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LOW-MOLECULAR-WEIGHT COMPOUNDS

Synthesis of Betulonic Aldehyde Derivatives

E. S. Kurbatov, V. V. Kostrub, and S. V. Kurbatov[1]

Southern Federal University, Department of Chemistry, ul. Sorge 7, Rostov-on-Don, 344090 Russia

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Abstract—Selective functionalization of betulonic aldehyde (the oxidation product of betulin) was studied with the aim of obtaining new physiologically active substances. We developed a method for the synthesis of azomethine derivatives at the C-28 aldehyde group and benzylidene derivatives at the 2-methylene group of the A ring. The structure of the synthesized products was proved by ^{1}H NMR.

Keywords: betulin, betulonic aldehyde, 3,4,5-trimethoxyaniline, nitrobenzaldehyde

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INTRODUCTION

It is known that betulin (I) contained in large amounts (30–40%) in the birch bark *Betula pendula*, and easily retrieved from it with accessible solvents [1], shows a wide range of biological activity [2]. Chemical transformations of betulin allow one to obtain its derivatives, which possess pronounced antitumor [3] and antiviral [4] activities combined with low toxicity [2]. The most developed and promising direction is the oxidation of betulin to betulinic [5] and betulonic acids and subsequent synthetic modification of these acids [2].

Against this background, an unexpectedly little-studied object is another oxidized derivative of betulin (I), namely betulonic aldehyde (II), the antiviral activity of which is also known [6, 7]. Despite the molecule of betulonic aldehyde containing several reactive fragments, only the Prince reaction at the C_{20}–C_{29} bond [8] and the reductive amination at the aldehyde group [9] are described to date according to Chemical Abstracts.

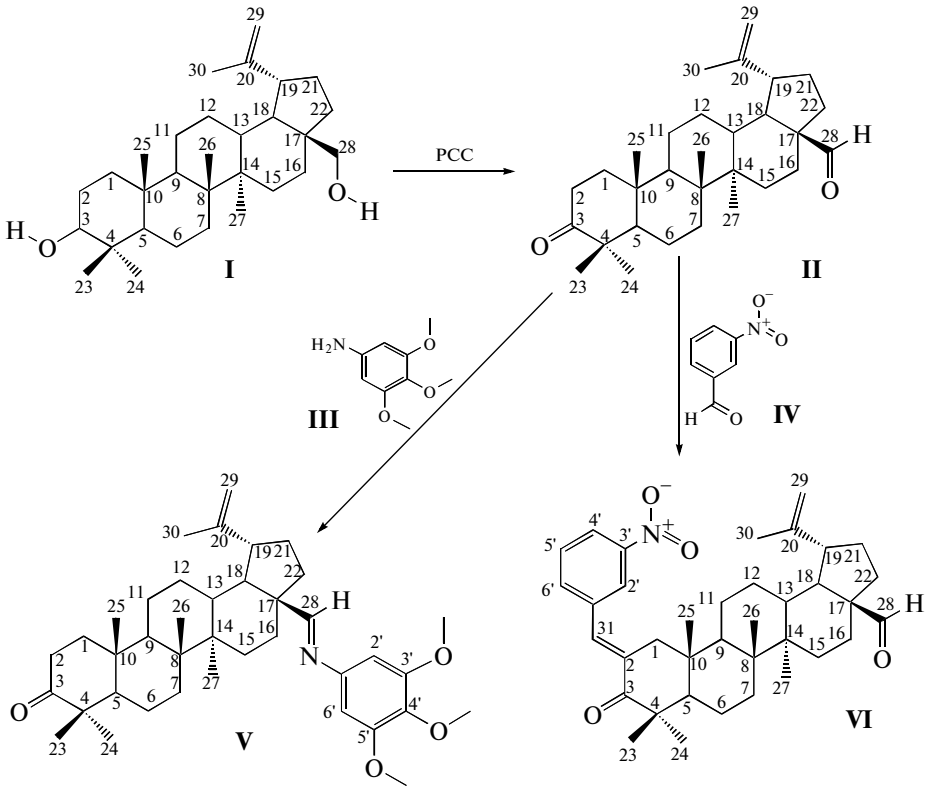
In this paper, we report first examples of the synthesis of betulonic aldehyde derivatives at the aldehyde group and the 2-methylene group of the A ring. Betulonic aldehyde (II) was synthesized by oxidation of betuline (I) with pyridinium chlorochromate (PCC) [6].

RESULTS AND DISCUSSION

The interaction of aldehyde (II) with 3,4,5-trimethoxyaniline (III) leads to azomethine (V). The choice of the aromatic amine is due to the following reasons. It is found that antitumor properties of colchicine from *Colchicum speciosum* are due to its ability to interact with tubulin because the structure of this alkaloid contains the trimethoxyphenyl fragment, which is complementary to one of the tubulin binding sites [10]. The usefulness of the introduction of the trimethoxyphenyl fragment to enhance antitumor properties of compounds of various classes is found experimentally (e.g., [11] and literature cited therein). The formation of azomethine (V) is confirmed by the appearance in ^{1}HNMR spectra of signals of protons of the methoxyl groups in the range of 3.8–3.9 ppm and aromatic protons at 6.21 ppm with the corresponding intensities. The signal of the azomethine proton appropriately shifts to 7.93 ppm.

