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

SYNTHESIS OF 3-DEOXY-3β-(3-AMINOPROPOXYAMINO) DERIVATIVES OF OLEANOLIC AND URSOLIC ACIDS

G. V. Giniyatullina, O. B. Kazakova,* and G. A. Tolstikov

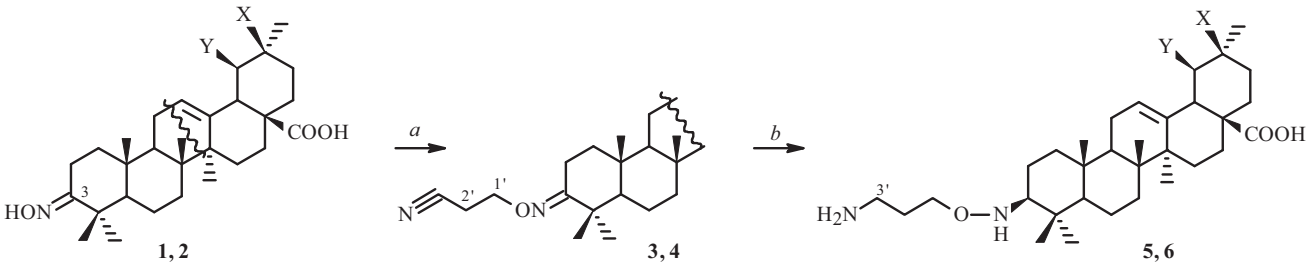
UDC 547.824:542.91:548.737

3-Deoxy-3β-(3-aminopropoxyamino) derivatives of oleanolic and ursolic acids were synthesized. 3-Deoxy-3-(2-cyanoethoxyimino)urs-12-en-28-oic acid was active in vitro *with selectivity index SI 30 against papilloma virus (strain HPV-11).*

Keywords: triterpenoids, ketoximes, cyanoethylation, 3β-(3-aminopropoxyamino) derivatives, antiviral activity.

Triterpene oximes exhibit valuable biological properties and are important starting materials for further transformations. Thus, medicinal forms of drugs for treating and preventing flu can be developed based on betulonic acid oxime [1, 2]. Acylation of the oximes of betulonic acid, its methyl ester, 20-oxoallobetulone, and ursolic acid by acetic, succinic, and phthalic anhydrides weakens their antiviral activity [3–6]. Reduction of the oxime of ursolic acid to the 3-deoxy-3-amino derivative produces in the latter cytotoxicity against HL-60, Bel-7402, and Hela cells. It was also found that the 3β-amino isomer is 20 times more active than the 3α isomer [7]. The products of Beckmann rearrangements (first- and second-order) of betulonic acid oxime exhibit antibacterial activity against *Streptococcus faecalis* and *Staphylococcus aureus* at concentrations 25–50 mg/mL [8]. Derivatives of oleanolic acid can be used in cosmetics because they transport biologically active compounds deep into tissue and make them more potent [9].

Herein we report the synthesis of 3-deoxy-3β-(3-aminopropoxyamino) derivatives of oleanolic and ursolic acids. Cyanoethylation of ketooximes of triterpenoids and their transformations have not been reported. Cyanoethylation of the ketoximes of oleanolic (**1**) and ursolic (**2**) acids by acrylonitrile in the presence of KOH solution synthesized 3-deoxy-3-(2-cyanoethoxyimino) derivatives **3** and **4** in 68 and 62% yields (Scheme 1). Their structures were established by rather characteristic PMR spectra in which resonances of H_2-2′ and H_2-1′ protons were observed at δ 2.62–2.73 and 4.14–4.31 ppm, respectively. Catalytic hydrogenation of **3** and **4** produced in 84 and 79% yield the target triterpenoids **5** and **6**. The resonance of C-3 in the ^{13}C NMR spectrum of **5** appeared at δ 65.1 ppm (whereas this resonance in the spectrum of starting **3** was observed at δ 167.8 ppm). The resonance of H-3 in the PMR spectrum appeared at 2.38–2.54 ppm; H_2-1′, 3.57–3.79 ppm; H_2-3′, 2.71–2.90 ppm.



1, 3, 5: X = CH_3, Y = H; **2, 4, 6:** X = H, Y = CH_3

a. CH_2=CHCN, 1,4-dioxane, 40% KOH, 6 h, 22°C; *b*. H_2, Raney nickel, MeOH, 9 h, 80°C, 100 atm.

Scheme 1

Institute of Organic Chemistry, Ufa Scientific Center, Urals Division, Russian Academy of Sciences, 450054, Ufa, prosp. Oktyabrya, 71, fax: (347) 235 60 66, e-mail: obf@anrb.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 640–641, September–October, 2010. Original article submitted March 12, 2010.

 0009-3130/10/4605-0760

It was found that 3-deoxy-3-(2-cyanoethoxyimino)urs-12-en-28-oic acid (**4**) was active *in vitro* with selectivity index SI 30 against papilloma virus (strain HPV-11).

