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## **Ozonolysis of Verbenone in Methanol**

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Abstract—The conditions of ozonolysis of verbenone in methanol strongly affect the mechanism of formation of the major product, (1R,3S)-3-acetyl-2,2-dimethylcyclobutane-1-carboxylic acid.

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Ozone is a potent and simultaneously selective oxidant, which is widely used in target-oriented syntheses of biologically active substances with a broad spectrum of action [1]. Proper consideration of the effect of substrate structure on the composition and behavior of peroxides formed in the course of ozonolysis makes it possible to plan the use of ozone in the design of complex molecules [2, 3].

With a view to reveal general relations holding in the reaction of ozone with  $\alpha,\beta$ -unsaturated ketones and optimize the procedure for the preparation of (1R,3S)-3-acetyl-2,2-dimethylcyclobutane-1-carboxylic acid (I), which is the key intermediate product in the synthesis of the citrus mealybug (Planococcus citri Risso) pheromone and other cyclobutane-containing biologically active substances, we examined ozonolysis of verbenone (II). We previously reported on the ozonolysis of verbenone (II) in acetonitrile and methylene chloride [4]. In continuation of these studies, the ozonolysis of II was performed in methanol; the results are collected in table. It is seen that the amount of ozone consumed for the oxidation process at -40 to -60°C does not depend on the solvent nature and is 1.1–1.2 mol of ozone per mole of the substrate. Excess

0.1–0.3 mol of the oxidant is likely to be consumed for reaction with the solvent or further oxidation of the ozonolysis products. The major ozonolysis product of verbenone (II) in methanol, as well as in acetonitrile, is keto acid I; in addition, its methyl ester III is formed (Scheme 1).

The reaction stoichiometry was determined according to [5]. Figure shows that in the initial period the amount of ozone absorbed at the inlet (curve 3) rapidly increases and reaches some constant value, i.e., ozone enters the reactor at a constant concentration. After 30 min at -60°C, the optical density of the reaction mixture at the outlet sharply increases (curve 2), indicating complete consumption of a compound reacting with ozone. The time corresponding to termination of  $O_3/O_2$  supply is marked with an arrow. Under these conditions, ~1–1.2 mol of ozone per mole of verbenone (**II**) was absorbed during the ozonolysis process. Raising the temperature to 0°C (curve 1) leads to increased consumption of ozone (2 mol of  $O_3$  per mole of **II**) due to its reaction with the solvent.

According to the NMR data, peroxides **IVa–IVc** generated by ozonolysis of **II** in methanol are stabilized via reaction with the solvent to produce methoxy



Scheme 1.

Ozonolysis of verbenone (II)

Temperature, °C	Solvent	Amount of absorbed ozone, mol per mole of verbenone	Yield of acid I, %
-60	Methylene chloride	1.1–1.3	70
	Methanol	1.1–1.2	63
-40	Acetonitrile	1.1–1.3	83
	Methylene chloride	1.1–1.3	71
	Methanol	~2	70
0	Acetonitrile	1.5–1.7	57
	Methanol	~2	45





hydroperoxides **Va–Vc** (Scheme 2). In the <sup>13</sup>C NMR spectrum recorded at –60°C immediately after ozonation of **II** in CD<sub>3</sub>OD, signals from the double-bonded carbon atoms in compound **Vc** appeared at  $\delta_{\rm C}$  130.01 and 131.25 ppm, and the carbon atoms linked to two oxygen atoms in **Va** and **Vb** resonated at  $\delta_{\rm C}$  109.25 and 116.63 ppm, respectively. The <sup>1</sup>H NMR spectrum of that mixture contained three downfield signals at  $\delta$  12.34, 12.70, and 13.41 ppm from the hydroperoxide protons in **Va–Vc**; a weak signal was also observed at  $\delta$  9.63 ppm. According to PM3 quantum-chemical calculations, tautomeric transformation like **Vb**  $\leftrightarrow$  **Vc** is possible. The total energies of tautomers **Vb** and **Vc** are –294245.467 and –294133.274 J/mol, respectively, i.e., the difference is as small as ~25 J/mol.

