a suspension of $NaBH_4$ (50 mg) in THF (5 mL), stirred at that temperature for 2 h, treated with dilute HCl solution until the pH was ~5, brought to room temperature, treated with CH_2Cl_2 (30 mL), washed with H_2O (2×), and dried over calcined $MgSO_4$. The solvent was removed. The products were chromatographed over a column of silica gel (60–200 μ) with elution by $CHCl_3$.

1-{(4*S*,4a*R*)-4,5,7-Trihydroxy-3,4a,6-trimethyl-1-phenyl-4,4a-dihydro-1*H*-benzofuro[3,2-f]indazol-8-yl)ethanone (5). Yield 96%, mp 155°C, $[\alpha]_D$ +152° (c 0.1, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1068, 1288, 1369, 1441, 1627, 3188, 3392.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.35 (3H, s, H-15), 2.03 (3H, s, H-10), 2.32 (3H, s, H-12), 2.61 (3H, s, H-14), 5.26 (1H, br.s, 1-OH), 5.33 (1H, d, J = 6, H-1), 5.87 (1H, s, H-4), 7.31–7.42 (5H, m, arom. H), 9.25 (1H, s, 9-OH), 13.31 (1H, s, 7-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 6.97 (C-10), 12.25 (C-12), 15.93 (C-15), 30.79 (C-14), 50.90 (C-9b), 74.30 (C-1), 88.99 (C-4), 101.03 (C-6), 106.56 (C-9a), 107.66 (C-8), 111.35 (C-2), 123.23, 127.39, 129.01 and 137.75 (2C, C, 2C, and C, all arom.), 138.10 (C-3), 146.22 (C-11), 156.84 (C-9), 157.26 (C-5a), 162.58 (C-7), 167.26 (C-4a), 200.58 (C-13).

Found: *m*/*z* 418.1521 $[M]^+$; $C_{24}H_{22}O_5N_2$; calcd: MW = 418.1523.

Reaction of 5 with $NaBH_4$. A solution of **5** (1 mmol) in THF (20 mL) was treated with a suspension of $NaBH_4$ (50 mg) in THF (5 mL), heated to 50°C, stirred for 2 h, brought to room temperature, treated with dilute HCl solution under the pH was ~5, treated with CH_2Cl_2 (30 mL), washed with H_2O (2×), and dried over calcined $MgSO_4$. The solvent was removed. The products were chromatographed over a column of silica gel (60–200 μ) with elution by $CHCl_3$.

(4*S*,4a*R*)-8-(1-Hydroxyethyl)-3,4a,6-trimethyl-1-phenyl-4,4a-dihydro-1*H*-benzofuro[3,2-f]indazol-4,5,7-triol (6a and 6b) (**6a**:**6b** ratio ~2:3 according to PMR data). Yield 71%, mp 233°C. IR spectrum (KBr, ν, cm^{-1}): 1041, 1067, 1174, 1440, 1504, 1627, 3271.

PMR spectrum of **6a** ($CDCl_3$, δ, ppm, J/Hz): 1.33 (3H, s, H-15), 1.47 (3H, d, J = 6, H-14), 2.04 (3H, s, H-10), 2.27 (3H, s, H-12), 4.00 (1H, br.s, 13-OH), 4.50 (1H, d, J = 7, 1-OH), 5.20 (1H, q, J = 6, H-13), 5.28 (1H, d, J = 7, H-1), 5.73 (1H, s, H-4), 7.28–7.38 (5H, m, arom. H), 8.24 and 8.67 (1H and 1H, s and s, 7-OH and 9-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.62 (C-10), 12.43 (C-12), 16.36 (C-15), 23.26 (C-14), 51.96 (C-9b), 65.78 (C-13), 74.85 (C-1), 88.07 (C-4), 104.39 (C-8), 107.00 (C-9a), 107.24 (C-6), 111.68 (C-2), 123.23, 127.35, 129.18 and 138.57 (2C, C, 2C, and C, all arom.), 138.45 (C-3), 146.74 (C-11), 150.14 (C-7), 152.05 (C-5a), 155.10 (C-9), 168.68 (C-4a).

Found: fragment ion (–H_2O) *m*/*z* 402.1570 $[M]^+$; $C_{24}H_{22}O_4N_2$.

PMR spectrum of **6b** ($CDCl_3$, δ, ppm, J/Hz): 1.34 (3H, s, H-15) and 1.50 (3H, d, J = 6, H-14), 2.04 (3H, s, H-10), 2.32 (3H, s, H-12), 3.77 (1H, br.s, 13-OH), 4.54 (1H, d, J = 7, 1-OH), 5.24 (1H, q, J = 6, H-13), 5.30 (1H, d, J = 7, H-1), 5.76 (1H, s, H-4), 7.28–7.38 (5H, m, arom. H), 8.30 and 8.64 (1H and 1H, s and s, 7-OH and 9-OH).

The following resonances in the ^{13}C NMR spectrum of **6b** could be assigned: 12.51 (C-12), 16.43 (C-15), 51.86 (C-9b), 66.06 (C-13), 88.00 (C-4), 107.36 (C-6), 111.62 (C-2), 146.59 (C-11), 150.24 (C-7), 152.12 (C-5a).

REFERENCES

1. K. Ingolfsdottir, *Phytochemistry*, **61**, 729 (2002).
2. J. Kutney and I. Sanchez, *Can. J. Chem.*, **54**, 2795 (1976).
3. B. Proksa, M. Sturdikova, N. Pronayova, and T. Liptaj, *Pharmazie*, **51**, 195 (1996).
4. F. Carey, *Organic Chemistry* (5th Ed.), McGraw—Hill, 2004.
5. L. A. Kutulya, N. S. Pivnenko, A. S. Petrenko, V. V. Vashchenko, and J. B. Gudbi, *Zh. Strukt. Khim.*, **42**, No. 1, 101 (2001).
6. N. F. Salakhutdinov, M. P. Polovinka, and M. Yu. Panchenko, RF Pat. No. 2,317,076 C1; *Byull. Izobret.*, No. 5 (2008).
7. M. Takai, U. Yoshimasa, and J. A. Beisler, *J. Med. Chem.*, **22**, No. 11, 1380 (1979).