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SYNTHESIS OF 1-CYANO-2,3-*seco*-DERIVATIVES OF GLYCYRRHETIC ACID

I. A. Tolmacheva, N. V. Galaiko, and V. V. Grishko*

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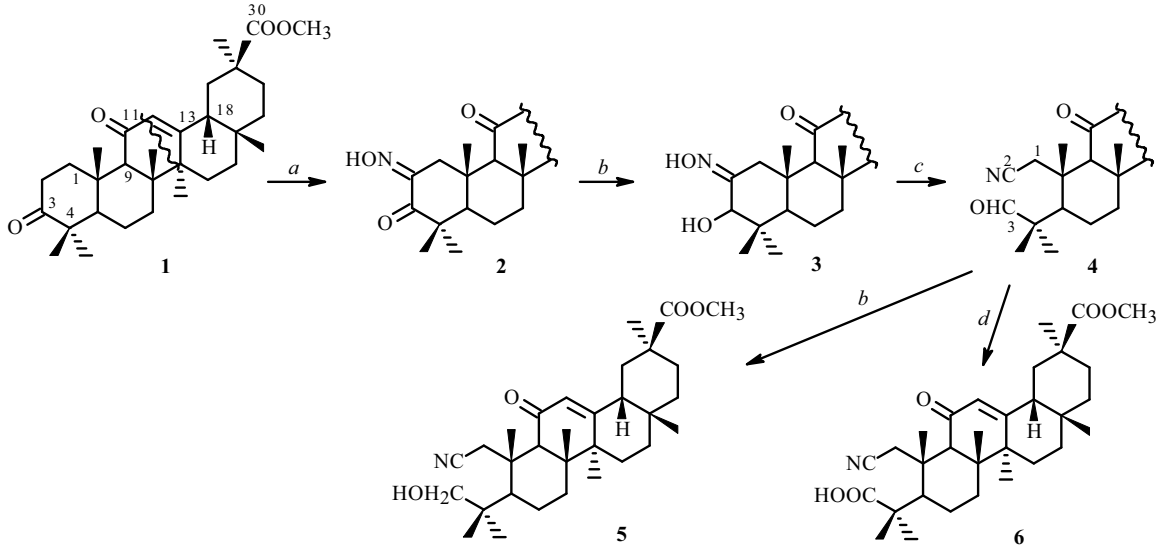
1-Cyano-2,3-seco-derivatives of the 18βH-oleanane series were synthesized from glycyrrhetic acid.

Keywords: 1-cyano-2,3-*seco*-triterpenoids, glycyrrhetic acid, Beckmann fragmentation.

The triterpene saponin glycyrrhizic acid is the principal biologically active component of *Glycyrrhiza glabra* L. and *G. uralensis* Fisher root extracts and is widely used in folk and official medicine [1–3]. Like glycyrrhizic acid, its triterpene aglycon and natural metabolite 18β-glycyrrhetic acid exhibits multifunctional pharmacological activity (including antiulcer, anti-inflammatory, immunomodulating, antiviral, and antitumor), is the active principle of many drugs, and is used as a base for preparing new biologically active derivatives [4, 5].

We synthesized previously from the available triterpenoid betulin C-3 *O*- and *N*-containing 2,3-*seco*-triterpene derivatives of the lupane and 19β,28-epoxy-18αH-oleanane series including some with antiviral, cytotoxic, and immunotropic activity [6-11]. The steroid chemistry method [12-14] that involves Beckmann fragmentation of the α-hydroxyoxime of glycyrrhetic acid was adapted to triterpenoids [5, 6] during the preparation of 2,3-*seco*-derivatives of the 18βH-oleanane series.

Hydroxyimino derivatives **2** and **3** were obtained from 3-oxoglycyrrhetic acid derivative **1** by the previously described method [6]. The presence of the hydroxyimino substituent on C-2 in **2** and **3** was confirmed by absorption bands in IR spectra at 3343–3282 and 1655–1654 cm^{-1}. PMR spectra taken from solutions of **2** and **3** in DMSO-d_6 showed hydroxyimine proton resonances at 11.65 and 10.42 ppm, respectively. The appearance in the PMR spectrum of **3** of a singlet for the hydroxyl proton at 3.84 ppm indicated that the C-3 oxo group was reduced.



