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syn- and *anti*-Isomers of a *O*-Methyloxime-Substituted Tricyclic Ozonide

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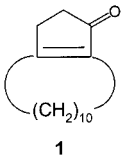
The ozonolysis of bicyclo[9.4.0]pentadec-1(11)-en-12-one (**4**) in pentane, followed by the treatment of the ozonolysis product with *O*-methylhydroxylamine afforded the stable ozonides *anti*-(**8**) and *syn*-2-*O*-methyloxime-16,17,18-trioxatricyclo[10.3.2.1]octadecane (**9**).

Introduction

In a previous paper[1] we had reported that the ozonolysis of **1** afforded the corresponding labile ozonide **3a**, which could be stabilized by the subsequent conversion into **3b**. To the best of our knowledge, this was the first example for the conversion of a bicyclic olefin of type **1** into the corresponding tricyclic ozonide by the transannular cycloaddition of the carbonyl oxide moiety with a carbonyl group in an intermediate of type **2.**



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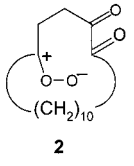

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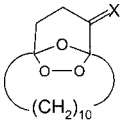

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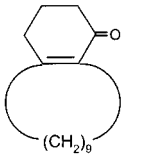
a: X = O
b: X = N-OCH$_3$

In the present investigation we have tried to assess the influence of different ring sizes of such bicyclic keto olefins upon the result of ozonolysis reactions. To this end, we have ozonized **4**, i.e. we have enlarged the size of the carbonyl-containing ring to cyclohexenone and we have reduced the size of the hydrocarbon ring to nine CH_2 groups.

Results and Discussion

The ozonolysis of **4** in pentane, followed by the treatment of the crude reaction product with *O*-methylhydroxylamine afforded two stable crystalline peroxidic products in yields of 60% and 10%, respectively. Characteristic signals in their ^{17}O NMR spectra[2] revealed that each of them had an ozonide structure. By analogy with previous results concerning the direction of ozone cleavage of α-oxoalkenes,[3] we assumed that **4** was predominantly cleaved to give intermediate **5**. As the carbonyl oxide moiety in **5** has a choice to undergo transannular cycloaddition with either one of the two carbonyl groups of **5**, we assumed that the two isolated ozonides corresponded to the structures **6b** and **7b**. X-ray crystallography revealed, however, that they both had structure **7** and that they differed only in the stereochemical arrangement of the methoxy groups. The major isomer (60%) is the *anti*-isomer **8**, and the minor isomer (10%) is the *syn*-isomer **9.**



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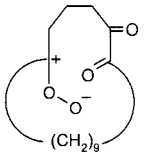

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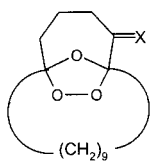

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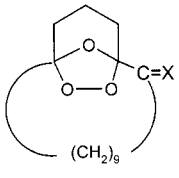

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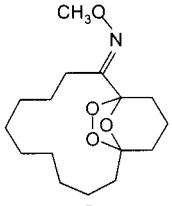
a: X = O
b: X = NOCH$_3$



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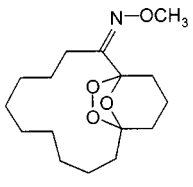

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These findings show, that by contrast with the results from the ozonolysis of the cyclopentenone substrate **1**, the ozonolysis of the cyclohexenone substrate **4** did not produce the ozonide corresponding to the parent olefin. This result is in line with the observation that the formation of cyclopentene ozonides is favored over the formation of cyclohexene ozonides.[3,4] The relatively high combined yields of the ozonides **8** and **9** are probably due to mutual activation of the two adjacent carbonyl groups in the intermediate **5**, as we had previously postulated for the high yields of ozonides derived from other α-oxocycloolefins.[1]

The solid-state structures of **8** and **9** are depicted in Figure 1 and Figure 2, respectively.[5] The crystal structures in each case consist of well separated molecules of the ozonides with no significantly short intermolecular contacts. The structurally novel tricyclo[10.3.2.$1^{1,12}$]trioxanonadecane molecular skeletons of the isomeric ozonides **8** and **9** are clearly evident. The O–O bond lengths [1.4823(14) and 1.486(3) Å] are slightly elongated compared to the standard value of 1.47 Å, which indicates a slight strain in the 1,2,4-trioxolane rings of both isomers. Otherwise, the remaining geometrical parameters estimated for both structures are in good agreement and lie well within the expected ranges.

