SYNTHESIS OF BETULIN DIBENZOATE AND DIPHTHALATE

V. A. Levdanskii,^{1,2} A. V. Levdanskii,¹ and B. N. Kuznetsov^{1,2*}

Betulin-3,28-dibenzoate and -3,28-diphthalate were synthesized for the first time by reacting betulin with melts of benzoic and phthalic acids at 190–200°C for 5 min.

Keywords: betulin, benzoic acid, phthalic acid, melt, esterification, betulin-3,28-dibenzoate, betulin-3,28-diphthalate.

Esters of betulin (1) and other lupane triterpenoids containing aliphatic and aromatic acids possess various biological activities [1-3]. Known methods for preparing betulin esters focus mainly on acylation of 1 by anhydrides or chlorides of the corresponding acids in Py or 1-methyl-2-pyrrolidinone [1-4]. It was shown in a patent [4] that 1 was acylated by phthalic anhydride at 70°C in 48 h in the presence of imidazole in 1-methyl-2-pyrrolidinone.



 $R = Bz (a), HOOCC_6H_4CO (b)$ a. BzOH, 190–200°C; b. C₆H₄(COOH)₂, 190–200°C

The development of simple and efficient methods for preparing esters of **1** was stimulated by their high biological activity. Replacing anhydrides and chlorides of organic acids by the corresponding available acids would simplify and reduce the cost of preparing esters of **1**.

The goal of the research was to study esterification of 1 by melts of benzoic and phthalic acids.

Esterification of 1 by propionic acid in the presence of H_3PO_4 in toluene with removal of the H_2O released by the reaction is known to give betulin-3,28-dipropionate [5].

The corresponding betulin esters could not be produced if the reaction of 1 with benzoic or phthalic acid was carried out in toluene in the presence of H_3PO_4 . It was found that 1 began to isomerize into all obstulin if the reaction was carried out for 6–8 h.

Betulin (1) was esterified by the aromatic acids upon fusion of 1 with benzoic or phthalic acid at 190–200°C to produce betulin-3,28-dibenzoate (2a) or betulin-3,28-diphthalate (2b).

The IR spectrum of **2a** differed from that of **1** by the lack of a broad OH absorption band at 3429 cm⁻¹ and the appearance of a C=O ester absorption band at 1719 cm⁻¹. The ¹³C NMR spectrum of **2a** showed resonances for all 44 C atoms, which agreed with the empirical formula $C_{44}H_{58}O_4$. Two ester resonances were found at 167.1 and 166.4 ppm. Resonances of C atoms located in the *o*-, *m*-, and *p*-positions relative to the ester were observed at 129.8, 130.3, 128.5, 128.6, 133.0, and 133.8 ppm. Resonances of quaternary C atoms associated with the ester groups appeared at 130.6 and 131.1 ppm.

¹⁾ Institute of Chemistry and Chemical Engineering, Siberian Branch, Russian Academy of Sciences, 50-24, Akademgorodok, Krasnoyarsk, 660036, fax: +7 (391) 249 48 94, e-mail: inm@icct.ru; 2) Siberian Federal University, 79 Svobodnyi Prosp., Krasnoyarsk, 660041. Translated from *Khimiya Prirodnykh Soedinenii*, No. 2, March–April, 2017, pp. 263–264. Original article submitted June 9, 2016.

Other resonances in the spectrum of 2a were close to those of 1. This indicated that the skeleton of 1 was unaffected during the reaction. The IR and NMR spectra of 2b agreed with those in the literature [3, 6].

Thus, betulin dibenzoate (2a) and diphthalate (2b) were prepared for the first time by heating 1 with benzoic and phthalic acids at 190–200°C. The structures and compositions of 2a and 2b were established using IR and NMR spectroscopy and elemental analysis.

EXPERIMENTAL

IR spectra were taken from KBr pellets (3 mg of sample per 300 mg of KBr) in the range 400–4000 cm⁻¹ on a Tensor-27 Fourier IR spectrometer (Bruker, Germany). ¹³C NMR spectra were recorded in $CDCl_3$ (TMS = 0) on a Bruker Avance III spectrometer (600 MHz). Elemental analyses were performed on a Flash EATM 1112 elemental analyzer (Thermo Quest, Italy). The amounts (%) of C, H, and O were determined simultaneously. Analytical data for **2a** and **2b** agreed with those calculated.

