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BECKMANN REARRANGEMENT OF 11-DEOXO-GLYCYRRHETIC ACID 3-KETOXIME

L. R. Mikhailova, M. V. Khudobko,*
L. A. Baltina, Jr., and L. A. Baltina

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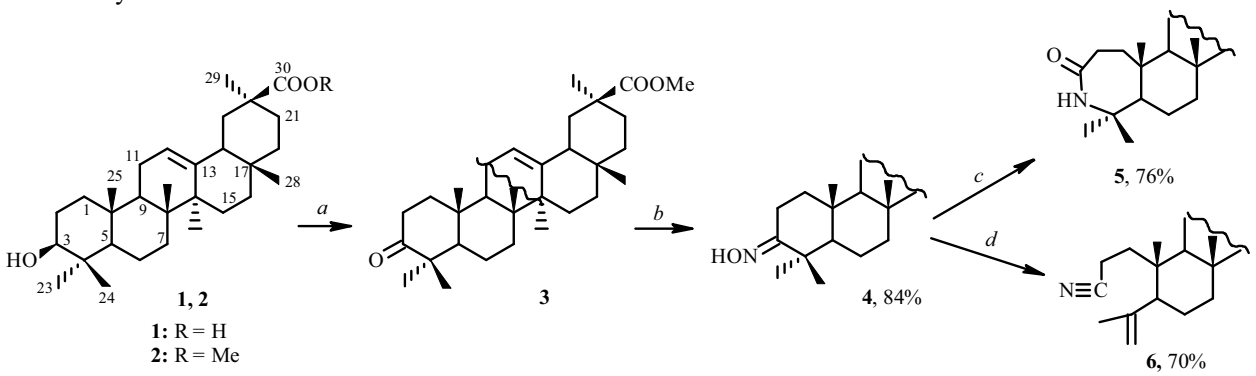
A-Homo-4-aza-3-oxo- and 3-cyano-3,4-seco-olean-4,12-diene derivatives of 11-deoxo-glycyrrhetic acid were synthesized by first- and second-order Beckmann rearrangement of 3-hydroxyiminoolean-12-en-30-oic acid methyl ester.

Key words: 11-deoxo-glycyrrhetic acid, Beckmann rearrangement, derivatives.

Synthetic transformations of bioactive plant metabolites represent an active direction of modern organic and bioorganic chemistry that seeks to synthesize new biologically active compounds with new structures that are promising in medicine [1, 2]. Beckmann rearrangement of triterpenoid ketoximes has been studied using as examples allobetulone [3], lupenone [4], β-amyrin [5], friedelin [6], 18α- and 18β-glycyrrhetic acids [7], and oleanolic acid [8]. As a rule, Beckmann rearrangement of triterpenoid 3-ketoximes forms lactams (aza derivatives) and 3,4-*seco*-nitriles. It was shown previously that aza derivatives of oleanolic acid are interesting as promoters of percutaneous transport of bioactive compounds [8]. This is very important for the development of external drug forms and cosmetics.

In order to prepare new biologically active derivatives of 11-deoxo-glycyrrhetic acid (GLA) (**1**), one of the minor triterpenoids from roots of *Glycyrrhiza glabra* L. and *G. uralensis* Fisher, we performed synthetic transformations of the methyl ester of 11-deoxo-GLA (**2**) on ring A (Scheme 1). Oxidation of **2** by pyridinium dichromate (PDC) in CH_2Cl_2 at room temperature produced the 3-ketone (**3**) in 70% yield, reaction of which with $NH_2OH{\cdot}HCl$ in anhydrous Py by refluxing for 1 h formed the pure (TLC) 3-hydroxyimine (3-ketoxime) (**4**) in 84% yield. Its stereochemistry was not determined. The ^{13}C NMR spectrum of **4** contained a resonance at δ 166.5 ppm, which was shifted to strong field by 51 ppm compared with the spectrum of starting **3** as a result of forming the C=N– bond.

