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# ANOMALOUS OZONOLYSIS PRODUCT OF 3$\beta$,28-DI-*O*-ACETYL-29-NORLUPAN-20-ONE-*O*-METHYLOXIME

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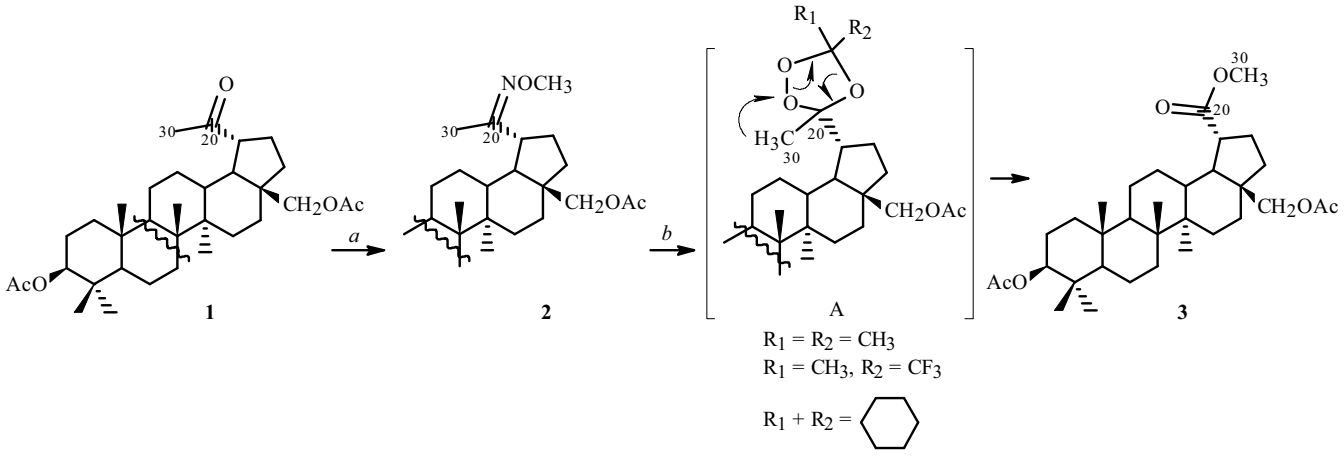
*Ozonolysis of 3*β*,28-di-*O*-acetyl-29-norlupan-20-one-*O*-methylketoxime in the presence of ketones was used as an example to show that secondary ozonides at the C20 position of betulin are unstable and decompose to form the "anomalous product" methyl-3*β*,28-di-*O*-acetyl-29,30-bisnorlupan-20-oate, the structure of which was proved by an x-ray crystal structure analysis.*

**Keywords:** triterpenoids, betulin, ozonolysis, methyl-3$\beta$,28-di-*O*-acetyl-29,30-bisnorlupan-20-oate.

A diacetylbetulin derivative (**1**) was used to synthesize 3$\beta$,28-di-*O*-acetyl-29-norlupan-20-one-*O*-methylketoxime (**2**) in order to prepare triterpene 1,2,4-trioxolanes, which are potential anticancer and antimalaria agents. Compound **1** was subsequently ozonolyzed together with acetone, methyltrifluoromethylacetone, or cyclohexanone in a $CH_2Cl_2$:cyclohexane mixture at 0°C (Griesbaum ozonolysis [1, 2]) (Scheme 1). An analysis of the results showed that the "anomalous product" of ozonolysis, methyl-3$\beta$,28-di-*O*-acetyl-29,30-bisnorlupan-20-oate (**3**), was formed in all instances regardless of the structure of the ketone. The expected ozonolysis products were not observed. We suggest that **3** was formed as a result of the rearrangement of the type A intermediate secondary ozonide, which includes rupture of the C–C $sp^3$ single bond and migration of the C30 methyl to the "positive" O atom. The mechanism of this conversion is similar to that of the Bayer–Villiger rearrangement of ketones in the presence of peroxo compounds [3].