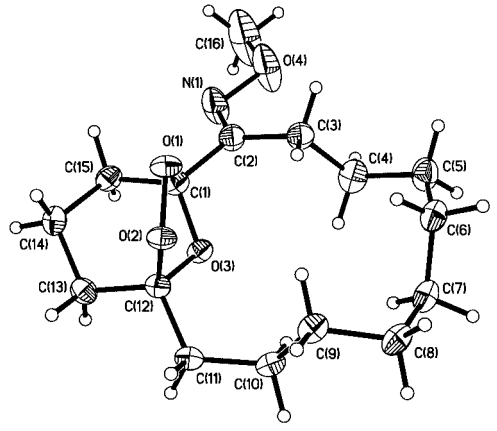

Figure 1. Solid-state structure of **8** (ORTEP,[9] 50% probability ellipsoids).

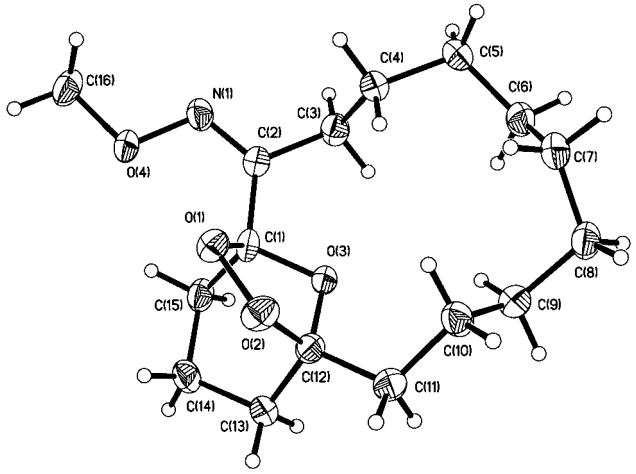

Figure 2. Solid-state structure of **9** (ORTEP,[9] 50% probability ellipsoids).

As a consequence of their structurally constrained environments, the 1,2,4-trioxolane rings adopt slightly distorted, puckered non-planar conformations. Superimposing the corresponding rigid bicyclo[3.2.1]trioxanonane subunits of each structure indicates a very good fit (rms deviation 0.035 Å). The presence of the *O*-methyloxime functionality at C(2) distorts the conformationally more flexible 10-carbon link by rotation about the C(1)–C(2) bond to minimize steric interactions. In the case of the *anti*-isomer **8**, the *O*-methyloxime moiety is accomodated by opening up the O(3)–C(1)–C(2)–C(3) torsion angle to almost 60°, whereas in the *syn*-isomer **9** the O(3)–C(1) and C(2)–C(3) bonds are almost eclipsed, directing the *O*-methyloxime unit away from the peroxide bridge.

Experimental Section

General: NMR spectra: Bruker AC 250. ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ with TMS as internal reference and ^{17}O NMR spectra in C_6D_6 by using H_2O as external reference. Chromatographic separations: flash chromatography[6] on silica gel.

Caution: *All reactions with ozone or ozonides and chromatographic separations must be carried out behind protective safety-glass shields in a hood. Ozonides were invariably transported in thick-walled steel containers. Safety glasses and gloves must be worn at all times when working with ozone or ozonides.*

Preparation of Bicyclo[9.4.0]pentadec-1(11)-en-12-one (4): A solution of bicyclo[10.3.0]pentadec-1(12)-ene[7] (4.48 g, 21.3 mmol) in a mixture of 50 mL of dichloromethane and 150 mL of methanol was treated with ozone at –66 °C until the solution turned blue. Residual ozone was flushed off with nitrogen. The reaction mixture was warmed to room temperature, admixed with 3.9 mL of dimethyl sulfide and stirred for 18 hours. The solvent was distilled off at room temperature under reduced pressure, and the solid residue (4.37 g) was recrystallized from pentane at –30 °C to give 3.23 g of colorless, solid cyclopentadecane-1,5-dione.[8] It was dissolved in 10 mL of ethanol, admixed with 52 mL of ethanol containing 10% of potassium hydroxide and refluxed for 21 hours. The solvent was partly distilled off at room temperature and reduced pressure to leave 10 mL of a liquid residue. The residue was admixed with 10 mL of water and extracted with diethyl ether. The combined extracts were sequentially washed with diluted hydrochloric acid and water and dried with $MgSO_4$. The solvent was distilled off at room temperature under reduced pressure and the liquid residue (2.63 g) was purified by flash chromatography (petroleum ether/diethyl ether, 4:1) to give 1.49 g (32%) of **4**.

Bicyclo[9.4.0]pentadec-1-(11)-en-12-one (4): Colorless liquid. ^{1}H NMR: δ = 1.21–1.44 (m, 10 H), 1.52–1.70 (m, 4 H), 1.92 (q, J = 6.4 Hz, 2 H), 2.30–2.47 (m, 8 H) ppm. ^{13}C NMR: δ = 22.54, 23.85, 25.32, 25.34, 25.72, 26.17, 26.20, 26.63, 29.84, 38.60, 136.89, 159.07, 199.32 ppm. MS: m/z (%) = 220 (36) $[M]^+$.