Reaction of **4** with $SOCl_2$ in anhydrous dioxane at 10°C formed lactam **5**, the methyl ester of A-homo-4-aza-3-oxo-11-deoxoolean-12-en-30-oic acid, as a result of a first-order Beckmann rearrangement. We demonstrated this previously using 3-hydroxyolean-9(11),12-dien-30-oic acid as an example [9]. The A-homo-4-aza derivative (**5**) was isolated in 76% yield after recrystallization from EtOH.



a. PDC, CH_2Cl_2; *b*. $NH_2OH{\cdot}HCl$, Py, 115°C; *c*. $SOCl_2$, 10°C, 1% KOH; *d. p*-TsCl, Py, 115°C, 5 h

Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, 450054, prosp. Oktyabrya, 71, fax: +7 347 235 60 66, e-mail: baltina@anrb.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 441–443, July–August, 2009. Original article submitted March 16, 2009.

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The structure of **5** has already been established using spectral methods. Thus, the resonance for C3 was shifted from 166.5 to 176.6 ppm (C=O) in the ^{13}C NMR spectrum of **5**. Resonances of C2 and C4 shifted simultaneously by 2–5 ppm to weak field. The IR spectrum of **5** showed an absorption maximum for the C=O group at 1662 cm^{-1}.

Refluxing **4** with *p*-TsCl in anhydrous Py for 5 h induced a second-order Beckmann rearrangement that formed the 3-cyano-3,4-*seco*-4-ene (**6**) in 70% yield. Its ^{13}C NMR spectrum showed a resonance for the nitrile at δ 121.3 ppm and for the new olefin bond at δ 167.1 and 116.7 ppm.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AM-300 and AMX-300 spectrometers at operating frequency 300 MHz (^1H) and 75.5 (^{13}C) with TMS internal standard. Resonances were assigned using the ACD LABS program set and literature data for GLA and its derivatives [10, 11]. IR spectra were recorded in mineral-oil mulls on an IR Prestige-21 spectrometer (Shimadzu). Molecular ions were determined by LC/MS in an LCMS-2010 instrument (Shimadzu) using atmospheric pressure chemical ionization (APCI) of MeOH solutions. Specific rotation was measured on a Perkin–Elmer 341 polarimeter in a 1-dm tube at 20-22°C (λ_{Na} 546 nm). Melting points were determined on a Boetius microstage.

Thin-layer chromatography (TLC) used Sorbfil (ZAO Sorbpolimer) plates. Spots were detected using phosphotungstic acid (20%) or H_2SO_4 (5%) in EtOH with subsequent heating at 110–120°C for 2–3 min. Solvents were purified by standard methods [12]. 11-Deoxo-GLA (**1**) and its methyl ester (**2**) were prepared by the literature methods [13, 14].

3-Oxoolean-12-en-30-oic Acid Methyl Ester (3). A solution of **2** (0.47 g, 1 mmol) in CH_2Cl_2 (3 mL) was treated with a solution of PDC (0.32 g, 1.5 mmol) in CH_2Cl_2 (2 mL) and stirred for 30 min with TLC monitoring. The black precipitate was filtered off. The mixture was washed with water, then saturated $NaHCO_3$ and NaCl solutions, and water again. The organic layer was passed over a thin layer of Al_2O_3 in a column. The colorless solution was evaporated. The solid was recrystallized from EtOH. Yield 0.34 g (70.5%), R_f 0.80 (toluene:EtOAc, 3:1), mp 186-188°C.

