Unusual ozonolysis pattern for 28-oxo-2,3-indoloallobetulin

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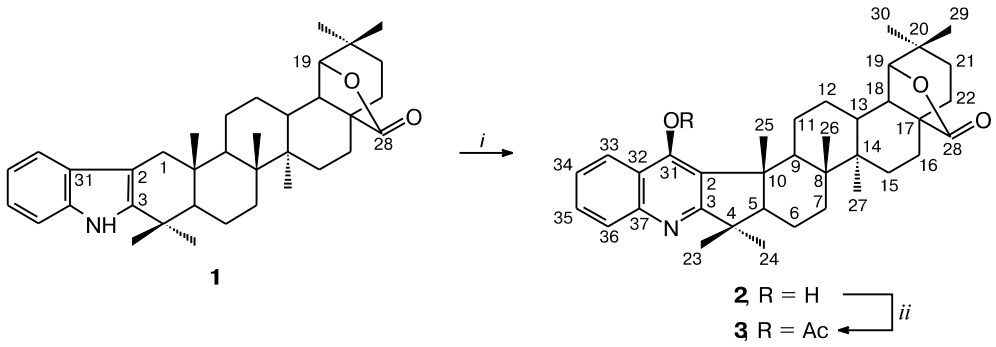
It is shown that ozonolysis of 2,3-indolotriterpenoids is a new approach for synthesis of 4-hydroxyquinolino-A-nortriterpanoids.

Key words: triterpenoids, ozonolysis, quinolines, indoles.

It is known that the ozonolysis of 2,3-indolosteroids obtained by the Fischer reaction from 3-oxo steroids normally involves cleavage of the C(2)C(3) double bond and formation of oxo lactams.[1] Attempted ozonolysis of 28-oxo-2,3-indoloallobetulin **1** gave 4-hydroxyquinoline derivative **2** (Scheme 1). When discussing the ozonolysis pathway for indolotriterpenoid **1**, one can assume that initially ozone adds to the C(2)=C(3) double bond to form an unstable 1,2,3-trioxolane ring. The decomposition of this ring is accompanied by sigmatropic rearrangements involving two H atoms and the C(2)—C(3) bond and gives a ketone, which is more stable in the form of hydroxyquinoline **2** (Scheme 2). Its structure was confirmed by X-ray diffraction study of acetate **3** (Fig. 1).

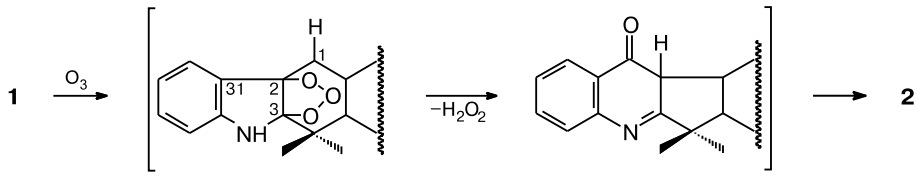
Thus, the ozonolysis of 2,3-indolotriterpenoids provides a novel route to 4-hydroxyquinolino-A-nortriterpenoids.

Scheme 1



Conditions: *i*. O_3, CH_2Cl_2, −40 °C; *ii*. Ac_2O/pyridine, 115 °C.

Scheme 2



Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1753—1754, August, 2011.

