Chemistry of Natural Compounds, Vol. 46, No. 5, 2010

OXIDATION OF USNINIC ACID

D. N. Sokolov,* O. A. Luzina, M. P. Polovinka,
D. V. Korchagina, Yu. V. Gatilov,
and N. F. Salakhutdinov

UDC 547.992

Reactions of usninic acid with various oxidants were studied. The oxidation occurred at the resorcinol ring. New derivatives of usninic acid were obtained from reactions with per-acids.

Keywords: usninic acid, oxidation, organic per-acids.

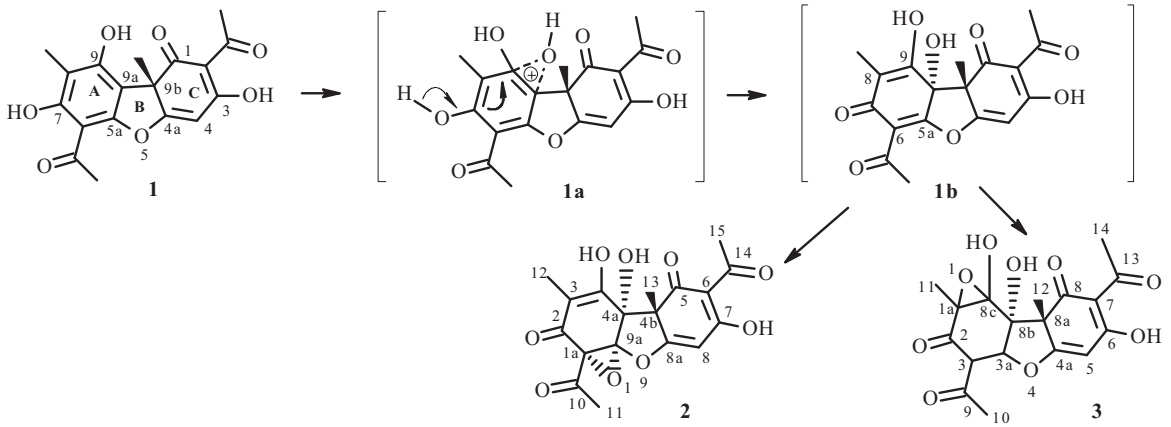
The isolation of plant metabolites and their chemical modification to produce novel drug candidates with high physiological activity is an active area in natural product chemistry.

An interesting subject for chemical modification is usninic acid (UA) (**1**), the principal constituent in extracts of most lichens and a compound with a broad spectrum of biological activity. Interest in UA has been unwavering for many decades [1]. Nevertheless, reactions involving oxidation of UA or its derivatives have been little studied. Thus, cleavage of the carbon skeleton of UA in the presence of base in alcohol and aqueous alcohol was reported [2–5]. Under these conditions, different researchers have obtained complicated mixtures of products, several of which were isolated in small yields. Oxidation of UA 7,9-diacetate by $KMnO_4$ occurred at ring C and also gave a complicated product mixture [6]. The action of H_2O_2 on UA was studied [7]. The reaction was carried out in pyridine and formed the 2-acetoxy derivative (83% yield).

Herein we report results from the reaction of UA with various oxidants. Reactions of **1** with conc. HNO_3 and CrO_3 reagents gave complicated product mixtures that resulted apparently from extensive destruction of the substrate.

On the other hand, **1** was not oxidized in the presence of oxidants such as $Pb(CH_3COO)_4$, KIO_4, O_2, *t*-BuOOH, Dess–Martin periodinan, H_2O_2 in $CHCl_3$ (in the presence of TEBA), and SeO_2 in the presence of H_2O_2.

The oxidation occurred at room temperature and formed two compounds if organic per-acids (MCPBA, CH_3CO_3H, MPPA) in $CHCl_3$ were used as oxidants. The products were most conveniently isolated from CH_3CO_3H because its decomposition product, CH_3CO_2H, was easily removed from the reaction mixture by washing with water. If MCPBA or MPPA were used, the products were difficult to isolate from the *m*-chlorobenzoic or phthalic acids, respectively, formed during the reaction because the standard work up with $NaHCO_3$ solution removed part of the UA oxidation products with the aqueous phase. Column chromatography over silica gel isolated **2** and **3** in yields of 41 and 27%, respectively (Scheme 1).



Scheme 1

Novosibirsk Institute of Organic Chemistry, Siberian Division, Russian Academy of Sciences, 630090, Novosibirsk, Russia, e-mail: dsokolov@nioch.nsc.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 616–618, September–October, 2010. Original article submitted March 3, 2010.