One of the side processes during the synthesis of benzylidene derivative (VI) could be the self-condensation of betulonic aldehyde. To avoid this, we used obviously more active nitro-benzaldehyde. Moreover, the presence of an electron-acceptor substituent in the system of conjugated C=C–C=O bonds must facilitate the subsequent reactions of nucleophilic addition and/or cycloaddition at the A ring [12]. ^{1}H NMR spectrum of (VI) contains proton signals of the nitrophenyl ring in the range of 7.5-8.2 ppm. Proton signals of the methylene group at the second position of the A ring of betulonic aldehyde, which are among the most weak field signals in the spectrum (and therefore can be easily identified), disappear.

[1] Corresponding author: e-mail: kurbatov@sfedu.ru.



The synthesized new derivatives of betulonic aldehyde demonstrate the possibility of its selective condensation at both the aldehyde group and 2-methylene group of the A ring that opens up new ways of functionalization of betulin and preparation of derivatives potentially useful in practice.

EXPERIMENTAL

^{1}H NMR spectra were registered on a Bruker DPX-250 spectrometer (250 MHz) in deuterochloroform kept on molecular sieves 4 Å. The internal standard was tetramethylsilane. Betulin, pyridinium chlorochromate, 3,4,5-trimethoxianiline, and *m*-nitro-bnzaldehyde were from Sigma-Aldrich (United States).

3-oxolup-20(29)-en-28-(3',4',5'-trimethoxyphenyl) aldimine (V). A mixture of betulonic aldehyde (II) (0.438 g, 1 mmol), 3,4,5-trimethoxyaniline (II) (0.183 g, 1 mmol), and acetic acid (0.1 mL) was bolide in methanol (15 mL) for 2 h. A precipitate after cooling was filtered off and recrystallized from methanol. The yield 0.38 g (63 %), colorless crystals, Tm 218°C. ^{1}H NMR spectra, δ, ppm: 0.90 s (3H, H_3C^{25}), 0.99 s (3H, H_3C^{26}), 1.01 s (3H, H_3C^{27}), 1.02 s (3H, H_3C^{24}), 1.06 s (3H, H_3C^{23}), 1.15–2.18 m (21H, $H_2C^{1,6,7,11,12,15,16a,21,22}$ and $HC^{5,9,13,18}$), 1.71 s (3H, H_3C^{30}), 2.35–2.52 m (3H, $H_2C^{2,16b}$), 2.65–2.80 m (1H, HC^{19}), 3.82 s (3H, $CH_3O^{4'}$), 3.87 s (6H, $CH_3O^{3',5'}$), 4.62 and 4.73 both br. s (both 1H, H_2C^{29}), 6.21 s (2H, $H^{2',6'}$), 7.93 s (1H, CH=N). Found, %: C 77.72, H 9.40, N 2.12. $C_{39}H_{57}NO_4$. Calculated, %: C 77.57, H 9.51, N 2.32.

2-(3'-nitro-bezylidene)-3-oxolup-20(29)-en-28-al (VI). *m*-Nitro-benzaldehyde (0.152 g, 1 mmol) and 0.05 mL of 40% aqueous KOH were added to a suspension of betulonic aldehyde (II) (0.438 g, 1 mmol) in 5mL of methanol. The reaction mixture was stirred for 10 min at room temperature followed by boiling for 15 min. A precipitate after cooling was filtered off and recrystallized from methanol. The yield 0.42 g (73%), colorless crystals, Tm 181°C. ^{1}H NMR spectra, δ, ppm: 0.78 s (3H, H_3C^{25}), 0.94 s (3H, H_3C^{26}), 0.99 s (3H, H_3C^{27}), 1.13 s (3H, H_3C^{24}), 1.14 s (3H, H_3C^{23}), 1.05–2.27 m (21H, $H_2C^{1,6,7,11,12,15,16a,21,22}$ and $HC^{5,9,13,18}$), 1.70 s (3H, H_3C^{30}), 2.80–3.05 m (2H, $HC^{16b,19}$), 4.64 and 4,75 both br.s (both 1H, H_2C^{29}), 7.46 s (1H, HC^{30}), 7.58 dd (1H, J = 8.2, 7.6 Hz, H5'), 7.67 d (1H, J = 7.6 Hz, H6'), 8.17 d (1H, J = 8.2 Hz, H4'), 8.22 s (1H, H2'), 9.64 s (1H, CH=O). Found, %: C 77.90; H 8.46; N 2.33. $C_{37}H_{49}NO_4$. Calculated, %: C 77.72; H 8.64; N 2.45.

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