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TRANSFORMATION OF TRITERPENE KETOXIMES INTO LACTAMS BY THE ACTION OF OZONE

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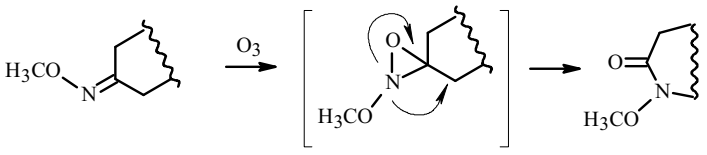
The principal ozonoysis products of triterpene ketoximes and O-*methylketoximes in* CH_2Cl_2 *at 0°C were triterpene lactams and* N-*methoxylactams.*

Keywords: triterpenoids, ozone, ketoximes, lactams.

Beckmann acid-catalyzed rearrangement of ketoximes is one of the principal methods for preparing cyclic lactams [1]. It is well studied and is used for a broad range of substrates including the class of terpenoids. Rearrangement of oximes of terpene ketones into lactams by the action of various acidic reagents is accompanied by the formation of seconitriles due to second-order Beckmann rearrangement [2–6].

Ozone is a strong oxidizing agent that does not exhibit the required acidic properties to catalyze effectively a rearrangement. However, in certain instances where ozonolysis of *O*-methyloximes of cycloalkanones is carried out in the presence of carbonyl compounds (Griesbaum ozonolysis [7, 8]), *N*-methoxylactams, i.e., analogs of the Beckmann rearrangement products, are formed as side products in small amounts. The corresponding amides of carboxylic acids are formed for linear *O*-methylketoximes.

The mechanism of these transformations differs from that of the Beckmann rearrangement. Apparently the methoxylactams are formed via epoxidation of the C=N bond of the *O*-methylketoxime by the action of ozone. Then, the unstable intermediate epoxide rearranges into the corresponding cyclic *N*-methoxylactam (Scheme 1) [7, 8]:



Scheme 1

We found that ozonolysis of triterpene oxime **3** or *O*-methylketoximes **4** and **5** in CH_2Cl_2 at 0°C formed lactams in yields of 42–51% (Scheme 2). Thus, 28-oxoallobetulone ketoxime **3**, which exists as one isomer [9], was transformed into a mixture of products from which lactam **6** was isolated and characterized after chromatographic purification. Evidence in favor of the rearrangement occurring was the presence of characteristic resonances for a carbonyl of cyclic amides at δ 176.6 ppm in the ^{13}C NMR spectrum and a broad singlet for the proton on the lactam N atom at δ 5.82 ppm. The other products could not be isolated pure. However, NMR spectra of the reaction mixture were consistent with further more extensive reactions with rupture of ring A. ^{13}C NMR spectra of the reaction mixture after ozonolysis to prepare 28-oxoallobetulone *O*-methylketoxime **4** from **1** contained resonances of two isomeric lactams at δ 176–177 ppm in a 2:0.5 ratio. Pure *N*-methoxylactam **7** was isolated and characterized after chromatographic purification.

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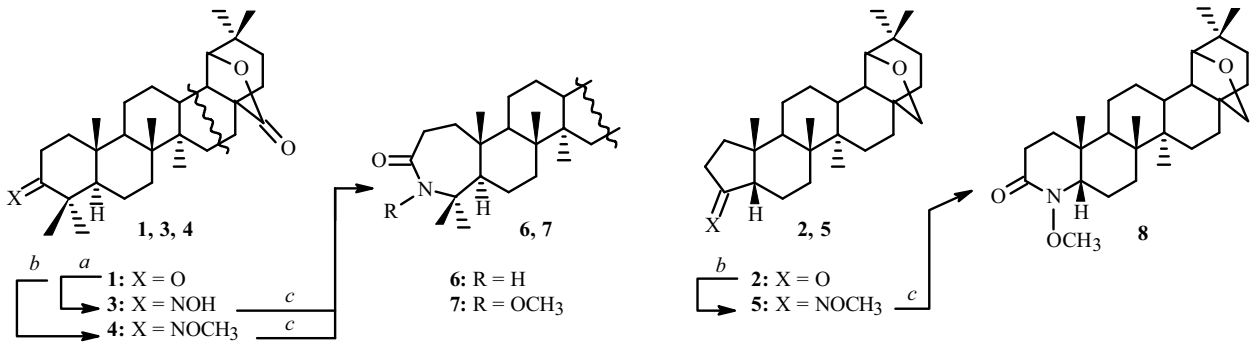

a. $NH_2OH \cdot HCl$, Py, 115°C; *b*. $CH_3ONH_2 \cdot HCl$, Py:MeOH (1:1), reflux, 6 h; *c*. O_3, 0°C, CH_2Cl_2