 0009-3130/10/4605-0730

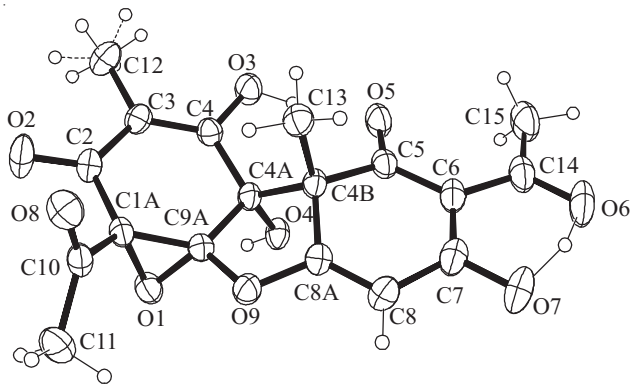
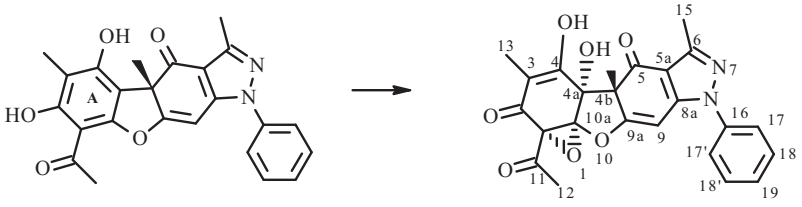


Fig. 1. Molecular structure of crystalline **2** (30% thermal ellipsoids).

The structures of **2** and **3** were elucidated using PMR and ^{13}C NMR spectra. The configuration of the epoxide ring of **3** was not established. The structure of **2**, including the configuration of the epoxide ring in it, were confirmed by an x-ray structure analysis (XSA) (Fig. 1). Ring C_{1a}-C_{9a} was planar within ±0.039 Å. Ring C_{4b}-C_{8a} had the chair conformation with C_{4b} deviating by 0.336(5) Å. The five-membered ring had the envelope conformation with atom C_{4b} deviating by 0.559(5) Å. Practically the same conformations of the rings was observed in starting UA [8, 9]. Head-to-tail chains of molecules along the *c* axis were formed via H-bonds O_4–H...O_8 [O–H 0.80(5), H...O 1.96(5) Å; O–H...O 174(5)°]. It is noteworthy that there was a strong intramolecular H-bond O_7–H...O_6 [O_7–H 1.22(6), H–O_6 1.29(6), O...O 2.427(5) Å; O_7–H–O_6 149(6)°] with parameters similar to those in UA.

The structures of **2** and **3** indicate that the oxidation occurred in resorcinol ring A of **1**. Taking into account this fact and literature data on the oxidation of substituted phenols by H_2O_2 [10], we proposed a possible mechanism for oxidation of **1** by per-acids (Scheme 1). Electrophilic addition to form intermediate **1a** apparently occurred in the first step. This then opened to form intermediate diol **1b** that was epoxidized at either the C_{5a}–C_6 or C_8–C_9 bond to give **2** and **3**, respectively.



4 **5**

Scheme 2

The 7,9-diacetate of UA with protected phenol hydroxyls did not react with CH_3CO_3H. However, the pyrazole derivative of UA (**4**), like UA, was oxidized in resorcinol ring A to form **5**, which was isolated by column chromatography in 43% yield (Scheme 2). A second oxidation product analogous to **3** was not formed even with an excess of CH_3CO_3H.

Thus, oxidation of UA and its pyrazole derivative **4** by organic per-acids occurred at ring A with destruction of the aromatic system and formation of compounds containing epoxide rings. Protection of the phenol hydroxyls of aromatic ring A by acetates prevented oxidation by organic per-acids.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded on a DRX-500 spectrometer (Bruker) at operating frequencies 500.13 (^1H) and 125.76 (^{13}C) MHz. IR spectra were taken on a Vector 22 spectrometer; mass spectra (70-eV ionizing electron energy), on a DFS high resolution mass spectrometer. UA was isolated from a mixture of *Usnea* spp. lichens by the literature method [11]. The 7,9-diacetate of **1** was synthesized as before [12]; the pyrazole derivative of UA (**4**), as before [13]. The oxidation of UA by HNO_3 used the literature method [14]. The oxidation by CrO_3 reagents used the literature methods [15].