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and CD_3OD on a Bruker AM-300 spectrometer (Germany, 300 and 75.5 MHz, respectively, δ, ppm, SSCC Hz) with TMS internal standard. Melting points were determined on a Boetius microstage. Optical absorption was measured on a Perkin–Elmer 241 MC polarimeter (Germany) in a 1-dm tube. TLC was performed on Sorbfil plates (ZAO Sorbpolimer, Russia) using $CHCl_3$:EtOAc (40:1). Compounds were detected using H_2SO_4 solution (10%) with subsequent heating at 100–120°C for 2–3 min. We used commercial oleanolic and ursolic acids (Aldrich Chemical Co.). Oximes of oleanolic and ursolic acids were prepared as before [10]. Raney nickel sponge catalyst was prepared according to the literature [11].

Synthesis of 3 and 4. A mixture of **1** or **2** (1 mmol), acrylonitrile (4 mL), and KOH solution (0.3 mL, 40%) in dioxane (15 mL) was stirred for 6 h at 20°C under Ar and poured onto ice (40 g) and HCl (5 mL). The precipitate was filtered, washed with water until neutral, and dried in air.

3-Deoxy-3-(2-cyanoethoxyimino)olean-12-en-28-oic Acid (3). Yield 0.35 g (68%), R_f 0.40, mp 134–136°C, $[\alpha]_D^{20}$ +37.6° (*c* 0.75, $CHCl_3$), $C_{33}H_{50}N_2O_3$ (MW 522.768).

PMR spectrum ($CDCl_3$, δ, ppm): 0.78, 0.89, 0.93, 1.01, 1.03, 1.11, 1.14 (21H, 7s, $7CH_3$), 1.22–2.37 (24H, m, CH_2, CH), 2.63–2.71 (2H, m, H-2′), 4.14–4.28 (2H, m, H-1′), 5.22–5.31 (1H, br, H-12).

^{13}C NMR spectrum (δ, ppm): 14.7, 17.0, 17.8, 18.2 (C-2′), 18.9, 22.7, 23.3, 23.4, 25.8, 27.3, 27.6, 29.6, 30.5, 32.2, 32.3, 32.9, 33.7, 37.0, 38.1, 39.2, 40.1, 40.8, 41.6, 45.7, 46.5, 47.0, 55.6, 67.2 (C-1′), 117.8 (C-3′), 122.4 (C-12), 143.5 (C-14), 167.8 (C-3), 184.5 (C-28).

3-Deoxy-3-(2-cyanoethoxyimino)urs-12-en-28-oic Acid (4). Yield 0.32 g (62%), R_f 0.42, mp 178–180°C, $[\alpha]_D^{20}$ +32.1° (*c* 0.65, $CHCl_3$), $C_{33}H_{50}N_2O_3$ (MW 522.768).

PMR spectrum ($CDCl_3$, δ, ppm): 0.78, 0.87, 0.93, 1.01, 1.03, 1.11, 1.14 (21H, 7s, $7CH_3$), 1.22–2.37 (24H, m, CH_2, CH), 2.62–2.73 (2H, m, H-2′), 4.16–4.31 (2H, m, H-1′), 5.22–5.31 (1H, br, H-12).

^{13}C NMR spectrum (δ, ppm): 14.7, 17.0, 17.8, 18.3 (C-2′), 18.9, 22.7, 23.3, 23.4, 25.8, 27.3, 27.6, 29.6, 30.5, 32.2, 32.3, 32.9, 33.7, 37.0, 38.1, 39.2, 40.1, 40.8, 41.6, 45.7, 46.5, 47.0, 55.6, 67.3 (C-1′), 117.9 (C-3′), 122.5 (C-12), 143.5 (C-14), 168.0 (C-3), 183.5 (C-28).

Synthesis of 5 and 6. Hydrogen was passed for 9 h at 100 atm through a solution of **3** or **4** (1 mmol) in MeOH (30 mL) containing activated Raney nickel (0.5 g). The catalyst was filtered off after the reaction was finished. The mixture was poured into water (100 mL). The precipitate was filtered off, dried, and recrystallized from EtOH:$CHCl_3$.

3-Deoxy-3β-(3-aminopropoxyamino)olean-12-en-28-oic Acid (5). Yield 0.44 g (84%), R_f 0.15, mp 119–123°C, $[\alpha]_D^{20}$ +29.1° (*c* 0.85, MeOH), $C_{33}H_{56}N_2O_3$ (MW 528.816).

PMR spectrum (CD_3OD, δ, ppm): 0.78, 0.87, 0.93, 1.01, 1.03, 1.11, 1.14 (21H, 7s, $7CH_3$), 1.22–2.03 (28H, m, CH_2, CH, H-2′, $N\underline{H}_2$, N<u>H</u>), 2.38–2.52 (2H, m, H-3′), 2.71–2.82 (1H, m, H-3), 3.27–3.33 (1H, m, H-11), 3.57–3.75 (2H, m, H-1′), 5.12–5.28 (1H, s, H-12).

