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CHEMISTRY

Spirocyclization of 2,3-Seco-19β,28-epoxy-28-oxo-18α-olean-2,3-dicarboxylic Anhydride with Benzylamines

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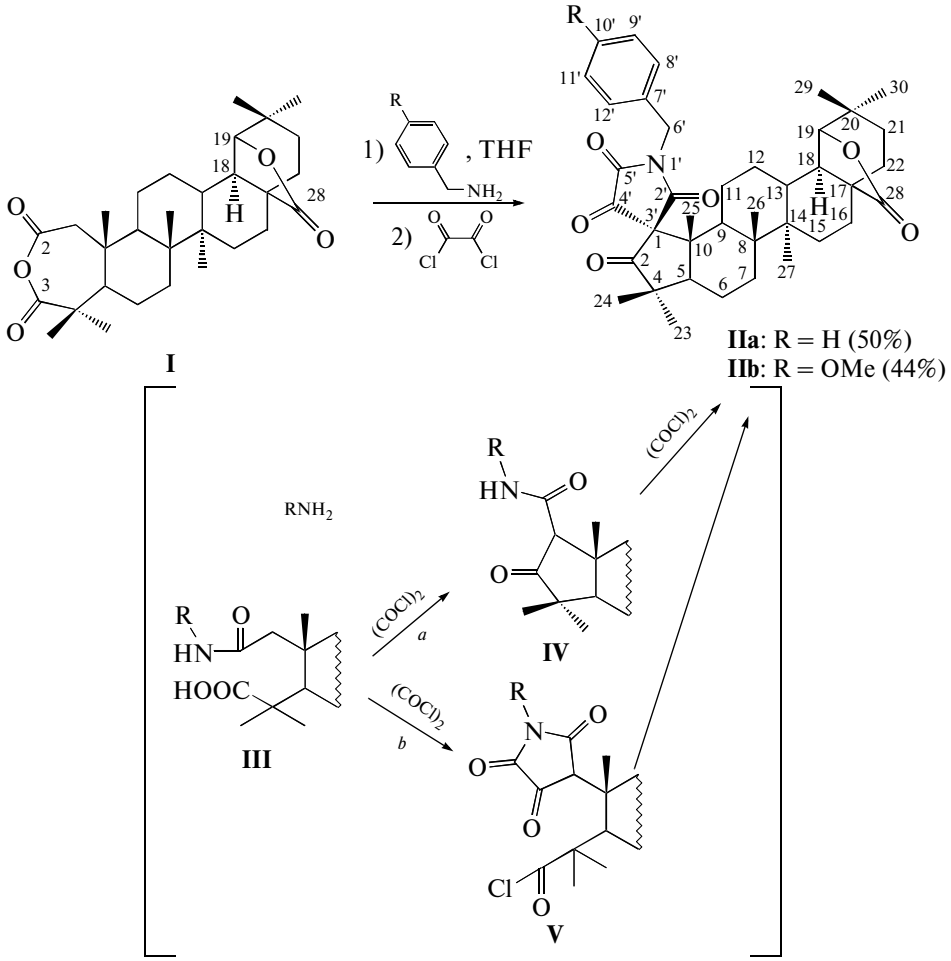
The cyclization of seco-dicarboxylic acids and their cyclic anhydrides into norketones upon heating (pyrolysis) in vacuum is widely used in steroid and triterpene chemistry [1]. For example, the oxidative cleavage of triterpene and steroid alcohols and ketones into seco-carboxylic acids and the further reaction of the latter with acetic anhydride followed by pyrolysis were used to establish their structure [2].



Scheme 1.

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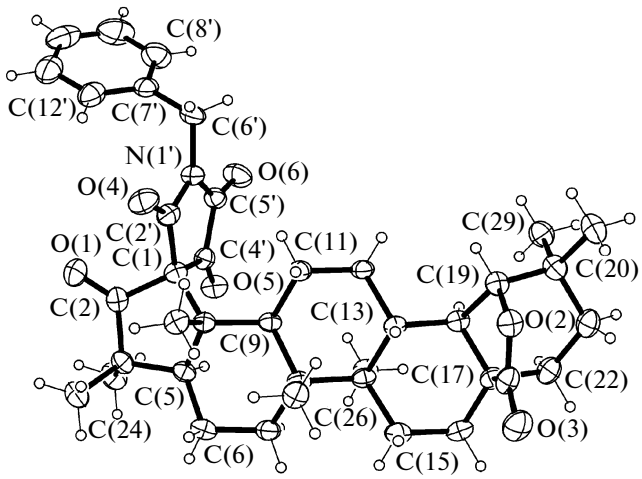
We have found a new transformation of a similar type resulting from the reaction of seven-membered cyclic anhydride **I**, readily available from corresponding 2,3-seco-dicarboxylic acid [3], with benzylamine or *p*-methoxybenzylamine in THF followed by treatment with oxalyl chloride (Scheme 1). The reaction leads to spironorketones **IIa**, **IIb** containing a pyrrolidinetrione fragment.