We used commercially available MCPBA (Aldrich). CH_3CO_3H was prepared as before [16]; MPPA, by the literature method [17]. The conversion of UA was monitored experimentally using PMR spectra. Column chromatography used silica gel (Merck, 60-200 μm).

Reaction of (+)-UA (1) and 4 with CH_3CO_3H. A solution of substrate (1 mmol, 5 mL) was treated with peracetic acid solution (3 mL, 1 mmol/mL) in $CHCl_3$, stirred at room temperature for 1 d, washed with water, dried over $MgSO_4$, and evaporated. The solid was chromatographed over a column of silica gel with elution by $CHCl_3$.

(1a*R*,4a*S*,4b*S*,9a*S*)-1a,6-Diacetyl-4,4a,7-trihydroxy-3,4b-dimethyl-1a*H*-benzo[*b*]oxireno[2,3-*h*]benzofuran-2,5(4a*H*,4b*H*)-dione (2). Yield 41%, mp 145°C ($CHCl_3$), $[\alpha]_D$ +36.8° (*c* 0.199, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm): 1.47 (3H, s, H-13), 1.78 (3H, s, H-12), 2.40(3H, s, H-11), 2.63 (3H, s, H-15), 3.51 (1H, s, OH-4a), 5.85 (1H, s, H-8), 11.28 (1H, s, OH-4), 18.81 (1H, s, OH-7).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.70 (C-12), 24.22 (C-13), 27.95 (C-15), 28.49 (C-11), 59.88 (C-4b), 65.67 (C-1a), 75.49 (C-4a), 95.26 (C-9a), 99.21 (C-8), 106.53 (C-6), 114.95 (C-3), 162.09 (C-4), 173.97 (C-8a), 185.81 (C-2), 191.53 (C-7), 194.46 (C-5), 198.00 (C-10), 202.15 (C-14).

IR spectrum (KBr, ν, cm^{-1}): 841, 1115, 1123, 1465, 1646, 1688, 1719, 2708, 3311. Mass spectrum (*m*/*z*, I_{rel}, %): 376.1 (36.27) $[M]^+$, 182.1 (43.78), 167.1 (100), 43.0 (48.46).

The XSA was performed at 296 K on a Bruker P4 diffractometer (Mo K_α-radiation, graphite monochromator, 2θ/θ-scanning for 2θ < 54°). A crystal of **1** (0.12 × 0.40 × 0.48 mm) was used. The crystallographic data were: $C_{18}H_{16}O_9$, monoclinic system, space group $P2_1$, a = 8.1390(7), b = 11.274(1), c = 9.3268(7), β = 93.712(6)°, V = 853.99(12) $Å^3$, Z = 2, d_{calc} = 1.459 g/cm^3, μ = 0.119 mm^{-1}. Intensities of 1978 independent reflections were measured. Absorption corrections were applied empirically (transmission 0.95–0.99). The structure was solved by direct methods using the SHELXS-97 program. Structure factors were refined by anisotropic full-matrix least-squares methods using the SHELXL-97 program. Parameters of hydroxyl H atoms were refined isotropically. Parameters of other H atoms were calculated in each refinement cycle using the coordinates of the corresponding C atoms. The methyl on C_3 was disordered over two positions in a 0.6:0.4 ratio. The final refinement of the structure over all F^2 gave wR_2 = 0.1027, S = 1.056, 261 parameters, and R_1 = 0.0368 for 1487 reflections with $I > 2\sigma(I)$. The data were deposited in the Cambridge Crystallographic Data Centre (No. CCDC 766124) and can be obtained free at the address http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi.

(8a*S*,8b*R*)-3,7-Diacetyl-6,8b,8c-trihydroxy-1a,8a-dimethyl-8b,8c-dihydrobenzo[*b*]oxireno[2,3-*e*]benzofuran-2,8(1a*H*,8a*H*)dione (3). Yield 27%, mp 90°C ($CHCl_3$), $[\alpha]_D$ +14.2° (*c* 0.138, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 760, 957, 1073, 1099, 1225, 1461, 1544, 1631, 1685, 3401. Mass spectrum (*m*/*z*, I_{rel}, %): 376.1 (7.64) $[M]^+$, 333.1 (43.38), 167.1 (56.48), 43.0 (100).