1066-5285/11/6008-1781

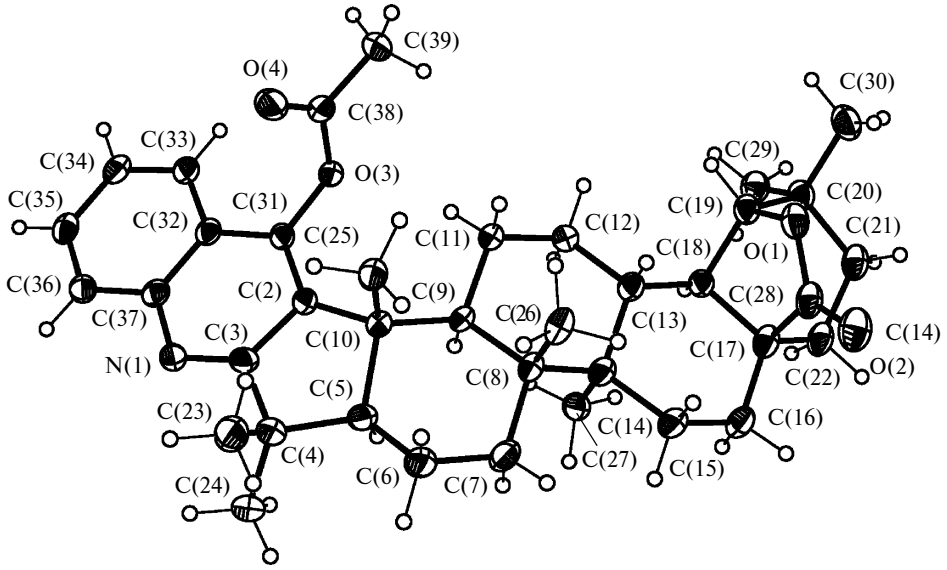


Fig. 1. Molecular structure **3**. This compound crystallizes as a 2 : 1 solvate with benzene. The solvate benzene molecule is omitted.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III pulse spectrometer (Germany) operated at 500.13 and 125.47 MHz, respectively, and equipped with a 5-mm PABBO Z-gradient probe (sample temperature 298 K, $SiMe_4$ as the internal standard). Melting points were determined on a Boetius microscope stage. Optical rotation was measured on a Perkin—Elmer 241 MC polarimeter (Germany) in a 1-dm-long tube. TLC analysis was carried out on Sorbfil plates (Sorbpolimer, Russia) in chloroform—ethyl acetate (40 : 1). Spots were visualized with 10% H_2SO_4 followed by heating at 100—120 °C for 2—3 min. An Ozon-2K ozonizer (Russia) was used. 28-Oxo-2,3-indoloallobetulin **1** was prepared from 28-oxoallobetulone according to the Fischer reaction as described earlier.[2]

9-Hydroxy-7,18,18,22,23,29,29-heptamethyl-30-oxa-16-azaoctacyclo[24.3.2.0^{2,26}.0^{3,23}.0^{6,22}.0^{7,19}.0^{8,17}.0^{10,15}]hentriaconta-8(9),10(15),11,13,16-pentaen-31-one (2) (compounds **2** and **3** are named according to the IUPAC recommendations cited at http://www.chem.qmul.ac.uk/iupac/vonBaeyer/). Ozone was bubbled at −40 °C through a solution of compound **1** (1.06 g, 2 mmol) in CH_2Cl_2 (30 mL) (monitoring by TLC). The solvent was concentrated *in vacuo* and the residue was chromatographed on silica gel with benzene as an eluent. Yield 0.78 g (71%), m.p. 215 °C, $[\alpha]_D^{20}$ +19.5 (*c* 0.5, $CHCl_3$). Found (%): C, 79.79; H, 8.72; N, 2.60. $C_{36}H_{47}NO_3$ (*M* = 541.76). Calculated (%): C, 79.81; H, 8.74; N, 2.59. ^{1}H NMR ($CDCl_3$; the atomic numbering in the NMR spectra of compounds **2** and **3** is the same as that in Scheme 1), δ: 0.89 (s, 3 H, Me(27)); 0.91 (s, 3 H, Me(29)); 1.01 (s, 3 H, Me(30)); 1.02 (s, 3 H, Me(26)); 1.04 (m, 1 H, H_{ax}C(12)); 1.15 (s, 3 H, Me(23)); 1.21 (m, 1 H, H_{eq}C(15)); 1.30 (s, 3 H, Me(25)); 1.36 (ddd, 1 H, HC(13), $^3J_{13-12_{ax}}$ = 13.1 Hz, $^3J_{13-18}$ = 11.5 Hz, $^3J_{13-12_{eq}}$ = 3.4 Hz); 1.41 (m, 2 H, H_{ax}C(15), H_{ax}C(16)); 1.42 (m, 1 H, H_{eq}C(21)); 1.43 (s, 3 H, Me(24)); 1.44 (m, 1 H, H_{ax}C(7)); 1.48 (m, 1 H, H_{ax}C(21)); 1.50 (m, 1 H, H_{eq}C(7)); 1.52 (m, 2 H, H_{ax}C(22), H_{eq}C(6)); 1.54 (m, 1 H, H_{eq}C(22)); 1.58 (m, 1 H, H_{ax}C(6)); 1.59 (m, 1 H, H_{eq}C(12)); 1.65 (dddd, 1 H, H_{ax}C(11), ^2J = 11.6 Hz, $^3J_{11_{ax}-12_{ax}}$ = 13.1 Hz, $^3J_{11_{ax}-9}$ = 12.4 Hz, $^3J_{11_{ax}-12_{eq}}$ = 4.5 Hz); 1.66 (dd, 1 H, HC(5), $^3J_{5-6_{ax}}$ = 13.4 Hz, $^3J_{5-6_{eq}}$ = 3.7 Hz); 1.73 (dd, 1 H, HC(18), $^3J_{18-13}$ = 11.5 Hz, $^3J_{18-19}$ = 0.7 Hz); 1.88 (m, 1 H, H_{eq}C(16)); 2.15 (dd, 1 H, HC(9), $^3J_{9-11_{ax}}$ = 12.4 Hz, $^3J_{9-11_{eq}}$ = 2.8 Hz); 3.57 (m, 1 H, H_{eq}C(11)); 3.91 (t, 1 H, HC(19), $^3J_{19-18}$ = 0.7 Hz, $^4J_{19-21_{eq}}$ = 0.7 Hz); 7.22 (ddd, 1 H, HC(35), $^3J_{35-36}$ = 8.3 Hz, $^3J_{35-34}$ = 6.9 Hz, $^4J_{35-33}$ = 1.0 Hz); 7.46 (ddd, 1 H, HC(34), $^3J_{34-33}$ = 8.3 Hz, $^3J_{34-35}$ = 6.9 Hz, $^4J_{34-36}$ = 1.0 Hz); 7.57 (br.d, 1 H, HC(33), $^3J_{33-34}$ = 8.3 Hz); 8.34 (dd, 1 H, HC(36), $^3J_{36-35}$ = 8.3 Hz, $^4J_{36-34}$ = 1.0 Hz); 10.55 (br.s, 1 H, C(31)OH). ^{13}C NMR, δ: 13.6 (C(27)), 16.6 (C(6)), 17.3 (C(26)), 19.1 (C(25)), 21.2 (C(23)), 23.9 (C(29)), 24.2 (C(11)), 25.7 (C(16)), 26.5 (C(12)), 27.0 (C(24)), 27.9 (C(15)), 28.7 (C(30)), 31.9 (C(22)), 32.3 (C(21)), 33.4 (C(20)), 34.6 (C(7)), 35.7 (C(13)), 40.6 (C(14)), 42.8 (C(8)), 43.3 (C(4)), 46.0 (C(17)), 46.8 (C(18)), 49.7 (C(9)), 50.7 (C(10)), 61.5 (C(5)), 86.3 (C(19)), 117.6 (C(33)), 123.1 (C(35)), 126.3 (C(36)), 127.0 (C(32)), 130.8 (C(34)), 131.1 (C(2)), 139.5 (C(37)), 161.9 (C(31)), 175.8 (C(3)), 180.4 (C(28)).