The structure of compound **IIa** determined by X-ray diffraction study is shown in the figure. The six-membered rings of oleanic skeleton have a common chair conformation, while the five-membered carbon ring has an envelope conformation with the C(10) atom being 0.710(5) Å out of the plane of the other atoms. The pyrrolidine ring is flat within ±0.022 Å. It is worth noting that the Cambridge Structural Database involves several structures containing the 4-methylenepyrrolidine-2,3,5-trione moiety and no data on the structure of the pyrrolidine-2,3,5-trione fragment. However, in both cases, the C(4')–C(5') bond lengths—1.533(5) Å in **IIa** and 1.544 and 1.530 Å in [4, 5]—are close to each other and to the length of 1.550 Å in bicyclo[3.2.2]nonane-6,7,8,9-tetraone [6]. The angle between the planes of spiro connected rings is 86.8(2)°. In the crystal, **IIa** molecules form chains along $a + b$ owing to C(10')–H···O(3) interactions (H···O is 2.53 Å, C–H···O angle is 151°) (the figure).

A new stereogenic center C(1) in **IIa** and **IIb** molecules results from the above reactions; therefore, they can exist as diastereomer pairs. However, according to NMR spectra, ketones **IIa** and **IIb** are individual compounds. We assign the configuration of the chiral center at C(1) in compounds **IIa** and **IIb** on the basis of the X-ray diffraction study of compound **IIa**. It is interesting to note that we found in the literature no other compounds containing the 2-azaspiro[4.4]nonane-1,3,4,6-tetraone fragment.

The formation of spironorketones **IIa** and **IIb** can be explained by the following mechanism (Scheme 1). It is known that acetamides can form pyrrolidine-2,3,5-triones in the reaction with oxalyl chloride [7–9]; therefore, intermediate amido acid **III**, resulting from the opening of the anhydride ring with amine, can produce compounds **IIa** and **IIb** under the action of oxalyl chloride through two routes. Route *a* includes the initial assembly of norketone ring **IV** followed by acylation of the resulting β-diketone fragment with oxalyl chloride and final intramolecular N-acylation. Route *b* involves the initial assembly of the pyrrolidinetrione ring to form acid chloride **V**, which undergoes intramolecular acylation of the resultant β-diketone fragment to give compounds **IIa** and **IIb**.

Thus, we have shown the new transformation of 2,3-seco-dicarboxylic acid anhydride of oleanic series into spiro derivatives of A-norketones. The disclosed transformation is probably to be a general method for the preparation of spironorketones of oleanic series comprising 2-azaspiro[4.4]nonane-1,3,4,6-tetraone fragment.



The structure of **IIa** molecule in crystal (30% ellipsoids are shown). Selected bond lengths (Å): N(1')–C(2'), 1.399(5); N(1')–C(5'), 1.373(5); C(1)–C(2'), 1.522(5); C(1)–C(4'), 1.527(5); C(2')–O(4), 1.205(4); C(4')–O(5), 1.197(4); C(4')–C(5'), 1.533(5); C(5')–O(6), 1.201(4); C(1)–C(2), 1.571(5); C(1)–C(10), 1.596(5); C(8)–C(14), 1.588(5). Selected torsion angles: C(5')N(1')C(6')C(7'), 83.7(4)°; N(1')C(6')C(7')C(12'), 67.7(5)°.