PMR spectrum ($CDCl_3$, δ, ppm): 1.52 (3H, s, H-11), 1.63 (3H, s, H-12), 2.45 (3H, s, H-10), 2.62 (3H, s, H-14), 5.63 (1H, s, OH-8b), 6.00 (1H, s, H-5), 7.58 (1H, s, OH-8c), 18.69 (1H, s, OH-6).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.85 (C-11), 25.24 (C-12), 27.56 (C-14), 31.51 (C-10), 61.77 (C-8a), 79.45 (C-8b), 79.68 (C-1a), 93.04 (C-8c), 100.67 (C-5), 107.38 (C-7), 115.82 (C-3), 170.20 (C-3a), 176.37 (C-4a), 191.51 (C-6), 192.15 (C-2), 194.58 (C-8), 196.33 (C-9), 201.62 (C-13).

(1a*R*,4a*S*,4b*S*,10a*S*)-1a-Acetyl-4,4a-dihydroxy-3,4b,6-trimethyl-8-phenyl-4b,8-dihydrooxireno[2′,3′:7,7a]benzofuro[3,2-*f*]indazol-2,5-(1a*H*,4a*H*)dione (5). Yield 43%, mp 205°C ($CHCl_3$), $[\alpha]_D$ +24° (*c* 0.236, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 761, 1006, 1027, 1221, 1279, 1455, 1483, 1513, 1644, 1676, 1725, 2713, 3100. Mass spectrum (*m*/*z*, I_{rel}, %): 448.1 (8.46) $[M]^+$, 268.1 (100), 254.1 (51.54), 77.0 (40.60).

PMR spectrum ($CDCl_3$, δ, ppm): 1.52 (3H, s, H-14), 1.82 (3H, s, H-13), 2.38 (3H, s, H-12), 2.55 (3H, s, H-15), 3.32 (1H, s, OH-4a), 6.12 (1H, s, H-9), 7.41-7.53 (5H, m, H-Ar), 11.36 (1H, s, OH-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.74 (C-13), 13.18 (C-15), 23.15 (C-14), 28.47 (C-12), 61.42 (C-4b), 66.08 (C-1a), 75.68 (C-4a), 89.65 (C-9), 95.24 (C-10a), 111.95 (C-5a), 114.88 (C-3), 123.99 (2C-17), 128.89 (C-19), 129.57 (2C-18), 137.54 (C-16), 148.39 (C-8a), 151.52 (C-6), 162.44 (C-4), 167.57 (C-9a), 186.03 (C-2), 192.26 (C-5), 198.32 (C-11).

REFERENCES

1. K. Ingolfsdottir, *Phytochemistry*, **61**, 729 (2002).
2. J. P. Kutney and I. H. Sanchez, *Can. J. Chem.*, **55**, 1079 (1977).
3. M. Takani and K. Takahashi, *Chem. Pharm. Bull.*, **28**, 177 (1980).
4. J. P. Kutney, I. H. Sanchez, and Y. Trevor, *Can. J. Chem.*, **54**, 3721 (1976).
5. J. P. Kutney, J. D. Leman, P. J. Salisbury, I. H. Sanchez, and Y. Trevor, *Can. J. Chem.*, **55**, 2336 (1977).
6. D. H. Barton and T. Bruun, *J. Chem. Soc.*, 603 (1953).
7. J. P. Kutney, J. D. Leman, P. J. Salisbury, I. H. Sanchez, and Y. Trevor, *Can. J. Chem.*, **62**, 320 (1984).
8. R. Norrestam, M. von Glehn, and C. A. Wachtmeister, *Acta Chem. Scand. B*, **28**, 1149 (1974).
9. F. R. Fronczek and N. H. Fischer, private communication, CCDC refcode USNICA11 (2006).
10. W. Adam, W. Herrmann, C. R. Saha-Moller, and M. Shimizu, *J. Mol. Catal.*, **97**, 15 (1995).
11. N. F. Salakhutdinov, M. P. Polovinka, and M. Yu. Panchenko, RF Pat. No. 2,317,076C1; *Byull. Izobret.*, No. 5 (2008).
12. E. Erba, D. Pocar, and L. M. Rossi, *Il Farmaco*, **53**, 718 (1998).
13. S. K. Manaktala, S. Neelakantan, and T. R. Seshadri, *Indian J. Chem.*, **5**, 29 (1967).
14. L. F. Tietze and T. Eicher, *Preparative Organic Chemistry* [translated from Ger.], Mir, Moscow, 1999.
15. L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 1967.
16. W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5528 (1957).
17. H. E. Baungarten (ed.), *Org. Synth. Coll.*, Vol. 5, Wiley, 1973, p. 805.