^{13}C NMR spectrum (δ, ppm): 14.7, 17.0, 17.8, 18.9, 22.7, 23.3, 23.4, 25.8, 27.3, 27.6, 28.0, 29.6, 30.5, 32.5 (C-2′), 32.8, 33.0, 33.7, 37.0, 38.1, 39.2, 41.5 (C-3′), 41.7, 41.8, 45.7, 46.5, 47.0, 52.6, 56.5, 59.3 (C-1′), 65.1 (C-3), 121.1 (C-12), 144.8 (C-14), 183.6 (C-28).

3-Deoxy-3β-(3-aminopropoxyamino)urs-12-en-28-oic Acid (6). Yield 0.42 g (79%), *Rf* 0.13, mp 153–156°C, $[\alpha]_D^{20}$ +28.0° (*c* 1.0, MeOH), $C_{33}H_{56}N_2O_3$ (MS 528.816).

PMR spectrum (CD_3OD, δ, ppm): 0.78, 0.87, 0.93, 1.01, 1.03, 1.11, 1.14 (21H, 7s, $7CH_3$), 1.22–2.03 (28H, m, CH_2, CH, H-2′, $N\underline{H}_2$, N<u>H</u>), 2.41–2.54 (2H, m, H-3′), 2.71–2.90 (1H, m, H-3), 3.26–3.39 (1H, m, H-11), 3.65–3.79 (2H, m, H-1′), 5.12–5.28 (1H, s, H-12).

^{13}C NMR spectrum (δ, ppm): 14.7, 17.0, 17.8, 18.9, 22.7, 23.3, 23.4, 25.8, 27.3, 27.6, 28.0, 29.6, 30.5, 32.5 (C-2′), 32.8, 33.0, 33.7, 37.0, 38.1, 39.2, 41.6 (C-3′), 41.7, 41.8, 45.7, 46.5, 47.0, 52.6, 56.5, 59.5 (C-1′), 65.2 (C-3), 121.0 (C-12), 144.9 (C-14), 183.9 (C-28).

Methods for studying the antiviral activity of **4** are given at www.niaid-aacf.org.

ACKNOWLEDGMENT

The work was supported financially by the RFBR (Project No. 8–03–00868). We thank the National Institute of Allergy and Infectious Diseases, NIAID, USA, www.niaid-aacf.org) for studying the antiviral activity of **4**.

REFERENCES

1. O. V. Savinova, N. I. Pavlova, and E. I. Boreko, *Antibiot. Khimioter.*, **54**, 5 (2009).
2. E. I. Boreko, N. I. Pavlova, O. V. Savinova, O. B. Flekhter, L. R. Nigmatullina, L. A. Baltina, F. Z. Galin, and G. A. Tolstikov, Rep. Belarus Pat. No. 7811, Nov. 10, 2005 (2005).
3. O. B. Flekhter, E. I. Boreko, L. R. Nigmatullina, N. I. Pavlova, N. I. Medvedeva, S. N. Nikolaeva, E. V. Tret′yakova, O. V. Savinova, L. A. Baltina, L. T. Karachurina, F. Z. Galin, F. S. Zarudii, and G. A. Tolstikov, *Khim.-farm. Zh.*, **38**, 31 (2004).
4. A. White, E. J. Horsington, N. Nedjar, and T. M. Peakman, *Tetrahedron Lett.*, **39**, 3031 (1998).
5. I.-C. Sun, H.-K. Wang, Y. Kashiwada, J.-K. Shen, L. M. Cosentino, C.-H. Chen, L.-M. Yang, and K.-H. Lee, *J. Med. Chem.*, **41**, 4648 (1998).
6. T. M. Peakman, H. L. Haven, and J. Rullkotter, *Tetrahedron*, **47**, 3779 (1991).
7. C.-M. Ma, S.-Q. Cai, J.-R. Cui, R.-Q. Wang, P.-F. Tu, M. Hattori, and M. Daneshtalab, *Eur. J. Med. Chem.*, **40**, 582 (2005).
8. I. Valterova, J. Klinot, V. Sumanova, and A. Vystrcil, *Collect. Czech. Chem. Commun.*, **48**, 649 (1983).
9. L. Zaprutko, D. Partyka, and B. Bednarczyk-Cwynar, *Bioorg. Med. Chem. Lett.*, **14**, 4723 (2004).
10. L. F. Tietze and T. Eicher, *Preparative Organic Chemistry* [translated from Ger.], Mir, Moscow, 1999.
11. L. F. Fieser and M. Fieser, *Organic Chemistry*, Reinhold Pub. Co., New York, 1950.