EXPERIMENTAL

IR spectra were recorded on a VECTOR 22 spectrophotometer as KBr pellets. Specific rotation was determined on a PolAAr 3005 spectrometer. Mass spectra (ionizing energy of 70 eV) were obtained on a Finnigan MAT 8200 instrument. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded on a Bruker DRX 500 spectrometer operating at 500.13 and 125.76 MHz, respectively. Chloroform solvent signals were used as the internal reference (δ_H 7.24 ppm, δ_C 76.90 ppm). Signal assignment in the obtained compounds was made on the basis of analysis of ^{1}H NMR spectra with the use of ^{1}H–^{1}H double resonance spectra and 2D spectra of homonuclear ^{1}H–^{1}H correlation and the analysis of ^{13}C NMR spectra recorded in the J-modulation mode (JMOD) with off-resonance proton decoupling and 2D spectra of heteronuclear ^{13}C–^{1}H correlation on direct and remote spin–spin coupling constants (C–H COSY, $^1J_{C,H}$ 135 Hz and COLOC $^{2,3}J_{C,H}$ 10 Hz, respectively). The X-ray diffraction study of compound **IIa** was accomplished on a Bruker P4 diffractometer (MoK_α radiation, graphite monochromator, λ 0.71073 Å, $2\theta < 52°$). An empirical absorption correction was applied. The structure was solved by direct methods with SIR2002 software [10]. Structure refinement was made by full-

matrix least squares for all F^2 in the anisotropic approximation for the non-hydrogen atoms using the SHELXL-97 program [11]. The hydrogen atoms were included in geometrically calculated positions and refined using the riding model.

2,3-Seco-19β,28-epoxy-28-oxo-18α-olean-2,3-dicarboxylic anhydride I was obtained by procedure [3]: decomp. >280°C (decomp. 290–292°C [3]). $[\alpha]_D^{23.4}$ +86.7° (*c* 0.782, pyridine) ($[\alpha]_D^{18}$ +85.7° (*c* 0.782, pyridine [3]). IR (ν, cm^{-1}): 1796 (O=C–O–C=O), 1765 (COOR). ^{1}H NMR (δ, ppm, *J*, Hz): 0.86 (s, 3H-27), 0.91 (s, 3H-26), 0.92 (s, 3H-30), 0.99 (s, 3H-29), 1.02 (s, 3H-25), 1.22 (s, 3H-24), 1.33 (s, 3H-23), 1.09 (dddd, H-12a, $J_{12a,12e} = J_{12a,11a} = J_{12a,13a}$ = 12.8, $J_{12a,11e}$ 3.8), 1.17 (ddd, H-15e, $J_{15e,15a}$ 13.3, $J_{15e,16a}$ 4.0, $J_{15e,16e}$ 2.4), 1.20–1.31 (m, H-11 and H-15a), 1.34 (m, H-13a), 1.37 (ddd, H-16a, $J_{16a,16e} = J_{16a,15a}$ 13.8, $J_{16a,15e}$ 4.0), 1.38–1.61 (m, 10H), 1.69 (dm, H-12e, $J_{12e,12a}$ = 12.8, $3J < 4$), 1.76 (dd, H-9a, $J_{9a,11a}$ = 12.3, $J_{9a,11e}$ = 2.2), 1.80 (d, H-18a, $J_{18a,13a}$ = 11.1), 1.84 (ddd, H-16e, $J_{16e,15a}$ = 13.8, $J_{16e,15a}$ = 3.6, $J_{16e,15e}$ = 2.4), 2.21 (d, H-1, $J_{1',1}$ = 13.9), 2.83 (d, H-1', $J_{1',1}$ = 13.9), 3.90 (s, H-19e). ^{13}C NMR (δ, ppm): 179.45 (s, C-28), 176.23 (s, C-3), 165.92 (s, C-2), 85.62 (d, C-19), 53.26 (d, C-5), 46.57 (t, C-1), 46.56 (s, C-4), 46.34 (d, C-18), 45.88 (s, C-17), 45.53 (d, C-9), 41.76 (s, C-10), 41.18 (s, C-8), 40.26 (s, C-14), 35.93 (d, C-13), 33.36 (s, C-20), 33.11 (t, C-7), 32.11 (t, C-21), 31.69 (t, C-22), 30.02 (q, C-23), 28.54 (q, C-29), 27.56 (t, C-15), 26.05 (t, C-12), 25.30 (t, C-16), 23.71 (q, C-30), 21.53 (t, C-11), 20.50 (q, C-25), 19.36 (q, C-24), 18.28 (q, C-6), 16.02 (q, C-26), 13.25 (t, C-27). MS (*m/z*): calcd. for $C_{30}H_{44}O_5$, 484.3183; found, 484.3180 $[M]^+$.

