Chemistry of Natural Compounds, Vol. 40, No. 2, 2004

SELECTIVE OXIDATION OF TRITERPENE ALCOHOLS BY SODIUM HYPOCHLORITE

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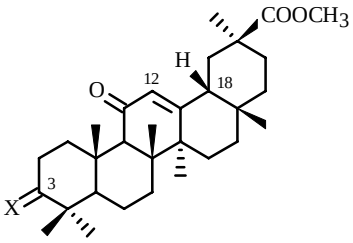
UDC 547.918:547.914.4.057

3-Oxo-triterpenoids were prepared by oxidation of the methyl esters of glycyrrhetic acid, allobetulin, and 20-oxo-29-nor-betulin with sodium hypochlorite in acetic acid or methylene chloride under phase-transfer conditions.

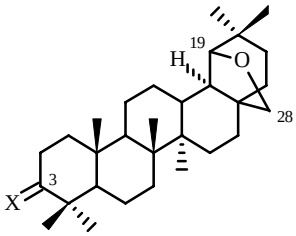
Key words: oxidation; sodium hypochlorite; selectivity; methyl esters of glycyrrhetic acid, allobetulin, 20-oxo-29-nor-betulin.

Sodium hypochlorite is used successfully for oxidation under mild conditions of secondary alcohols to ketones [1-3] and allylic chlorination of terminal olefins [4]. The oxidation of triterpene alcohols by NaOCl has not been reported. Traditional oxidants such as Cr(VI) [6], *m*-CPBA (*m*-chloroperbenzoic acid) [7], "activated" dimethylsulfoxide [8] and others, which often lead to several side products [7-9], are used to prepare 3-oxo-derivatives of triterpenoids, which are valuable intermediates in the synthesis of several biologically active compounds [5].

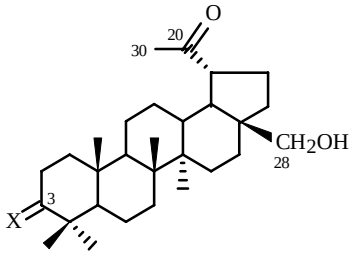
We observed that NaOCl oxidizes the 3β-hydroxyl of certain triterpenoids. The methyl esters of glycyrrhetic acid (**1**), allobetulin (**2**), and 20-oxo-29-nor-betulin (messagenin) (**3**) give 3-oxo-derivatives **4**-**6**. The reaction was carried out in acetic acid [10] or methylene chloride in the presence of the phase-transfer catalyst hexadecyltrimethylammonium bromide [11] using three equivalents of NaOCl. The formation of the ketone on C-3 in compounds **4**-**6** was inferred from the presence of a signal at 217.1-218.2 ppm and the absence of a signal for proton H-3 at 3.10-3.20 ppm, which is observed in NMR spectra of the starting triterpene alcohols. Signals belonging to the primary alcohol in NMR spectra of **6** persist, confirming that the oxidation is selective. This is consistent with the known reactivity of NaOCl [10].



1, 4



2, 5



3, 6

1 - 3: X = 

4 - 6: X = O

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EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded on an AM-300 spectrometer (Bruker, 300 and 75.5 MHz, respectively) in $CDCl_3$ with $SiMe_4$ internal standard. Melting points were determined on a Boetius microstage. TLC was performed on Silufol plates (Chemapol, Czech Rep.) using the solvent systems $CHCl_3$:CH_3OH (20:1, A; 25:1, B). Compounds were detected using phosphotungstate solution in EtOH (10%) with subsequent heating at 100-120°C for 2-3 min. Aqueous NaOCl (1 M, OAO Ufakhimprom, Rep. of Bashkortostan) was used in the experiments.

The methyl esters of glycyrrhetic acid (**1**), allobetulin (**2**), and 20-oxo-29-nor-betulin (**3**) were prepared as before [12-14]. Elemental analyses agreed with those calculated.

Oxidation of 1-3. Method a) A solution of **1-3** (1 mmol) in acetic acid (10 mL) was stirred and treated dropwise with NaOCl solution (0.60 mL, 3 eq., 1M), held at room temperature for 1 h, and treated with KOH solution (50 mL, 5%). The resulting precipitate was filtered off, washed with water until the washings were neutral, and dried. Yield 90-95%.

