

Ozonolysis of 3-Caren-5-one

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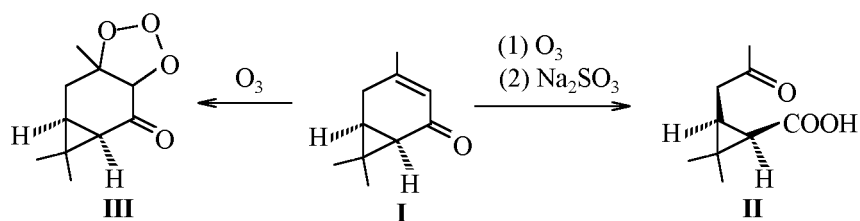
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Abstract—Cleavage by ozonolysis of a cyclic unsaturated ketone, 3-carene-5-one, was investigated under different conditions. The main reaction product is ketocaronic acid. A scheme of ketocaronic acid formation was suggested basing on kinetics of ozone reaction with 3-carene-5-one and thermal decomposition of peroxides.

The ozonolysis of cyclic olefins provides a possibility to prepare under mild conditions α,ω -bi-functional oxygen-containing compounds fit for further syntheses. For instance, starting with the ozonolysis products of chiral cyclic terpenes, (+)- α -pinene and (+)-3-carene, were carried out the syntheses of optically active pheromones, juvenoids, and pyrethroids [1, 2]. The ozonolysis of cyclic unsaturated ketones considerably differs from that of cyclenes, and it is relatively poorly investigated. The study of ozone cleavage of 3-carene-5-one that is

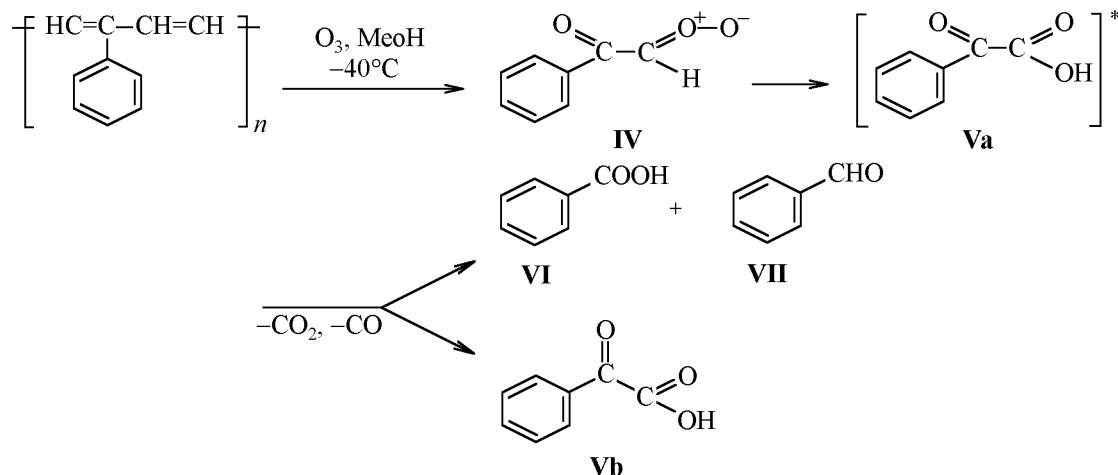
produced by (+)-3-carene oxidation in the liquid phase [3] would extend the number of these reactions and provide a possibility to obtain new derivatives possessing useful properties.

According the data on some cases of ozonolysis carried out with α,β -unsaturated cyclic ketones [4] the reaction took an abnormal course with CO_2 ejection. We established that from the reaction of excess ozone with carenone (**I**) in a fair yield was obtained (-)-(1*R*,3*S*)-2,2-dimethyl-3-(2-oxopropyl)-cyclopropanecarboxylic acid (**II**) [3].



Several attempts were made to rationalize this reaction course. For instance, a possible mechanism [5] was suggested by an example of polyphenylacetyl-

ene ozonolysis involving an ejection of carbon oxides and a stabilization of an intermediate zwitterion **IV**.