Scheme 2

Analogous rearrangement of *A*-norallobetulin *O*-methylketoxime **5**, which was a mixture of the *syn*- and *anti*-isomers in a 3:1 ratio, produced *N*-methoxylactam **8** as the principal product. The isomeric lactam could not be isolated pure after column chromatography. Like for **7**, PMR spectra of **8** also exhibited strong singlets for methoxyls at δ 3.66 and 3.76 ppm, respectively. Apparently these transformations also occurred by the mechanism described above via epoxidation of the C=N bond of the *O*-methylketoxime by the action of ozone.

Thus, the principal products from ozonolysis of triterpene ketoximes and *O*-methylketoximes in CH_2Cl_2 at 0°C were triterpene lactams and *N*-methoxylactams. These transformations were the first example of preparative synthesis of triterpene *N*-methoxylactams. The synthesized derivatives are interesting for pharmacological screening.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS internal standard on a Bruker AM-300 spectrometer (operating frequency 300 and 75.5 MHz, respectively). Chemical shifts are given on the δ-scale. Melting points were determined on a Boetius microstage. Specific rotation angles were measured on a Perkin–Elmer 241 MS polarimeter. TLC used Sorbfil plates and the solvent system $CHCl_3$:EtOAc (40:1). Compounds were detected by H_2SO_4 solution (10%) with subsequent heating at 100–120°C for 2–3 min. Compounds **1**–**3** were synthesized as before [9, 10].

Synthesis of 4 and 5. A solution of **1** or **2** (1 mmol) in anhydrous MeOH:Py (1:1, 30 mL) was treated with *O*-methylhydroxylamine hydrochloride (0.17 g, 2 mmol) and refluxed for 6 h. The reaction mixture was poured into HCl solution (150 mL, 5%). The precipitate was filtered off, washed with H_2O, and dried.

28-Oxo-19β,28-epoxy-18α-olean-3-one-*O*-methyloxime (4). Yield 0.44 g (92%), mp 198–200°C, $[\alpha]_D^{20}$ +29° (*c* 0.33, $CHCl_3$), $C_{31}H_{49}NO_3$ (MW 483.73).

PMR spectrum ($CDCl_3$, δ, ppm): 0.85, 0.91, 0.93, 0.95, 1.02, 1.02, 1.13 (21H, 7s, $7CH_3$), 1.19–2.26 (22H, m, CH, CH_2), 2.83–2.89 (2H, m, H-2), 3.81 (3H, s, OCH_3), 3.93 (1H, s, H-19)

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.4, 161. 17.6, 18.9, 21.2, 23.0, 23.9, 25.5, 26.5, 27.3, 27.5, 27.8, 28.7, 31.9, 32.3, 33.3, 33.5, 36.1, 37.2, 39.0, 40.0, 40.6, 46.1, 46.7, 50.8, 55.6, 55.7, 61.0, 85.9 (C-19), 166.5 (C-3), 179.8 (C-28).

A-Trisnor-5βH-19β,28-epoxy-18α-olean-3-one-*O*-methyloxime (5). Yield 0.40 g (95%), mp 153–155°C, $[\alpha]_D^{20}$ +190° (*c* 0.33, $CHCl_3$), $C_{28}H_{45}NO_2$ (MW 427.66).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.78, 0.82, 0.92, 1.01, 1.07 (15H, 5s, $5CH_3$), 1.11–2.26 (25H, m, CH, CH_2), 2.32–2.47 (2H, m, H-2), 3.45 and 3.80 (2H, both d, J = 7.7, H-28), 3.53 (1H, br.s, H-19), 3.83 and 3.85 (3H, s, OCH_3, *syn*-:*anti*- 3:1), 3.81 and 4.29 (1H each, both d, J = 11, H-28).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.1, 15.2, 19.0, 23.1, 23.6, 24.5, 25.6, 26.2, 26.4, 26.5, 26.6, 28.8, 32.7, 34.6, 36.2, 36.7, 37.5, 38.1, 39.8, 40.8, 41.4, 43.5, 46.7, 49.9, 61.4 (OCH_3), 71.2 (C-28), 87.8 (C-19), 166.8 and 167.6 (C-3, *syn*-:*anti*- 3:1).