*a*. $CH_3ONH_2 \cdot HCl$, pyridine—methanol, 115°C, 6 h, 95%; *b*. $O_3$, ketone (acetone, trifluoroacetone, or cyclohexanone), 0°C, $CH_2Cl_2$:hexane

Scheme 1

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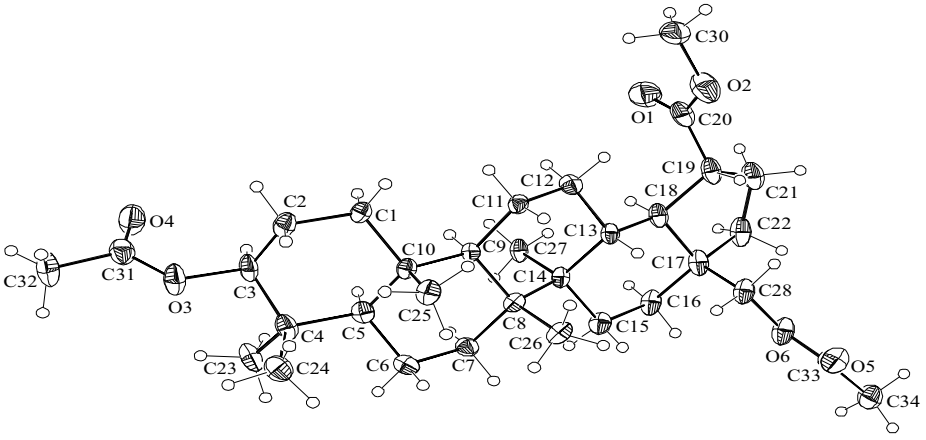


Fig. 1. Molecular structure of methyl-3$\beta$,28-di-*O*-acetyl-29,30-bisnorlupan-20-oate (**3**) showing atoms as 50% probability thermal ellipsoids.

An analogous rearrangement was observed during ozonolysis of a 3$\beta$-*O*-acetylbetulinic acid ester in EtOAc:MeOH at –70°C where the methyl ester of the 29,30-dinor-20-oic acid was isolated in 4% yield as a side product in addition to the 29-nor-20-ketone main product [4].

In our instance **3** was the main product. Apparently this was related to the influence of the substituent on the trioxolane ring.

Rearrangements of peroxide ozonolysis products are well known [5]. They have been reported for a significant number of compounds and are most characteristic of allyl alcohols, $\alpha,\beta$-unsaturated ketones, indoles, and benzofurans [6].

The result observed by us proves that secondary ozonides at the betulin C20 position are unstable and decompose. Even adding highly reactive trifluoromethylketone did not affect the outcome of the Griesbaum co-ozonolysis reaction.

The structure of **3** (Fig. 1) was similar to those of betulin derivatives that were prepared and characterized by us earlier [7, 8]. The six-membered rings A, B, C, and D had the chair conformation and were *trans* positioned relative to each other. The five-membered ring E had a slightly distorted envelope shape.

## EXPERIMENTAL

PMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ with TMS internal standard on a Bruker AM-300 spectrometer (300 and 75.5 MHz operating frequency, respectively). Chemical shifts are given on the δ scale. The x-ray crystal structure analysis was performed on a Bruker Smart Apex II diffractometer. The melting point was determined on a Boetius microstage. Specific rotation angles were measured on a Perkin–Elmer 241 MC polarimeter. TLC was carried out on Sorbfil plates using 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. Compound **1** was synthesized by the literature method [7].

**3$\beta$,28-Di-*O*-acetyl-29-norlupan-20-one-*O*-methyloxime (2).** A solution of **1** (0.53 g, 1 mmol) in dry MeOH:Py (1:1, 30 mL) was treated with *O*-methylhydroxylamine hydrochloride (0.17 g, 2 mmol), refluxed for 16 h, and poured into HCl solution (5%, 150 mL). The precipitate was filtered off, washed with $H_2O$, and dried. Yield 0.5 g (95%), mp 93–95°C, $[\alpha]_D^{20}$ +3° (*c* 0.03, $CHCl_3$), $C_{34}H_{55}NO_5$ (MW 557.80).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.83, 0.83, 0.83, 0.94, 1.02 (15H, 5s, 5$CH_3$), 1.11-2.00 (24H, m, CH, $CH_2$), 1.75 (3H, s, H-30), 2.03 and 2.05 (6H, both s, 2OAc), 2.55-2.65 (1H, m, H-19), 3.79 (3H, s, $OCH_3$), 3.81 and 4.29 (both 1H, both d, J = 11, H-28), 3.77-4.49 (1H, m, H-3).