Melting points were measured on an Electrothermal A9100 apparatus. TLC used Silufol plates (Chemapol, Czech Rep.) and solvent system $CHCl_3$ -MeOH (20:1) with detection by phosphotungstic acid solution (20%) in EtOH followed by heating at 100–200°C for 2–3 min and by I₂ vapor. Betulin was prepared by the literature method [7].

3*β***,28-Dibenzoxylup-20(29)-ene (2a).** A 50-mL three-necked flask equipped with a stirrer, thermometer, and reflux condenser was charged with **1** (4.42 g, 0.01 mol) and benzoic acid (3.66 g, 0.03 mol). The mixture was stirred on an oil bath at 190–200°C for 5 min, cooled, treated with EtOH (60 mL), filtered hot, and transferred to a beaker for crystallization. Yield of **2a**, 89%, mp 139–140°C. $C_{44}H_{58}O_4$. IR spectrum (KBr, v, cm⁻¹): 3069, 2939, 2868, 1719, 1642, 1603, 1452, 1316, 1272, 1176, 1111, 1070, 1027, 711. ¹³C NMR spectrum (CDCl₃, δ, ppm): 38.9 (C-1), 24.2 (C-2), 81.7 (C-3), 38.4 (C-4), 55.5 (C-5), 18.3 (C-6), 34.3 (C-7), 41.1 (C-8), 50.4 (C-9), 36.6 (C-10), 20.8 (C-11), 25.4 (C-12), 37.8 (C-13), 42.8 (C-14), 27.2 (C-15), 30.0 (C-16), 46.9 (C-17), 49.0 (C-18), 47.8 (C-19), 150.3 (C-20), 29.9 (C-21), 34.9 (C-22), 28.0 (C-23), 16.7 (C-24), 16.1 (C-25), 15.5 (C-26), 14.8 (C-27), 63.4 (C-28), 110.1 (C-29), 19.2 (C-30), 167.1, 166.4 (O–C=O), 130.6, 131.1, 129.8, 130.3, 128.5, 128.6, 133.0, 133.8 (C₆H₅).

3,28-Diphthaloxylup-20(29)-ene (2b) was synthesized analogously to **2a**, yield 87%, mp 168–170°C (lit. mp 173–175°C [6]). $C_{46}H_{58}O_8$.

ACKNOWLEDGMENT

The work was supported financially by the Ministry of Education of Russia (Project RFMEF160714X0031). Instruments at the Krasnoyarsk Regional Center for Collective Use, SB, RAS, were used.

REFERENCES

- 1. K.-T. Chue, M.-S. Chang, and L. N. Ten, Chem. Nat. Compd., 47, 583 (2011).
- 2. O. B. Flekhter, N. I. Medvedeva, L. T. Karachurina, L. A. Baltina, F. Z. Galin, F. S. Zarudii, and G. A. Tolstikov, *Pharm. Chem. J.*, **39** (8), 401 (2005).
- 3. M. Kvasnica, J. Sarek, E. Klinotova, P. Dzubak, and M. Hajduch, *Bioorg. Med. Chem.*, 13 (10), 3447 (2005).
- 4. P. A. Krasutsky, R. M. Carlson, and R. Karim, US Pat. No. 6,642,217, Nov. 4, 2003.
- 5. V. A. Levdanskii, A. V. Levdanskii, and B. N. Kuznetsov, RU Pat. No. 2,579,519, Apr. 10, 2016.
- O. B. Flekhter, L. T. Karachurina, V. V. Poroikov, L. P. Nigmatullina, L. A. Baltina, F. S. Zarudii, V. A. Davydova, L. V. Spirikhin, I. P. Baikova, F. Z. Galin, and G. A. Tolstikov, *Russ. J. Bioorg. Chem.*, 26 (3), 192 (2000).
- 7. V. A. Levdanskii and A. V. Levdanskii, *Khim. Rastit. Syr'ya*, No. 1, 131 (2014).