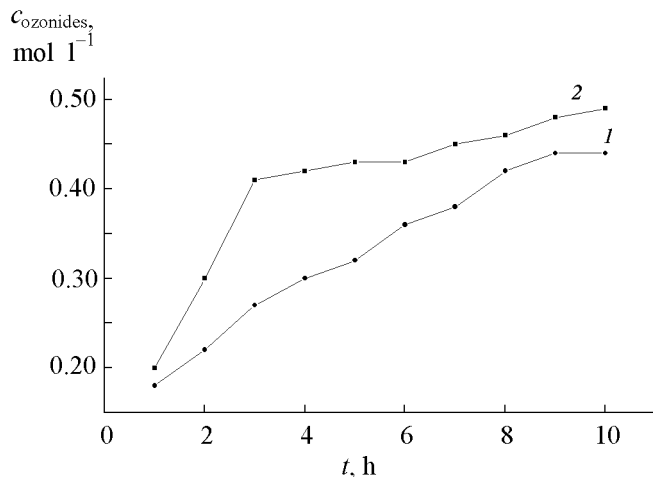


Fig. 1. Kinetics of peroxides accumulation at ozonization of carenone (**I**) in CH₃CN at -20°C (**1**) and 22°C (**2**), carenone c_0 0.24 mol l⁻¹.

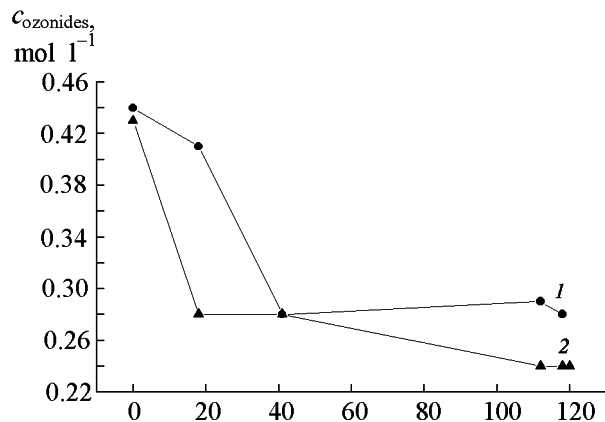
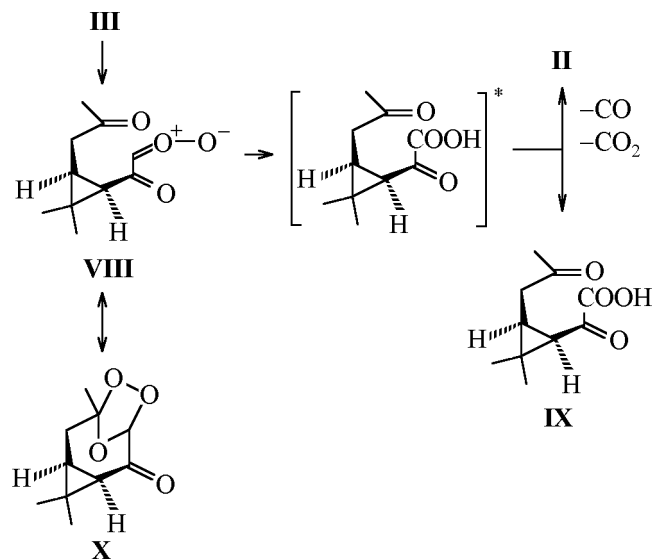


Fig. 2. Kinetics of peroxides decomposition in CH₃CN at -20°C (**1**) and 22°C (**2**) at O₃ olefin molar ratio 2.7 (**1**) and 3.1 (**2**).