(1*S*)-1'-Benzyl-2,2',4',5',28-pentaoxo-19β,28-epoxyspiro[3-nor-18α-olean-1,3'-pyrrolidine] IIa. A solution of benzylamine (0.126 g, 1.18 mmol) in 3 mL of THF was added to a solution of compound **I** (0.554 g, 1.14 mmol) in 8 mL of THF. The mixture was kept for 1 day. A solution of oxalyl chloride (0.15 mL, 1.72 mmol) in 1 mL of THF was added and the mixture was kept for 1 day. Additional portion of oxalyl chloride (0.15 mL, 1.72 mmol) was added and the mixture was kept for 4 days. The precipitate was filtered off to give 0.358 g (50%) of compound **IIa**, decomp. above 290°C. IR (ν, cm^{-1}): 1757 (COOR), 1736 (C=O), 1715 (C=O). ^{1}H NMR (δ, ppm, *J*, Hz): 0.78 (s, 3H-27), 0.86 (s, 3H-26), 0.89 (s, 3H-30), 1.00 (s, 3H-29), 1.09 (s, 3H-24), 1.14 (s, 3H-23), 1.23 (s, 3H-25), 0.23 (dddd, H-11e, $J_{11e,11a}$ = 13.0, $J_{11e,12a}$ = 4.3, $J_{11e,9a}$ = 3.0, $J_{11e,12e}$ = 2.0), 0.63 (dddd, H-12a, $J_{12a,12e} = J_{12a,11a} = J_{12a,13a}$ = 13.0, $J_{12a,11e}$ = 4.3), 1.03–1.21 (m, H-12e, H-13a, and 2H-15), 1.26 (dddd, H-11a, $J_{11a,11e} = J_{11a,9a} = J_{11a,12a}$ = 13.0, $J_{11a,12e}$ = 4.2), 1.34 (ddd, H-16a, $J_{16a,16e} = J_{16a,15a}$ = 13.4, $J_{16a,15e}$ = 3.8), 1.36–1.50 (m, 2H-21, 2H-7, 2H-22), 1.51–1.57 (m, 2H-6), 1.65 (d, H-18a, $J_{18a,13a}$ = 11.1), 1.82 (dm, H-h16e, $J_{16e,16a}$ = 13.4), 1.90 (dd, H-9a, $J_{9a,11a}$ = 13.0, $J_{9a,11e}$ = 3.0), 2.66 (t, H-5, $J_{5.6}$ = 7.6), 3.72 (s, H-19), 4.88 (s, 2H-6'), 7.26–7.33 (m, 2H-9', H-10'), 7.39 (br d, 2H-8', $J_{8',9'}$ = 7.9). ^{13}C NMR (δ, ppm): 209.80 (s, C-2), 189.13 (s, C-4'), 179.25 (s, C-28), 170.09 (s, C-5'), 158.90 (s, C-2'), 133.83 (s, C-7'), 129.00 (d, C-8' and C-12'), 128.67 (d, C-9' and C-11'), 128.28 (d, C-10'), 85.75 (d, C-19), 76.60 (s, C-1), 56.90 (s, C-10), 53.08 (d, C-5), 48.32 (s, C-4), 46.38 (d, C-18), 45.82 (s, C-17), 43.19 (t, C-6'), 42.72 (d, C-9), 41.70 (s, C-8), 40.59 (s, C-14), 35.38 (d, C-13), 33.36 (s, C-20), 32.30 (t, C-7), 32.01 (t, C-21), 31.74 (t, C-22), 28.65 (q, C-29), 27.76 (t, C-15), 27.04 (q, C-23), 25.47 (t, C-12), 25.21 (t, C-16), 24.65 (t, C-11), 23.81 (q, C-30), 22.07 (q, C-24), 17.02 (t, C-6), 16.70 (q, C-25), 15.89 (q, C-26), 13.63 (q, C-27). MS (*m/z*): calcd. for $C_{39}H_{49}NO_6$, 627.3554; found, 627.3552 $[M]^+$. Crystallographic data for **IIa**: $C_{39}H_{49}NO_6$, MW 627.79, colorless prism of 0.8 × 0.6 × 0.18 mm, orthorhombic space group $P2_12_12_1$, at 296 K, a = 12.070(2) Å, b = 13.462(2) Å, c = 20.500(3) Å, V = 3330.9(9) $Å^3$, Z = 4, μ (MoK_α) = 0.083 mm^{-1}, d_{calcd} = 1.252 g · cm^{-3}, 3669 independent reflections, 2445 observed reflections with $F_o > 4\sigma(F_o)$, 415 parameters. Final parameters: R = 0.0440 (observed) and wR_2 = 0.1231 (for all reflections), GOOF = 1.008, largest difference peaks 0.18 and –0.14 e/$Å^3$.