Method b) A suspension of hexadecyltrimethylammonium bromide (0.020 mmol) in CH_2Cl_2 (10 mL) and water (10 mL) was stirred, treated with **1-3** (1 mmol) and then dropwise with NaOCl solution (0.60 mL, 3 eq., 1 M), and held at room temperature for 1-2 h (TLC monitoring). The organic layer was separated, washed with water (2 × 10 mL), dried over $MgSO_4$, and evaporated in vacuum. The solid was dissolved in $CHCl_3$ (10 mL), passed over a layer of aluminum oxide (1 cm), and evaporated in vacuum. Yield 76-81%.

Methyl Ester of 3,11-Dioxo-18β-olean-12-en-20β-oic Acid (4). Yield 0.45 g (93%) (method a) and 0.37 g (76%) (method b) from **1**, R_f 0.85 (system A), mp 248°C, lit. [15] mp 248-249°C, $C_{31}H_{46}O_4$.

PMR spectrum (δ, ppm, J/Hz): 0.80, 1.04, 1.08, 1.13, 1.14, 1.25, 1.35 (7s, 21H, $7CH_3$), 1.15-2.10 (m, CH, CH_2), 2.32 (s, 1H, H-9), 2.80 (d, 1H, J = 13.5, H-18), 3.67 (s, 3H, OCH_3), 5.68 (br.s, 1H, H-12).

^{13}C NMR spectrum (δ, ppm): 15.6. 18.5, 18.7, 21.3, 21.4, 23.4, 26.4, 26.5, 28.2, 28.5, 31.0, 31.7, 32.0, 34.1, 36.4, 37.6, 39.6, 41.1, 43.2, 44.9, 45.2, 47.7, 48.3, 51.8, 55.3, 61.0 (C-9), 128.4 (C-12), 169.5 (C-13), 176.8 (C-30), 199.4 (C-11), 217.1 (C-3).

19β,28-Epoxy-18α-olean-3-one (5). Yield 0.42 g (95%) (method a) and 0.35 g (79%) (method b) from **2**, R_f 0.82 (system B), mp 230°C, lit. [16] mp 230-231°C, $C_{30}H_{48}O_2$.

PMR spectrum (δ, ppm, J/Hz): 0.80, 0.92, 0.93, 0.95, 1.02, 1.04, 1.10 (7s, 21H, $7CH_3$), 1.15-2.00 (m, CH, CH_2), 2.46 (m, 2H, H-2), 3.47 and 3.80 (both d, 1H each, J = 6, H-28), 3.55 (s, 1H, H-19).

^{13}C NMR spectrum (δ, ppm): 13.00, 15.4, 16.2, 18.6, 19.4, 20.8, 21.2, 21.6, 24.1, 25.3, 25.7, 25.8, 25.9, 28.2, 32.2, 33.0, 33.5, 35.8, 36.2, 38.7, 40.2, 40.4, 41.0, 46.8, 48.8, 51.7, 56.6, 70.6 (C-28), 87.4 (C-19), 218.0 (C-3).

3,20-Dioxo-29-nor-lup-28-ol (6). Yield 0.41 g (92%) (method a) and 0.36 g (81%) (method b) from **3**, R_f 0.52 (system B), mp 125°C, $C_{29}H_{46}O_3$.

PMR spectrum (δ, ppm, J/Hz): 0.67, 0.74, 0.88, 0.91, 0.92 (5s, 15H, $5CH_3$), 1.00-2.00 (m, CH, CH_2), 2.16 (s, 3H, H-30), 2.40-2.45 (m, 1H, H-19), 3.25 (d, 1H, J = 11, H-28), 3.80 (d, 1H, J = 11, H-28).

^{13}C NMR spectrum (δ, ppm): 14.5, 15.8, 15.9, 16.3, 17.9, 19.6, 21.3, 26.8, 27.0, 27.3, 27.7, 28.7, 29.5, 33.3, 33.8, 36.1, 36.9, 37.6, 38.1, 40.6, 42.4, 46.1, 49.2, 49.9, 51.5, 55.1, 60.5 (C-28), 211.0 (C-20), 218.2 (C-3).

ACKNOWLEDGMENT

The work was supported by the Russian Basic Research Foundation (project 02-03-81007) and grants of the RF President and Young Russian Scientists and Leading Scientific Schools (projects MK-543.2003.03, NSh-1488.2003.3). We thank the Russian Foundation for Science Support (Young Investigators Program).

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