Razumovskii *et al.* assume that the key stage of the process is the rearrangement of zwitterion **IV** resulting in excited state of phenylglyoxalic acid (**Va**). The molecule may be stabilized either by dissipation of the energy excess and formation of a stable ketocarboxylic acid **Vb** or by ejection of carbon oxides and formation benzoic acid (**VI**) or benzaldehyde (**VII**). At the same time the bipolar ion **IV** and acid **Vb** in the course of the experiment do not react with ozone, and this permits to exclude the possibility of oxidative cleavage of acid **Vb** by ozone. In keeping with this mechanism it should be expected that in ozonolysis of carenone (**I**) alongside ketoacid **II** form a comparable amount of diketoacid **IX**.



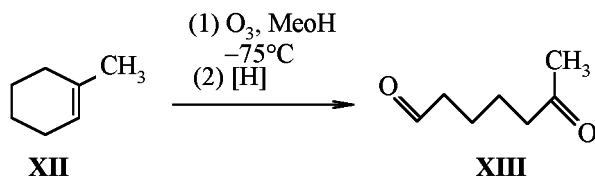
However the lack in the reaction products of compound **IX** and the requirement of twofold excess of ozone for obtaining acid **II** in high yield permitted us to presume that the reaction took another route involving the formation of a new double bond consuming the second molar equivalent of ozone in its cleavage.

Our assumption was corroborated by kinetic study of ozone consumption and ozonides accumulation (Fig. 1). The ozone consumption after complete disappearance of 3-carene-5-one (**I**) was due to deeper oxidation of unsaturated ketone (**I**), and to obtain the maximum yield of ketoacid **II** was required at least a double ozone excess. The character of the curves of ozone consumption and ozonides accumulation evidences that the rates of ozone reaction with substrate and the primary product of its oxidation are different. The high rate of ozone consumption at the beginning of the reaction is due to sufficiently effective compensation by the inductive effect of the methyl group of the displacement of the double bond electron density to the carbonyl carbon atom. Beside the electronic effects the reaction rate is affected by steric factors due to the shielding of the keto group in zwitterion **VIII** by the bulky *gem*-dimethylcyclopropane fragment of the molecule. Therefore the stabilization of the zwitterion by formation of ozonide **X** becomes improbable. The rates of O₃ absorption and of peroxides formation notably decrease after complete disappearance of the initial ketone **I** from the reaction mixture: It is evidenced by a definite bend on the curves of ozone consumption and peroxides accumulation (Fig. 1).

The study of thermal stability of ozonides obtained at different ratios O₃-3-carene-5-one showed that in the reaction products were present at least two kinds of peroxides (Fig. 2).

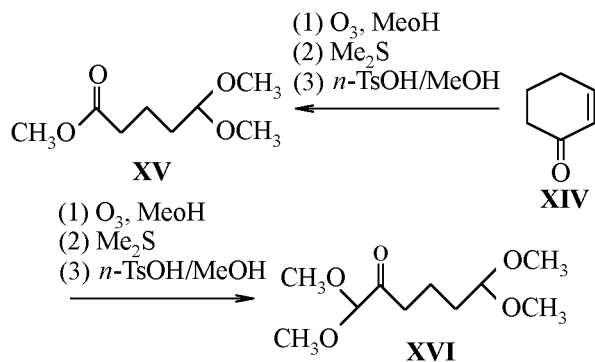
We believe that in bipolar intermediate **VIII** the keto groups in α -position with respect to the reaction site favor its stabilization in the form of peroxyenol **XI**. This is in agreement with the published data that 1,2-dicarbonyl compounds are prone to enolization [6, 7]. The sole product of enolate **XI** ozonolysis is ketoacid **II**. The decrease in ozone absorption at the second reaction rate may be ascribed to electron deficiency of the double bond in the peroxide intermediate **XI**.

In order to corroborate the assumed reaction mechanism and to establish the substituents effect we studied the ozonolysis of 1-methylcyclohexene (**XII**) and cyclohexenone (**XIV**).



