SYNTHESIS OF THE LUPININE ESTER OF BETULONIC ACID

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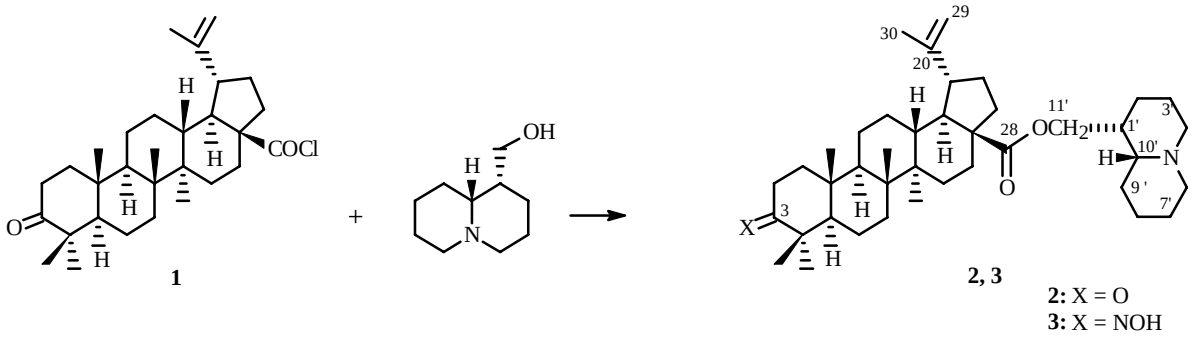
UDC 547.824:542.91:548.737

The lupinine ester and 3-oxime of betulonic acid were prepared for the first time.

Key words: triterpenoid, alkaloid, ester, betulonic acid, lupinine.

The availability and biological activity of plant lupane triterpenoids (betulin, betulonic acid, etc.) and alkaloids (lupinine) have attracted the attention of synthetic chemists for many years [1]. Esters of betulin and betulinic acid include compounds with distinct antiviral, antitumor, and hepatoprotective activity [2-5]. Several lupinine esters exhibit local anesthetic properties [6] and anticholinesterase activity [7]. However, syntheses of triterpene derivatives, including alkaloids, are practically unreported in the literature.

We present for the first time an example of the synthesis of a lupane triterpenoid containing an alkaloid moiety.



Reaction of betulonic acid chloride (**1**) with lupinine was performed in dry CCl_4 in the presence of triethylamine. The yield of ester after recrystallization from alcohol was 75%. The structure of **2** was confirmed by PMR and ^{13}C NMR spectra. Signals for the ester C atoms appear at δ 175.9 (C-28) and 63.1 ppm (C-11′). In addition to signals for the skeleton of betulonic acid, signals of lupinine (19.6, 21.3, 21.4, 32.0, 36.9, 56.5, 63.1 ppm) are found. The oxime derivative was prepared from **2** by reaction with hydroxylamine (87% yield). Compounds **2** and **3** are interesting for studying their biological activity.

EXPERIMENTAL

^{13}C NMR and PMR spectra were recorded on a Bruker AM-300 spectrometer (75.5 and 300 MHz, respectively) in $CDCl_3$ with $SiMe_4$ internal standard. Melting points were determined on a Boetius microstage. TLC was carried out on Silufol plates (Chemapol, Czech Rep.) using $CHCl_3$:CH_3OH (20:1). Compounds were detected by phosphotungstic acid solution (10%) in ethanol with subsequent heating at 100-120°C for 2-3 min. Optical density was measured on a Perkin—Elmer 241 MC polarimeter with a 1-dm tube. Elemental analyses corresponded with those calculated. Betulonic acid chloride (**1**) was prepared by the literature method [8].

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0009-3130/04/4006-0569

Lupinine Ester of Betulonic Acid [1-(1-isopropenyl-5a,5b,8,8,11a-pentamethyl-9-oxoperhydrocyclopenta-[*a*]chrysen-3-ylcarbonylhydroxymethyl)perhydroquinolizine] (2). A solution of **1** (1 mmol, 0.49 g) in dry CCl_4 (20 mL) was treated with lupinine (1.3 mmol, 0.22 g) and Et_3N (1.8 mL), refluxed for 3 h, washed with HCl solution (5%, 2 × 50 mL) and water (1 × 50 mL), and dried over $CaCl_2$. Solvent was removed in vacuum. The solid was recrystallized from ethanol.