$^{13}$C NMR spectrum ($CDCl_3$, δ, ppm): 11.1, 14.6, 15.9, 16.0, 16.4, 18.1, 20.7, 20.9, 21.2, 23.7, 25.2, 27.0, 27.3, 27.9, 29.7, 34.1, 34.6, 36.9, 37.1, 37.8, 38.4, 40.9, 42.6, 45.3, 46.2, 49.0, 50.1, 55.4, 61.0 ($OCH_3$), 62.5 (C-28), 80.9 (C-3), 161.2 (C-20), 170.8, 171.2.

**Methyl-3$\beta$,28-di-*O*-acetyl-29,30-bisnorlupan-20-oate (3).** A solution of **2** (0.56 g, 1 mmol) and ketone (1.5 mmol) (acetone, trifluoroacetone, or cyclohexanone) in $CH_2Cl_2$:cyclohexane (3:1, 40 mL) was ozonolyzed at 0°C until the starting material disappeared (TLC monitoring). The mixture was evaporated in vacuo. The solid was chromatographed over a

column of $Al_2O_3$ (eluents benzene and $CHCl_3$). Yield 0.22 g (40%), 0.23 g (42%), or 0.25 g (45%), respectively, mp 85–90°C, $[\alpha]_D^{20}$ –1° (*c* 0.03, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.84, 0.85, 0.85, 0.98, 1.02 (15H, 5s, $5CH_3$), 0.93–2.15 (24H, m, CH, $CH_2$), 2.04 and 2.07 (6H, both s, 2OAc), 2.42–2.52 (1H, m, H-19), 3.65 (3H, s, $OCH_3$), 3.73 and 4.23 (both 1H, both d, J = 11, H-28), 4.45–4.50 (1H, m, H-3).

$^{13}C$ NMR spectrum ($CDCl_3$, δ, ppm): 14.6, 15.9, 16.1, 16.5, 18.1, 20.7, 20.9, 21.3, 23.7, 25.7, 26.9, 27.9, 28.1, 29.4, 34.0, 34.4, 36.5, 37.1, 37.8, 38.4, 40.8, 42.5, 44.1, 46.2, 50.1, 51.2, 51.7, 55.4, 62.5 (C-28), 80.9 (C-3), 170.9 (C-31), 171.4 (C-33), 178.2 (C-20).

**X-ray Crystal Structure Analysis of 3.** Colorless crystals (thin needles), $C_{33}H_{52}O_6$ (MW = 544.75) at 100 K were orthorhombic, $a = 12.474(2)$, $b = 15.242(2)$, $c = 15.723(2)$ Å, $V = 2989.4(7)$ Å$^3$, space group $P2_12_12_1$, $Z = 4$, $d_{calcd} = 1.210$ g/cm$^3$. A dataset of 25,669 reflections was collected on a Bruker Smart Apex2 CCD diffractometer at 100 K (λ Mo Kα-radiation, $\theta_{max} = 30°$) using a single crystal (0.11 × 0.03 × 0.02 mm). The initial set of measured intensities was processed using the SAINT and SADABS programs included in the APEX2 program set [9]. The structure was solved by direct methods and refined by anisotropic full-matrix least-squares methods for nonhydrogen atoms (over $F^2_{hkl}$). Hydrogen atoms were placed in their geometrically calculated positions and refined using a rider model [$U_{iso}(H) = nU_{eq}(C)$, where $n = 1.5$ for methyls and 1.2 for other C atoms]. The refinement used 4854 independent reflections ($R_{int} = 0.0998$). The agreement of the refinement over all independent reflections $wR_2 = 0.1327$ [$R_1 = 0.0572$ for 3257 reflections with $I > 2\sigma(I)$]. All calculations were performed using an IBM PC and the SHELXTL program set [10]. Atomic coordinates and temperature factors were deposited in the Cambridge Crystallographic Data Centre (CCDC), No. 807942 (http://www.ccdc.cam.ac.uk/products/csd/request/).


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