9-Acetoxy-7,18,18,22,23,29,29-heptamethyl-30-oxa-16-azaoctacyclo[24.3.2.0^{2,26}.0^{3,23}.0^{6,22}.0^{7,19}.0^{8,17}.0^{10,15}]hentriaconta-8(9),10(15),11,13,16-pentaen-31-one (3). Acetic anhydride (1 mL) was added to a solution of compound **2** (0.55 g, 1 mmol) in pyridine (25 mL). The reaction mixture was refluxed for 2 h and poured into 5% HCl (100 mL). The precipitate that formed was filtered off, washed, dried, and recrystallized from benzene. Yield 0.53 g (90%), m.p. 236 °C, $[\alpha]_D^{20}$ +18 (*c* 0.1, $CHCl_3$). Found (%): C, 78.16; H, 8.44; N, 2.38. $C_{38}H_{49}NO_4$ (*M* = 583.82). Calculated (%): C, 78.18; H, 8.46; N, 2.40. ^{1}H NMR ($CDCl_3$), δ: 0.91 (s, 3 H, Me(27)); 0.98 (s, 3 H, Me(29)); 1.06 (s, 3 H, Me(30)); 1.09 (s, 3 H, Me(26)); 1.19 (m, 1 H, H_{ax}C(12)); 1.20 (s, 6 H, Me(23), Me(25)); 1.27 (m, 1 H, H_{eq}C(15)); 1.41 (m, 1 H, H_{ax}C(15)); 1.43 (m, 1 H, H_{ax}C(16)); 1.44 (m, 1 H, H_{eq}C(21)); 1.45 (s, 3 H, Me(24)); 1.48 (m, 1 H, HC(13)); 1.50 (m, 1 H, H_{ax}C(7)); 1.53 (m, 1 H, H_{ax}C(22)); 1.54 (m, 1 H, H_{ax}C(21)); 1.55 (m, 1 H, H_{eq}C(22)); 1.57 (m, 1 H, H_{eq}C(7)); 1.66 (m, 1 H, H_{eq}C(6)); 1.72 (m, 1 H, H_{ax}C(6)); 1.74 (m, 1 H,