Yield 0.45 g (75%) of a light-yellow compound, R_f 0.20, mp 148°C, $[\alpha]_D^{20}$ +25° (*c* 0.04, $CHCl_3$), $C_{40}H_{63}NO_3$.

PMR spectrum: 0.93, 0.96, 0.98, 1.00, 1.06, 1.67 (6s, 18H, $6CH_3$), 1.15-2.00 (m, 21H, CH_2, CH), 2.17-2.30 (m, 11H, H1′-H3′, H7′-H9′), 2.34-2.54 (m, 8H, H13, H16, H4′, H6′, H10′), 2.98-3.03 (m, 1H, H19), 4.21-4.33 (m, 2H, H11′), 4.59 and 4.72 (both br.s, 2H, H29).

^{13}C NMR spectrum: 14.6, 15.7, 15.8, 15.9, 16.0, 19.2, 19.3, 19.6 (C-7′), 21.0, 21.3 (C-2′, C-3′), 21.4 (C-8′), 25.5, 26.6, 29.7, 30.6, 32.0 (C-1′), 33.6, 34.0, 36.7, 36.8, 36.9 (C-9′), 37.0, 37.8, 38.3, 40.6, 42.4, 47.1, 47.2, 49.3, 49.9, 56.4, 56.5 (C-4′, C-6′), 63.1 (C-10′, C-11′), 109.6 (C-29), 150.5 (C-20), 175.9 (C-28), 218.0 (C-3).

Lupinine Ester of Betulonic Acid 3-Oxime [1-(9-oximino-1-isopropenyl-5a,5b,8,8,11a-pentamethylperhydro-cyclopenta[*a*]chrysen-3-ylcarbonylhydroxymethyl)perhydroquinolizine] (3). A solution of **2** (1 mmol, 0.61 g) in anhydrous pyridine (30 mL) was treated with $NH_2OH \cdot HCl$ (7 mmol, 0.5 g), refluxed for 2 h, cooled, and poured into HCl solution (150 mL, 5%). The solid was filtered off, washed with water, and dried.

Yield 0.54 g (87%) of a yellow compound, R_f 0.13, mp 177-179°C, $[\alpha]_D^{20}$ +1.4° (*c* 0.1, $CHCl_3$), $C_{40}H_{64}N_2O_3$.

PMR spectrum: 0.76, 0.96, 1.05, 1.13, 1.26, 1.70 (6s, 18H, CH_3), 1.31-1.82 (m, 21H, CH_2, CH), 1.92-2.10 (m, 11H, H1′-H3′, H7′-H9′), 2.15-2.43 (m, 8H, H13, H16, H4′, H6′, H10′), 2.96-3.04 (m, 1H, H19), 4.61 (br.s, 3H, H29, H11′), 4.74 (br.s, 1H, H29), 8.55-8.61 (m, 1H, –NO<u>H</u>).

^{13}C NMR spectrum: 14.5, 15.5, 15.7, 15.9, 16.1, 18.5, 19.1, 19.3 (C-7′), 21.2 (C-2′, C-3′), 21.3 (C-8′), 22.9, 25.5, 27.4, 29.6, 29.7, 30.5, 32.3 (C-1′), 33.9, 34.5, 36.8, 37.2 (C-9′), 37.5, 38.3, 38.6, 40.3, 40.7, 42.4, 46.9, 49.4, 50.1, 55.5, 56.3 (C-4′, C-6′), 63.2 (C-10′, C-11′), 109.5 (C-29), 150.6 (C-20), 167.5 (C-3), 176.4 (C-28).

ACKNOWLEDGMENT

The work was supported financially by the Russian Foundation for Basic Research (project 02-03-81007) and grants from the RF President for support of young Russian scientists and leading scientific schools (MK-543.2003.03, NSh-1488.2003.3). O. B. F. thanks the Foundation for Domestic Scientific Collaboration (Young Science Candidates Program).

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