1 **2** **3** **4** **5** **6**

a. *i*-$C_5H_{11}NO_2$/*t*-C_4H_9OH/*t*-C_4H_9OK; *b*. $NaBH_4$/CH_3OH; *c*. TsCl/C_5H_5N; *d*. CrO_3/H_2SO_4/$(CH_3)_2CO$

Institute of Mechanical Chemistry, Ural Branch, Russian Academy of Sciences, 614013, Russia, Perm; e-mail: grishko@aport.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 226–228, March–April, 2011. Original article submitted September 2, 2010.

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Beckmann rearrangement of ring A of **3** [6] produced 2,3-*seco*-aldehydonitrile **4**, the structure of which was confirmed by spectral data. The IR spectrum of **4** had an absorption band at 2238 cm^{-1} that corresponded to nitrile vibrations. The PMR spectrum showed a singlet with chemical shift 9.67 ppm for the C-3 aldehyde proton. The ^{13}C NMR spectrum had characteristic resonances for the nitrile (119.14 ppm) and aldehyde (205.46 ppm) C atoms.

The corresponding 3-hydroxy- (**5**) and 3-carboxy- (**6**) derivatives were obtained from **4**. The presence in the IR spectrum of **5** of a broad absorption band in the region 3483 cm^{-1} was consistent with the presence of a C-3 hydroxyl. The C-3 methylene protons of **5** were detected in PMR spectra as doublets centered at 3.33 and 3.58 ppm with geminal SSCC 11.1 Hz. The ^{13}C NMR spectra of **5** and **6** showed the C-3 resonance at 72.11 and 183.47 ppm, respectively.

Thus, 1-cyano-2,3-*seco*-triterpenoids **4**-**6** of the 18βH-oleanane series were prepared and are of interest as key intermediates for synthesizing new biologically active compounds.

EXPERIMENTAL

IR spectra (ν, cm^{-1}) were recorded from mineral-oil mulls on an IFS 66/S IR-Fourier spectrometer (Bruker, Germany). PMR and ^{13}C NMR spectra (δ, ppm, *J*/Hz) were recorded from $CDCl_3$ or DMSO-d_6 solutions with HMDS internal standard on a Mercury+ spectrometer (Varian, USA) at operating frequency 300 or 75.5 MHz. The initial melting point at heating rate 1°C/min was determined on an OptiMelt MPA 100 instrument (USA). Specific optical rotation was measured in $CHCl_3$ solutions on a 341 polarimeter (Perkin–Elmer, USA) at wavelength 589 nm. TLC was performed on Sorbfil plates (Russia) using hexane:EtOAc. Compounds were detected by treatment with H_2SO_4 (5%) with subsequent heating at 95–100°C for 2–3 min. Column chromatography used Merck silica gel (60–200 μm). The eluent for each compound was selected individually.