Synthesis of 6–8. A solution of **3**, **4**, or **5** (1 mmol) in CH_2Cl_2 (50 mL) was ozonolyzed at 0°C until the starting compound disappeared (TLC monitoring). The reaction mixture was warmed to room temperature and evaporated *in vacuo*. The solid was chromatographed over a column of Al_2O_3 (elution by C_6H_6, $CHCl_3$, and $CHCl_3$:MeOH 100:1).

A-Homo-3a-aza-19β,28-epoxy-18α-olean-3,28-dione (6). Yield 0.23 g (48%), mp >330°C, $[\alpha]_D^{20}$ +22° (*c* 0.67, $CHCl_3$), $C_{30}H_{47}NO_3$ (MW 469.70).

PMR spectrum ($CDCl_3$, δ, ppm): 0.77, 0.85, 0.87, 0.93, 0.96, 1.13, 1.23 (21H, 7s, $7CH_3$), 1.26–2.49 (24H, m, CH, CH_2), 3.86 (1H, s, H-19), 5.82 (1H, br.s, NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.3, 15.2, 18.6, 21.9, 22.4, 23.8, 25.4, 26.5, 27.1, 27.3, 27.7, 28.6, 31.8, 31.8, 32.2, 32.8, 33.4, 36.1, 39.7, 39.9, 40.1, 40.4, 46.1, 46.5, 51.7, 52.6, 56.2, 85.9 (C-19), 176.6 (C-3), 180.0 (C-28).

A-Homo-3a-methoxyaza-19β,28-epoxy-18α-olean-3,28-dione (7). Yield 0.25 g (51%), mp 252–254°C, $[\alpha]_D^{20}$ +40° (*c* 0.33, $CHCl_3$), $C_{31}H_{49}NO_4$ (MW 499.73).

PMR spectrum ($CDCl_3$, δ, ppm): 0.87, 0.95, 0.97, 1.04, 1.15, 1.38 (21H, 7s, $5CH_3$), 0.85-2.64 (24H, m, CH, CH_2), 3.65 and 3.66 (3H, both s, OCH_3), 3.95 (1H, s, H-19).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.3, 15.9, 21.5, 22.1, 22.4, 22.5, 23.9, 25.5, 26.7, 27.5, 27.8, 28.7, 31.9, 32.3, 32.8, 33.2, 33.5, 36.4, 39.3, 39.6, 40.1, 40.8, 46.1, 46.5, 49.2, 51.9, 62.6, 68.0 ($O\underline{C}H_3$), 85.7 (C-19), 176.7 (C-3), 179.7 (C-28).

A-Homo-A-trisnor-5β*H*-4a-methoxyaza-19β,28-epoxy-18α-olean-3-one (8). Yield 0.19 g (42%), mp 95–97°C, $[\alpha]_D^{20}$ +41° (*c* 0.33, $CHCl_3$), $C_{28}H_{45}NO_3$ (MW 443.66).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.80, 0.90, 0.94, 1.05, 1.09 (15H, 5s, $5CH_3$), 1.13–2.45 (23H, m, CH, CH_2), 3.48 and 3.73 (1H, both d, J = 7.8, H-28), 3.53 (1H, br.s, H-5), 3.76 (3H, s, OCH_3), 3.78 (1H, s, H-19).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.2, 13.3, 16.7, 20.6, 21.5, 23.2, 24.5, 26.1, 26.4, 26.5, 28.8, 29.2, 32.7, 33.1, 34.4, 36.2, 36.3, 36.5, 36.7, 39.8, 41.3, 41.5, 46.8, 60.8 (C-5), 65.3 (OCH_3), 71.3 (C-28), 87.9 (C-19), 167.1 (C-3).

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