After absorption of one mol equiv of ozone with 1-methylcyclohexene (**XII**) in methanol at -75°C followed by reduction of the peroxide ozonolysis product with hydrogen on Lindlar catalyst was obtained ketoaldehyde **XIII**.

The crucial difference was observed in the reaction products of ozone with cyclohexen-2-one (**XIV**). After passing 3 mol equiv of ozone through the methanol solution of ketone **XIV** at -40°C followed by reduction of the peroxide reaction products with dimethyl sulfide and boiling of the reaction mixture in methanol with *p*-toluenesulfonic acids we separated 1,1,6,6-tetramethoxy-2-hexanone (**XVI**). Its structure was proved by ¹H and ¹³C NMR spectroscopy.



In the ¹H NMR spectrum at 3.25 and 3.38 ppm appear signals from 12 protons of the dimethoxy groups. In the ¹³C NMR spectrum of the compound the signal at 53.97 ppm corresponds to the dimethoxy group close to the keto group, and at 51.88 ppm to that far from the keto group. The chemical shift of the carbonyl carbon is 204.55 ppm. If the amount of the ozone-oxygen mixture passed through the solution of ketone **XIV** is increased to 12 mol equiv of O₃ per 1 mol of alkene the above workup procedure afforded methyl 5,5-dimethoxypentanoate (**XV**). In the ¹³C NMR spectrum of compound **XV** appears a signal at 3.52 ppm twice less intensive compared to the signals of dimethoxy groups at 3.25 ppm and equal in intensity to that of CH₃O of the ester group of compound **XV**. In the ¹³C NMR spectrum of the compound the carboxy group carbon gives a peak at 173.35 ppm, and the characteristic signal of keto group in 200 ppm region is lacking. The mass spectrum also is consistent with the assumed structure.

Obviously the conjugation of the double bond and the carbonyl group is decisive for the route of ozonolytic cleavage of cyclohexenes. At the same time it should be noted that the presence of an electron-acceptor group reduces the electron density on the double bond and therewith considerably decelerates the ozone attack thereto. In carenone (**I**) the *gem*-dimethylcyclopropane fragment of the molecule largely compensates the displacement of the electron density of the double bond to the carbonyl carbon and thus facilitates the ozone addition and accelerates the reaction.

EXPERIMENTAL

IR spectra of compounds were registered on UR-20 spectrophotometer from thin film. The specific rotation was measured on Perkin-Elmer 141 instrument in CHCl₃ solutions. ¹H NMR spectra were recorded on spectrometer Tesla BS-576 (100 MHz), ¹³C NMR spectra were run on spectrometer JEOL FX-90 Q (22.5 MHz), solvent CDCl₃, internal reference TMS. GLC was carried out on chromatograph Chrom-5, column 1200×4 mm, stationary phase 5% SE-30 on Chromaton N-AW-DMCS, oven temperature 50-300°C, carrier gas helium. Mass spectrum was measured on MKh-1320 instrument at ionizing electrons energy 70 eV. Elemental analyses of compounds obtained were in agreement with the calculated figures.