PMR spectrum ($CDCl_3$, δ, ppm): 0.76 (3H, s, CH_3-28), 0.98 (3H, s, CH_3-25), 1.02 (3H, s, CH_3-26), 1.04 (3H, s, CH_3-24), 1.06 (3H, s, CH_3-23), 1.10 (3H, s, CH_3-27), 1.14 (3H, s, CH_3-29), 1.20-1.95 (2H, m, CH_2), 3.67 (3H, s, OCH_3), 5.26 (1H, s, H-12).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 39.6 (C-1), 34.0 (C-2), 217.5 (C-3), 48.1 (C-4), 55.2 (C-5), 19.5 (C-6), 32.0 (C-7), 39.2 (C-8), 46.7 (C-9), 36.5 (C-10), 23.5 (C-11), 122.2 (C-12), 144.3 (C-13), 44.1 (C-14), 26.4 (C-15), 26.0 (C-16), 31.8 (C-17), 47.3 (C-18), 41.5 (C-19), 42.7 (C-20), 31.2 (C-21), 38.3 (C-22), 26.8 (C-23), 21.4 (C-24), 15.1 (C-25), 16.6 (C-26), 25.7 (C-27), 28.1 (C-28), 28.4 (C-29), 177.5 (C-30), 51.5 (C-31).

Mass spectrum (*m*/*z*): $[M + H]^+$ 470. $C_{31}H_{48}O_3$, MW 468.7; lit. [15] mp 190°C, $[\alpha]_D^{20}$ +143°.

3-Hydroxyiminoolean-12-en-30-oic Acid Methyl Ester (4). A solution of **3** (0.19 g, 0.4 mmol) in anhydrous Py (8 mL) was treated with $NH_2OH \cdot HCl$ (0.38 g), refluxed for 1 h, and diluted with cold water. The precipitate was filtered off, washed with water, and dried. The dry product was recrystallized from EtOH. Yield 0.16 g (84.2%), R_f 0.30 (C_6H_6:MeOH, 50:1), mp 265–267°. IR spectrum (ν, cm^{-1}): 3450-3100 (OH), 1660 (C=N–).

PMR spectrum ($CDCl_3$, δ, ppm): 0.78 (3H, s, CH_3-28), 0.90 (3H, s, CH_3-25), 1.00 (3H, s, CH_3-26), 1.13, 1.14 (each 3H, s, CH_3-24, CH_3-23), 1.28, 1.29 (each 3H, both s, CH_3-27, CH_3-29), 1.30-1.95 (**C**H, m, CH_2), 3.66 (3H, s, OCH_3), 5.25 (1H, s, H-12), 8.30 (1H, br.s, =N–OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 38.6 (C-1), 28.1 (C-2), 166.5 (C-3), 40.2 (C-4), 55.8 (C-5), 19.0 (C-6), 32.4 (C-7), 39.8 (C-8), 47.1 (C-9), 36.9 (C-10), 23.5 (C-11), 122.4 (C-12), 144.3 (C-13), 44.2 (C-14), 26.9 (C-15), 26.0 (C-16), 31.9 (C-17), 48.2 (C-18), 41.6 (C-19), 42.7 (C-20), 31.2 (C-21), 38.3 (C-22), 27.2 (C-23), 20.8 (C-24), 16.9 (C-25), 16.7 (C-26), 23.2 (C-27), 28.4 (C-28), 29.6 (C-29), 177.5 (C-30), 51.4 (C-31).

Found (%): N 2.74. $C_{31}H_{49}O_3N$, calc. (%): N 2.89, MW 483.7.

A-Homo-4-aza-3-oxoolean-12-en-30-oic Acid Methyl Ester (5). A solution of **4** (0.28 g, 0.6 mmol) in anhydrous dioxane (30 mL) was cooled (+10°C), treated with freshly distilled $SOCl_2$ (0.6 mL), stirred for 10 min, and diluted with cold KOH solution (1%). The precipitate was filtered off, washed with water, and dried to afford **5** (0.3 g) that was recrystallized from EtOH. Yield 0.21 g (76.4%), R_f 0.69 ($CHCl_3$:MeOH, 20:1), mp 236–238°C; $[\alpha]_D^{20}$ +126° (*c* 0.04, $CHCl_3$.