Rise in temperature leads to spontaneous decomposition of peroxide ozonolysis products, which does not require the presence of a reducing agent, and crystalline acid I gradually separates from the solution with time. We presumed that increased temperature favors shift of the equilibrium toward methoxy hydroperoxide **Vb** which is converted into acid I and ester III via intramolecular rearrangements (Scheme 3). Ester III was separated from acid I by column chromatography and was identified by GLC using an authentic sample and by NMR. Methyl formate liberated during the rearrangement was detected by GLC using a capillary column. Traditional procedures for decomposition of ozonides, e.g., by the action of dimethyl sulfide, ensured considerably lower yield of acid I and ester III (48 and 18%, respectively).

Intermediate formation of compound Va is confirmed by the presence of a signal at  $\delta$  9.63 ppm typ-



Variation of ozone absorption in the ozonolysis of verbenone (II) in methanol at (1) 0 and (2)  $-60^{\circ}$ C; (3) reactor inlet.



ical of an aldehyde proton in the <sup>1</sup>H NMR spectrum of the verbenone ozonolysis products in methanol. We failed to isolate compound VII because of its instability under conditions of chromatographic purification, but treatment of the product mixture with sodium triacetoxyhydridoborate gave the corresponding reduction product, alcohol VIII, which was isolated and identified (Scheme 4). The IR spectrum of VIII contained absorption bands due to stretching vibrations of ketone (1705 and 1720 cm<sup>-1</sup>) and hydroxy groups  $(3260 \text{ cm}^{-1})$ . Compound VIII displayed in the <sup>1</sup>H NMR spectrum two singlets at  $\delta$  2.06 and 3.88 ppm from protons in the acetyl and  $C(O)CH_2$  groups, respectively. Protons on  $C^1$  and  $C^3$  in the cyclobutane fragment resonated as doublets of doublets at  $\delta$  3.51 and 2.69 ppm, respectively, signals from magnetically nonequivalent methylene protons on C<sup>4</sup> were observed at  $\delta$  1.82 and 2.76 ppm, and the OH signal was located at  $\delta$  5.31 ppm.

The ozonation of verbenone (II) in methanol at 0-20°C required  $\sim$ 2 mol of O<sub>3</sub> per mole of **II**. Excess ozone oxidizes aldehyde and methoxy hydroperoxide groups and partly the solvent (MeOH). In this case, the reaction is likely to follow the scheme described in [6] (Scheme 5).

## **EXPERIMENTAL**

The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 and 75.46 MHz, respectively, from solutions in CDCl<sub>3</sub>; the chemical shifts are given relative to tetramethylsilane. The IR spectra were measured from thin films on a Specord M-80 spectrometer. The optical rotations were determined on a Perkin Elmer 241 MS polarimeter from solutions in chloroform. GLC analysis was performed using Chrom-5 (1200×3-mm column packed with 5% SE-30 on Chromaton N-AW-DMCS; carrier gas helium) and Shimadzu GC-2014 instruments (DB-35MS capillary column, 25 m; flame ionization detector; carrier gas helium; oven temperature programming from 50 to 300°C at a rate of 10 deg/min). Silica gel (Macherey-Nagel, 0.063-0.2 mm) was used for preparative column chromatography. The amount of absorbed ozone was determined by spectrophotometry by measuring the optical density of ozone in the gas phase at the inlet and outlet of the reactor ( $\lambda$  300 nm, SF-46 spectrophotometer, cell path length 5.2 cm).

(1R,3S)-3-Acetyl-2,2-dimethylcyclobutane-1-carboxylic acid (I) and its methyl ester III. a. An ozone-oxygen mixture was passed at -60°C through a solution of 0.5 g (3.3 mmol) of verbenone (II) in 5 ml of anhydrous methanol until initial compound II disappeared completely (TLC, petroleum ether–ethyl acetate, 3:2). The mixture was purged with argon, left to stand for 48 h at 20°C, and evaporated under reduced pressure, and the residue (0.52 g) was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>–petroleum ether (1.5:2.5) to isolate acid I. Yield 0.34 g (63%), white crystals, mp 98.5–100°C [7],  $[\alpha]_D^{20} = +28.5^\circ$  (c = 0.62).