(-)-(1R,3S)-2,2-Dimethyl-3-(2-oxopropyl)cyclopropanecarboxylic acid (II). Through a solution of 0.45 g (3 mmol) of 3-caren-5-one (**I**) in 10 ml of anhydrous acetonitrile at 0°C was bubbled an ozone-oxygen mixture (1.5–2 wt% of O₃) at the flow rate 5.4 l h⁻¹ till the end of ozone absorption. The ozone concentration at the input and output of the reactor was monitored by iodometric titration. On completion of reaction the reaction mixture was flushed with argon, then 0.31 g (2.48 mmol) of Na₂SO₃ was added, and the mixture was left standing at room temperature till complete reduction of peroxides (till negative test with the acidified aqueous solution of KI). The reaction mixture was filtered, the solvent was distilled off, and to the residue was added by portions 15 ml of concentrated NaHCO₃ solution till CO₂ evolution ceased. Then the reaction mixture was washed with ethyl ether (3×50 ml), the water solution was acidified with 50% H₂SO₄ till pH 2–3, and the organic layer was separated. Into the remaining water layer was added NaCl till saturation, acid **II** was extracted with ethyl ether (3×50 ml). The combined organic solutions were washed with water and dried on MgSO₄. On distilling off the solvent we obtained 0.74 g of oily substance that was subjected to column chromatography on SiO₂ (eluent hexane-ether, 1:1). Yield of ketoacid 0.44 g (60%); n_D^{24} 1.4750, $[\alpha]_D^{22}$ -32° (*c* 1.0, CHCl₃). IR spectrum (ν , cm⁻¹): 1130, 1180, 1240, 1370–1380, 1450, 1700–1730, 2400–3600. ¹H NMR spectrum (δ , ppm, *J*, Hz): 1.17 s (3H, α -CH₃C²), 1.24 s (3H, β -CH₃C²), 1.45–1.65 m (2H, C¹H, C³H), 2.18 s (3H, CH₃CO), 2.80–3.00 q.d (2H, CH₂, *J* _{α,β 33.01, *J*_{2,1} 18.9, *J*_{2,10} 6.73 Hz), 11.08 s (1H, CO₂H). ¹³C NMR spectrum (δ_C , ppm): 14.24 (α -C²), 26.45 (C²), 27.96 (C³), 28.45 (β -C²), 28.52 (C¹), 29.92 (C³), 37.94 (C¹), 178.33 (C²), 208.60 [C(O)O].}

2-Oxoheptanal (XIII). Through a solution of 10 g (104 mmol) of 1-methyl-1-cyclohexene (**XII**) in 150 ml of methanol at -70°C was bubbled an ozone-oxygen mixture (5 wt% of O₃) at a flow rate 5.4 l h⁻¹ till the solution got blue. The reaction mixture was flushed with argon, 0.5 g of Lindlar catalyst was added, and the reaction mixture was stirred under hydrogen atmosphere till negative test for peroxides with acidified water solution of KI. The catalyst was filtered off. The purification and identification of ketoaldehyde **XIII** was carried out by converting it into dimethylacetal by treating the filtrate with 8.7 g (162 mmol) of NH₄Cl and keeping it standing for 24 h. Then a solution of CH₃ONa in methanol was added till stable alkaline reaction. Methanol was

distilled off at 10 mm Hg, the residue was dissolved in ether, the solution was washed with water, dried with MgSO₄, and the ether was distilled off. We obtained 16.2 g (91%) of 2-oxoheptanal (**XIII**) dimethylacetal, bp 55–60°C (1 mm Hg), n_D^{20} 1.4297. IR spectrum (ν , cm⁻¹): 840, 960, 1060, 1705. ¹H NMR spectrum (δ , ppm, *J*, Hz): 1.58 m (6H, CH₂), 1.98 s (3H, CH₃CO), 2.45 m (2H, CH₂CO), 3.10 s (6H, OCH₃), 4.18 t (1H, OCHO, *J* 5.5 Hz). Mass spectrum, *m/z* (*I*_{rel}, %): 174 [M]⁺ (0.1), 173 (5.0), 156 [M-H₂O]⁺ (40.0), 143 [M-OCH₃]⁺ (10.1), 110 [M-2CH₃OH]⁺ (6.2), 75 (100).