(1*S*)-1'-p-Methoxybenzyl-2,2',4',5',28-pentaoxo-19b,28-epoxyspiro[3-nor-18a-olean-1,3'-pyrrolidine] IIb. A solution of *p*-methoxybenzylamine (0.172 g, 1.23 mmol) in 2 mL of THF was added to a solution of compound **I** (0.553 g, 1.14 mmol) in 5 mL of THF. The mixture was kept for 1 day. A solution of oxalyl chloride (0.30 mL, 3.43 mmol) in THF was added and the mixture was kept for 2 days. The solvent was removed. The residue was purified by column chromatography on SiO_2 (Merck, 60–200 μm, 10 g of the sorbent, CH_2Cl_2–Et_2O (40 : 1) as eluent). Recrystallization from EtOH afforded 0.333 g (44%) of compound **IIb**, mp 252–255°C. IR (ν, cm^{-1}): 1773 (COOR), 1736 (C=O), 1712 (C=O).

^{1}H NMR (δ, ppm, *J*, Hz): 0.10 (dm, H-11e, $J_{11e,11a}$ = 13.2), 0.54 (dddd, H-12a, $J_{12a,12e} = J_{12a,11a} = J_{12a,13a}$ = 13.0, $J_{12a,11e}$ = 4.3), 0.76 (s, 3H-27), 0.84 (s, 3H-26), 0.89 (s, 3H-30), 0.99 (s, 3H-29), 1.02 (dm, H-12e, $J_{12e,12a}$ = 13.0), 1.07–1.29 (m, H-13a, 2H-15, H-11a), 1.09 (s, 3H-24), 1.14 (s, 3H-23), 1.21 (s, 3H-25), 1.33 (ddd, H-16a, $J_{16a,16e} = J_{16a,15a}$ = 13.5, $J_{16a,15e}$ = 3.8), 1.36–1.50 (m, 2H-21, 2H-7, 2H-22), 1.50–1.56 (m, 2H-6), 1.63 (d, H-18, $J_{18a,13a}$ = 11.1), 1.79–1.85 (m, H-16e, H-9a), 2.64 (t, H-5, $J_{5,6}$ = 7.7), 3.71 (s, H-19), 3.76 (s, 3H-13'), 4.79 and 4.85 (d, 2H-6', J = 13.7, AB system), 6.80 (d, H-9', H-11', J = 8.6), 7.34 (d, H-8', H-12', J = 8.6). ^{13}C NMR (δ, ppm):

209.88 (s, C-2), 189.36 (s, C-4'), 179.25 (s, C-28), 169.93 (s, C-5'), 159.60 (s, C-10'), 158.87 (s, C-2'), 130.63 (d, C-8', C-12'), 126.06 (s, C-7'), 113.95 (d, C-9' and C-11'), 85.71 (d, C-19), 76.46 (s, C-1), 57.09 (s, C-10), 55.17 (q, C-13'), 52.93 (d, C-5), 48.23 (s, C-4), 46.33 (d, C-18), 45.78 (s, C-17), 42.77 (d, C-9), 42.64 (t, C-6'), 41.69 (s, C-8), 40.51 (s, C-14), 35.56 (d, C-13), 33.33 (s, C-20), 32.26 (t, C-7), 31.99 (t, C-21), 31.70 (t, C-22), 28.57 (q, C-29), 27.73 (t, C-15), 26.90 (q, C-23), 25.41 (t, C-12), 25.18 (t, C-16), 24.58 (t, C-11), 23.76 (q, C-30), 22.08 (q, C-24), 17.02 (t, C-6), 16.73 (q, C-25), 15.86 (q, C-26), 13.59 (q, C-27). MS (*m/z*): calcd. for $C_{40}H_{51}NO_7$, 657.3660; found, 657.3649 $[M]^+$.

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