Ozonolysis of 4: A solution of 698 mg (3.03 mmol) of **4** in 200 mL of pentane was treated with ozone at –75 °C until it turned blue. Residual ozone was flushed off with nitrogen, the reaction product was combined with a solution of 438 mg (5.24 mmol) of *O*-methylhydroxylamine hydrochloride in 10 mL of pyridine and the mixture was kept at –30 °C for 6 days. Then it was warmed to room temperature, and the solvent was distilled off under reduced pressure. The residue was dissolved in 50 mL of diethyl ether and washed with water. The ether phase was dried with $MgSO_4$, and the solvent

was distilled off at room temperature under reduced pressure. From the remaining viscous liquid (798 mg), 514 mg (60%) of **8** and 83 mg (10%) of **9** have been isolated by flash chromatography (petroleum ether/diethyl ether, 10:1).

***anti*-2-*O*-Methyloxime-16,17,18-trioxatricyclo[10.3.2.1]octadecane (8):** Colorless solid, m.p. 82 °C. ^{1}H NMR: δ = 1.37–1.88 (m, 20 H), 2.20–2.41 (m, 4 H), 3.88 (s, 3 H) ppm. ^{13}C NMR: δ = 16.81, 21.11, 23.09, 23.27, 24.18, 24.28, 26.94, 27.07, 27.65, 29.75, 32.09, 33.36, 62.21, 108.47, 111.65, 156.00 ppm. ^{17}O NMR: δ = 135.7 (–O–), 162.0 (OCH_3), 313.1 (O–O) ppm. $C_{16}H_{27}NO_4$ (297.39): calcd. C 64.62, H 9.15, N 4.71; found C 64.70, H 9.33, N 4.49.

***syn*-2-*O*-Methyloxime-16,17,18-trioxatricyclo[10.3.2.1]octadecane (9):** Colorless solid, m.p. 67 °C. ^{1}H NMR: δ = 1.21–1.92 (m, 20 H), 2.18–2.47 (m, 4 H), 3.84 (s, 3 H) ppm. ^{13}C NMR: δ = 16.63, 20.99, 24.89, 27.00, 27.19, 27.50, 28.04, 30.42, 30.53, 32.35, 33.36, 62.03, 107.96, 110.06, 154.28 ppm. ^{17}O NMR: δ = 118.5 (-O-), 170.0 (OCH_3), 316.3 (O–O) ppm. $C_{16}H_{27}NO_4$ (297.39): calcd. C 64.62, H 9.15, N 4.71; found C 64.60, H 9.26, N 4.54.

X-ray Crystallographic Analyses of Tricyclic Ozonides 8 and 9: Single crystals of the two solid tricyclic ozonides suitable for X-ray crystallographic analysis were grown from dichloromethane/ethanol solutions by slow evaporation. The X-ray diffraction data were collected with a Bruker AXS P4 diffractometer at 160 K using graphite-monochromated Mo-K_α (λ = 0.71073 Å). The structure was solved by direct methods and refined using least-squares techniques. All crystallographic calculations and preparation of structure plots and Tables were carried out using the SHELXTL PC suite of programs.[9]

Crystal Data for $C_{16}H_{27}NO_4$ (8): M = 297.39, colorless blocks, crystal size 0.78 × 0.56 × 0.40 mm^3, monoclinic, space group $C2/c$, a = 31.464(3), b = 5.8230(10), c = 17.9490(3) Å, β = 102.130(5)°, U = 3215.1(7) Å^3, Z = 8, $D_{calcd.}$ = 1.229 g cm^{-3}, F(000) = 1296, μ(Mo-K_α) = 0.087 mm^{-1}, 3616 reflections measured, 2818 unique (R_{int} = 0.026) which were used in all calculations. The final discrepancy factors were: R_1 = 0.049 and $wR(F^2)$ = 0.1047 (all data).

Crystal Data for $C_{16}H_{27}NO_4$ (9): M = 297.39, colorless blocks, crystal size 0.37 × 0.20 × 0.12 mm^3, monoclinic, space group $P2_1/c$, a = 13.500(2), b = 5.9810(10), c = 20.162(3) Å, β = 102.480(10)°, U = 1589.5(4) Å^3, Z = 4, $D_{calcd.}$ = 1.243 g cm^{-3}, F(000) = 648, μ(Mo-K_α) = 0.088 mm^{-1}, 3766 reflections measured, 2758 unique (R_{int} = 0.050) which were used in all calculations. The final discrepancy factors were: R_1 = 0.0628 and $wR(F^2)$ = 0.1196 [for $I > 2\sigma(I)$].

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