Methyl 5,5-dimethoxy-pentanoate (XV). Through a solution of 1 g (10.42 mmol) of 2-cyclohexenone (**XIV**) in 15 ml of anhydrous methanol at -40°C was bubbled an ozone-oxygen mixture (5 wt% of O₃) until 12 mmol of O₃ was consumed per 1 mmol of cyclohexenone **XIV**. The reaction mixture was flushed with argon, 1.14 ml (15.53 mmol) of (CH₃)₂S was added, the mixture was stirred for 1 h and left standing at room temperature for 12 h. The solvent was distilled off, the residue was dissolved in 50 ml of anhydrous methanol and boiled for 3 h in the presence of 0.012 g (0.07 mmol) of *p*-toluenesulfonic acid. Then a solution of CH₃ONa in methanol was added till stable alkaline pH, methanol was distilled off at 10 mm Hg. The residue was dissolved in ether, the solution was washed with water, and dried on MgSO₄. On removing the solvent we obtained 1.21 g of oily reaction product that was subjected to vacuum distillation to afford 0.41 g (22%) of ester **XV**, bp 38°C (3 mm Hg), n_D^{17} 1.4491. IR spectrum (ν , cm⁻¹): 1150, 1220, 1370–1380, 1460, 1715–1750. ¹H NMR spectrum (δ , ppm): 1.52 m (2H, C⁴H₂), 1.83 m (2H, C³H₂), 2.22 m (2H, C²H₂), 3.16 s (6H, OCH₃), 3.52 m [3H, C(O)OCH₃], 4.22 t (1H, OCHO). ¹³C NMR spectrum (δ_C , ppm): 19.72 (C³), 31.51 (C⁴), 33.58 (C²), 51.31 (C-O), 52.31 (C-O-C⁵), 103.87 (C⁵), 173.35 (C¹). Mass spectrum, *m/z* (*I*_{rel}, %): 145 [M-OCH₃]⁺ (5.8), 128 [M-OCH₃-OH]⁺ (2.9), 113 (3.6), 101 [M-75]⁺ (3.9), 75 [(CH₃O)₂CH]⁺ (100), 71 (36.9), 58 (56.9).

1,1,6,6-Tetramethoxy-2-hexanone (XVI). Through a solution of 1 g (10.42 mmol) of 2-cyclohexenone (**XIV**) in 15 ml of anhydrous methanol at -40°C was bubbled an ozone-oxygen mixture (5 wt% of O₃) until 3 mmol of O₃ was consumed per 1 mmol of cyclohexenone **XIV**. The reaction mixture was flushed with argon, 1.14 ml (15.53 mmol) of (CH₃)₂S was added, the mixture was stirred for 1 h and left standing at room temperature for 12 h. The solvent

was distilled off, the residue was dissolved in 50 ml of anhydrous methanol and boiled in the presence of 0.012 g (0.07 mmol) of *p*-toluenesulfonic acid till the disappearance of the initial cyclohexenone **XIV** (TLC monitoring; Silufol, ethyl-acetate-hexane, 1:1). Then a solution of CH₃ONa in methanol was added till stable alkaline pH, methanol was distilled off at 10 mm Hg. The residue was dissolved in ether, the solution was washed with water, and dried on MgSO₄. On removing the solvent we obtained 1.32 g of reaction product that was subjected to vacuum distillation to afford 0.67 g (30%) of tetramethoxy-2-hexanone (**XVI**), bp 80–95°C (2 mm Hg), n_D^{17} 1.4410. IR spectrum (ν , cm⁻¹): 1150, 1220, 1330, 1380, 1460, 1715, 1730. ¹H NMR spectrum (δ , ppm): 1.56 m (6H, CH₂), 3.25 m [6H, CH₃OC(O)], 3.38 s (6H, CH₃O), 4.32 m (1H, OC⁶HO), 4.43 s (1H, OC¹HO). ¹³C NMR spectrum (δ_C , ppm): 17.3 (C⁴), 31.13 (C⁵), 36.14 (C³), 51.88 (C–O–C⁶), 53.97 (C–O–C¹), 103.45 (C⁶), 103.58 (C¹), 204.55 (C²). Mass spectrum, m/z (I_{rel} , %): 221 (2.5), 203 [*M*–OH]⁺ (65.0), 214 (3.7), 189 [*M*–CH₃O]⁺ (6.7), 173 (2.7), 157 (1.3), 145 [*M*–CH(OCH₃)₂]⁺ (0.9), 144 (5.8), 130 (6.2), 75 [CH(OCH₃)₂] (100).

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