2-Hydroxyimino-11,30-dioxo-30-methoxy-18βH-olean-12(13)-ene (2). Compound **1** (1.45 g, 3 mmol) was dissolved in *t*-BuOH (50 mL) containing *t*-BuOK (2.4 g, 21 mmol), stirred at room temperature for 30 min, treated dropwise with freshly prepared isoamylnitrite (1.1 mL, 9 mmol), and stirred for 2 h. The formation of products was monitored using TLC. The mixture was treated with aqueous KOH (30 mL, 1%). The products were extracted by EtOAc (2 × 30 mL). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was evaporated. The solid was purified by column chromatography with elution by hexane:EtOAc (5:1). Yield of **2** 0.94 g (61%), R_f 0.15 (hexane:EtOAc, 7:3), mp 192.3° (hexane:EtOAc, 5:1), $[\alpha]_D^{25}$ +214.1° (*c* 0.7, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3343 (OH), 1727 ($COOCH_3$), 1702 (C=O), 1655 (C=O, C=N).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.82, 1.13, 1.22, 1.38 (3H each, s, CH_3), 1.15 (9H, s, $3CH_3$), 2.23 and 4.04 (1H each, d, J_{AB} = 19.4, H-1), 2.53 (1H, s, H-9), 3.70 (3H, s, $COOC\underline{H}_3$), 5.74 (1H, s, H-12). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 11.65 (1H, br.s, N-OH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 16.36, 17.75, 19.53, 21.67, 23.20, 26.38, 26.47, 28.28, 28.58, 29.23, 31.12, 31.25, 31.83, 35.22, 37.73, 41.24, 42.18, 43.35, 44.03, 44.84, 45.96, 48.36, 51.82, 52.70, 59.06, 128.45 (C-12), 154.13 (C-2), 169.95 (C-13), 176.90 (C-30), 198.52 (C-11), 202.95 (C-3).

3-Hydroxy-2-hydroxyimino-11,30-dioxo-30-methoxy-18βH-olean-12(13)-ene (3). A solution of **2** (0.5 g, 0.9 mmol) in CH_3OH (50 mL) was stirred, treated in portions with $NaBH_4$ (0.34 g, 9 mmol), and stirred for 40 min at room temperature and for 5 min under reflux. The CH_3OH was evaporated. The resulting solid was diluted with HCl (10%, 50 mL). The products were extracted by EtOAc (2 × 30 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated. The solid was purified using column chromatography with elution by hexane:EtOAc (7:3). Yield of **3** 0.27 g (53%), R_f 0.48 ($CHCl_3$:CH_3OH, 20:1), mp 181.4°C (hexane:EtOAc, 7:3), $[\alpha]_D^{25}$ +144.0° (*c* 0.6, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3282 (br.) (OH), 1723 ($COOCH_3$), 1654 (C=O, C=N).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.75, 0.81, 1.06, 1.12, 1.13, 1.14, 1.38 (3H each, s, CH_3), 2.10 and 4.52 (1H each, d, J_{AB} = 13.1, H-1), 2.50 (1H, s, H-9), 3.69 (3H, s, $COOC\underline{H}_3$), 3.84 (1H, s, H-3), 5.70 (1H, s, H-12). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 10.42 (1H, br.s, N-OH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 15.72, 16.94, 17.46, 18.34, 23.42, 26.39, 26.51, 28.29, 28.39, 28.52, 29.66, 31.12, 31.81, 32.43, 37.74, 38.70, 40.46, 41.12, 42.94, 43.25, 44.03, 45.48, 48.32, 51.79, 54.46, 60.52, 128.45 (C-12), 157.80 (C-2), 169.39 (C-13), 176.92 (C-30), 199.08 (C-11).

11,30-Dioxo-30-methoxy-1-cyano-2,3-seco-18βH-olean-12(13)-en-3-al (4). A mixture of **3** (0.21 g, 0.4 mmol) and *p*-toluenesulfonyl chloride (0.15 g, 0.8 mmol) in C_5H_5N (10 mL) was refluxed for 4–5 h. The course of the reaction was monitored by TLC. The mixture was treated with aqueous HCl until slightly acidic. The resulting precipitate was filtered off,

washed with H_2O, and purified by column chromatography with elution by hexane:EtOAc (5:1). Yield of **4** (0.10 g 54%), R_f 0.46 (hexane:EtOAc, 7:3), mp 170.6°C (hexane:EtOAc, 5:1), $[\alpha]_D^{25}$ +114.4° (*c* 0.3, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 2238 (C≡N), 1725 ($COOCH_3$), 1653 (C=O).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.80, 1.13, 1.14, 1.15, 1.18, 1.26, 1.45 (3H each, s, CH_3), 2.31 and 4.04 (1H each, d, J_{AB} = 18.3, H-1), 3.03 (1H, s ,H-9), 3.69 (3H, s, $COOC\underline{H}_3$), 5.72 (1H, s, H-12), 9.67 (1H, s, H-3).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 18.12, 18.47, 19.47, 19.83, 22.98, 23.36, 26.30, 26.48, 28.22, 28.59, 30.33, 31.09, 31.67, 31.89, 37.68, 41.03, 41.19, 43.88, 44.00, 45.07, 48.37, 49.06, 50.54, 51.79, 54.85, 119.14 (C-2), 128.33 (C-12), 170.57 (C-13), 176.84 (C-30), 198.70 (C-11), 205.46 (C-3).