HC(5)); 1.75 (m, 1 H, $H_{ax}C(11)$); 1.79 (m, 1 H, $H_{eq}C(12)$); 1.81 (dd, 1 H, HC(18), $^3J_{18-13}$ = 11.5 Hz, $^3J_{18-19}$ = 0.7 Hz); 1.91 (m, 1 H, $H_{eq}C(16)$); 2.26 (dd, 1 H, HC(9), $^3J_{9-11ax}$ = 12.3 Hz, $^3J_{9-11_{eq}}$ = 2.8 Hz); 2.49 (s, 3 H, Me(39)); 2.68 (m, 1 H, $H_{eq}C(11)$); 3.99 (t, 1 H, HC(19), $^3J_{19-18}$ = 0.7 Hz, $^4J_{19-21_{eq}}$ = = 0.7 Hz); 7.47 (ddd, 1 H, HC(34), $^3J_{34-33}$ = 8.3 Hz, $^3J_{34-35}$ = = 6.9 Hz, $^4J_{34-36}$ = 1.0 Hz); 7.63 (dd, 1 H, HC(33), $^3J_{33-34}$ = = 8.3 Hz, $^4J_{33-35}$ = 1.0 Hz); 7.64 (ddd, 1 H, HC(35), $^3J_{35-36}$ = = 8.3 Hz, $^3J_{35-34}$ = 6.9 Hz, $^4J_{35-33}$ = 1.0 Hz); 8.07 (br.d, 1 H, HC(36), $^3J_{36-35}$ = 8.3 Hz). ^{13}C NMR, δ: 13.5 (C(27)), 17.0 (C(6)), 17.4 (C(26)), 19.9 (C(25)), 21.3 (C(39)), 22.4 (C(23)), 24.0 (C(29)), 24.2 (C(11)), 25.6 (C(16)), 26.5 (C(12)), 27.9 (C(15)), 28.7 (C(24)), 28.8 (C(30)), 31.9 (C(22)), 32.3 (C(21)), 33.6 (C(20)), 34.3 (C(7)), 35.7 (C(13)), 40.8 (C(14)), 43.4 (C(8)), 43.9 (C(4)), 46.0 (C(17)), 46.7 (C(18)), 48.1 (C(9)), 50.5 (C(10)), 61.9 (C(5)), 85.9 (C(19)), 121.2 (C(33)), 122.2 (C(32)), 126.1 (C(34)), 128.9 (C(35)), 129.0 (C(36)), 136.2 (C(2)), 148.8 (C(37)), 159.9 (C(31)), 168.3 (C(38)), 175.1 (C(3)), 179.8 (C(28)).

X-ray diffraction study of compound 3. Colorless crystals of **3** · $1/2C_6H_6$ ($C_{41}H_{52}NO_4$, M = 622.84), trigonal prisms, space group $P3_121$; at 100 K, a = 16.4198(3) Å, c = 24.5412(7) Å, V = 5730.1(2) Å^3, Z = 6, d_{calc} = 1.083 g cm^{-3}, $F(000)$ = 2022, μ = 0.068 mm^{-1}. The unit cell parameters and the intensities of 54 579 reflections were measured on a Bruker SMART Apex-II CCD automatic diffractometer (T = 100 K, λMoKα radiation, graphite monochromator, φ and ω scan modes, θ_{max} = 26°). The structure was solved by the direct method and refined by the full-matrix least-squares method on F^2 in the anisotropic approximation for the non-hydrogen atoms. The hydrogen atoms were located geometrically and refined isotropically with fixed coordinates (using a riding model) and thermal parameters ($U_{iso}(H) = 1.5U_{eq}(C)$ for the Me groups and $U_{iso}(H) = 1.2U_{eq}(C)$ for all the other groups). Final residuals are R_1 = 0.055 for 3669 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.147 for all 4128 independent reflections, S = 1.001. All calculations were performed with the SHELXTL program package.[3] The tables of the atomic coordinates, bond lengths, bond angles, and anisotropic thermal parameters for structure **3** · $1/2C_6H_6$ have been deposited with the Cambridge Crystallographic Data Center (CCDC No. 781689).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 09-03-00831) and the Council on Grants at the President of the Russian Federation (State Support Program for Young Russian Scientists, Grant MD-3852.2009.3.).

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Received July 30, 2010;
in revised form November 26, 2010