IR spectrum (ν, cm^{-1}): 3400-3100 (NH), 1730 (COOMe), 1662 (CONH).

PMR spectrum ($CDCl_3$, δ, ppm): 0.86 (3H, s, CH_3-28), 1.05 (3H, s, CH_3-25), 1.12 (3H, s, CH_3-26), 1.13 (3H, s, CH_3-27), 1.15 (3H, s, CH_3-24), 1.28, 1.30 (each 3H, both s, CH_3-29, CH_3-23), 1.35–2.00 (CH, m, CH_2), 3.68 (3H, s, OCH_3), 5.29 (1H, s, H-12), 5.75 (1H, br.s, NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 38.3 (C-1), 34.5 (C-2), 176.6 (C-3), 42.5 (C-4), 55.5 (C-5), 19.1 (C-6), 32.4 (C-7), 39.8 (C-8), 47.0 (C-9), 37.2 (C-10), 23.8 (C-11), 122.5 (C-12), 144.1 (C-13), 44.2 (C-14), 26.3 (C-15), 26.0 (C-16), 31.9 (C-17), 48.0 (C-18), 40.2 (C-19), 41.7 (C-20), 31.2 (C-21), 37.7 (C-22), 26.9 (C-23), 21.7 (C-24), 16.8 (C-25), 16.5 (C-26), 25.6 (C-27), 28.1 (C-28), 28.5 (C-29), 177.5 (C-30), 51.5 (C-31).

Found (%): N 2.84. $C_{31}H_{49}O_3N$, calc. (%): N 2.89, MW 483.7.

3-Cyano-3,4-*seco*-olean-4,12-dien-30-oic Acid Methyl Ester (6). A solution of **4** (0.24 g, 0.5 mmol) and *p*-toluenesulfonylchloride (0.8 g) in anhydrous Py (5 mL) was refluxed without admitting moisture for 5 h and treated with HCl (50 mL, 5%). The precipitate was filtered off, washed with water, and dried. The product (0.24 g) was recrystallized from EtOH:$CHCl_3$. Yield 0.17 g (70.0%), R_f 0.87 (C_6H_6:EtOH, 20:1), mp 252–253°C, $[\alpha]_D^{20}$ +126° (*c* 0.06, CH_2Cl_2).

IR spectrum (ν, cm^{-1}): 2300–2200 (CN), 1728 (COOMe), 1215, 1157, 929, 734.

PMR spectrum ($CDCl_3$, δ, ppm): 0.77 (3H, s, CH_3-28), 0.98 (3H, s, CH_3-25), 1.05 (3H, s, CH_3-26), 1.06 (3H, s, CH_3-23), 1.10 (6H, s, CH_3-24, CH_3-27), 1.16 (3H, s, CH_3-29), 1.20-2.20 (CH, m, CH_2), 3.67 (3H, s, OCH_3), 5.27 (2H, s, $=CH_2$-24), 5.61 (1H, s, H-12).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 38.5 (C-1), 26.9 (C-2), 121.3 (C-3), 167.1 (C-4), 55.6 (C-5), 19.0 (C-6), 32.4 (C-7), 39.8 (C-8), 47.2 (C-9), 36.9 (C-10), 23.2 (C-11), 122.4 (C-12), 144.4 (C-13), 44.2 (C-14), 26.2 (C-15), 25.8 (C-16), 31.9 (C-17), 48.2 (C-18), 40.3 (C-19), 41.7 (C-20), 31.3 (C-21), 38.6 (C-22), 27.0 (C-23), 116.7 (C-24), 17.0 (C-25), 16.8 (C-26), 23.6 (C-27), 28.2 (C-28), 28.5 (C-29), 177.8 (C-30), 51.5 (C-31).

Found (%): N 2.64. $C_{31}H_{47}O_2N$, calc. (%): N 3.00, MW 465.7.

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