3-Hydroxy-11,30-dioxo-30-methoxy-1-cyano-2,3-*seco*-18*β*H-olean-12(13)-ene (5). Compound **4** (0.51 g, 1 mmol) was dissolved in CH_3OH (50 mL), stirred, treated in portions with $NaBH_4$ (0.53 g, 14 mmol), and stirred for 40 min at room temperature and 5 min under reflux. The CH_3OH was evaporated. The resulting solid was dissolved in HCl (10%, 100 mL). The product was extracted by EtOAc (2 × 30 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated. The solid was purified by column chromatography with elution by hexane:EtOAc (5:1). Yield 0.16 g (59%), R_f 0.25 (hexane:EtOAc, 7:3), mp 105.3°C (hexane:EtOAc, 5:1), $[\alpha]_D^{22}$ +122.1° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3483 (OH), 2237 (C≡N), 1728 ($COOCH_3$), 1654 (C=O).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.79, 0.80, 0.97, 1.13, 1.37, 1.39, 1.43 (3H each, s, CH_3), 2.82 and 3.89 (1H each, d, J_{AB} = 18.2, H-1), 3.03 (1H, s, H-9), 3.33 and 3.58 (1H each, d, J_{AB} = 11.1, H-3), 3.69 (3H, s, $COOC\underline{H}_3$), 5.71 (1H, s, H-12).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 17.83, 18.15, 20.46, 22.84, 24.16, 24.76, 26.34, 26.42, 26.47, 28.25, 28.57, 30.24, 31.08, 31.85, 31.91, 37.68, 40.31, 41.44, 43.98, 45.29, 45.87, 47.75, 48.36, 51.77, 55.43, 72.11 (C-3), 120.16 (C-2), 128.50 (C-12), 170.22 (C-13), 176.89 (C-28), 199.34 (C-11).

11,30-Dioxo-30-methoxy-1-cyano-2,3-*seco*-18*β*H-olean-12(13)-en-3-oic Acid (6). A solution of **4** (0.51 g, 1 mmol) in acetone (50 mL) was stirred and treated with Jones reagent (2.5 mL). The course of the reaction was monitored by TLC. The solvent was evaporated. The residue was treated with a large volume of H_2O. The resulting precipitate was filtered off, washed with H_2O, and purified by column chromatography with elution by hexane:EtOAc (1:1). Yield 0.17 g (62%), R_f 0.13 (hexane:EtOAc, 1:1), mp 171.5°C (hexane:EtOAc, 5:1), $[\alpha]_D^{22}$ +66.6° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 2241 (C≡N), 1726 (COOH, $COOCH_3$), 1653 (C=O).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.80, 1.12, 1.14, 1.31, 1.44 (3H each, s, CH_3), 1.32 (6H, s, $2CH_3$), 2.53 and 3.98 (1H each, d, J_{AB} = 18.0, H-1), 3.09 (1H, s, H-9), 3.69 (3H, s, $COOC\underline{H}_3$), 5.71 (1H, s, H-12).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 18.14, 18.34, 20.15, 23.10, 24.30, 26.34, 26.44, 26.56, 28.21, 28.58, 29.64, 31.11, 31.76, 31.88, 37.70, 41.04, 41.39, 43.90, 44.01, 45.16, 46.22, 48.36, 50.10, 51.78, 55.42, 119.24 (C-2), 128.36 (C-12), 170.45 (C-13), 176.91 (C-28), 183.47 (C-3), 198.92 (C-11).

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