The mother liquor was subjected to column chromatography (petroleum ether–ethyl acetate, 8.5:1.5) to isolate 0.13 g (21%) of ester **III** as a colorless oily substance. The spectral parameters of **III** were identical to those reported in [4]. IR spectrum, v, cm<sup>-1</sup>: 1710 (C=O), 1735 (C=O, ester). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 0.98 s and 1.40 s (3H each, 2-CH<sub>3</sub>), 2.03 s (3H, CH<sub>3</sub>CO), 2.11 d.d.d (1H, 4-H<sub>cis</sub>, J<sub>4,1</sub> = J<sub>4,3</sub> = 8.0, <sup>2</sup>J = 11.0 Hz), 2.53 d.d.d (1H, 4-H<sub>trans</sub>, J<sub>4,1</sub> = J<sub>4,3</sub> = <sup>2</sup>J = 11.0 Hz), 2.66 d.d and 3.06 d.d (2H, 1-H, 3-H, J = 8.0, 8.0, 11.0 Hz), 3.63 s (3H, OCH<sub>3</sub>). Found, %: C 65.23; H 8.70. C<sub>10</sub>H<sub>16</sub>O<sub>3</sub>. Calculated, %: C 65.22; H 8.70.

b. The procedure was the same as in a, but the ozonolysis was carried out at 0°C. As a result, 0.24 g (45%) of acid I and 0.12 g (18%) of ester III were isolated.

*c*. The ozonation procedure was the same as in *a*. After purging with argon, 0.36 ml of dimethyl sulfide was added, and the mixture was stirred for 20 min at  $-60^{\circ}$ C, allowed to warm up to room temperature, left to stand for 48 h, and evaporated under reduced pressure. The residue was diluted with chloroform, and the solution was washed with a saturated solution of sodium chloride, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated. The residue (0.52 g) was separated as described in *a* to isolate 0.26 g (48%) of I and 0.11 g (18%) of III.

1-[(1*R*,3*S*)-3-Acetyl-2,2-dimethylcyclobutan-1yl)-2-hydroxyethanone (VIII). Ozone, 6.6 mmol, was passed at  $-60^{\circ}$ C through a solution of 1 g (6.6 mmol) of II in 10 ml of anhydrous methanol. The mixture was purged with argon, the solvent was distilled off, the residue was dissolved in 10 ml of methylene chloride, the solution was added to a preliminarily prepared suspension of NaBH(OAc)<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> [8], and the mixture was stirred for 3 h. Water, 20 ml, was added dropwise, and the organic layer was separated, washed twice with a saturated solution of sodium chloride, and

dried over MgSO<sub>4</sub>. The drying agent was filtered off, the solvent was distilled off from the filtrate, 20 ml of anhydrous petroleum ether was added to the residue (1.02 g), crystals of acid I (0.37 g, 34.3%) were filtered off, the mother liquor was evaporated, and the residue was subjected to column chromatography (petroleum ether-ethyl acetate, 9:1) to isolate 0.22 g (16%) of ester III and 0.4 g (30%) of alcohol VIII as a light yellow oily substance. IR spectrum, v, cm<sup>-1</sup>: 1705 s, 1720 s (C=O); 3260 br.s (OH). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 0.85 s and 1.59 s (3H each, 2-CH<sub>3</sub>), 1.82 d.d.d (1H, 4-H<sub>cis</sub>,  $J_{4,1} = J_{4,3} = 8.0$ , <sup>2</sup>J = 11.0 Hz), 2.06 s (3H, CH<sub>3</sub>CO), 2.76 d.d.d (1H, 4-H<sub>trans</sub>,  $J_{4,1}$  =  $J_{4.3} = {}^{2}J = 11.0$  Hz), 2.96 d.d and 3.51 d.d (2H, 1-H, 3-H,  $J_{1,4-cis} = J_{3,4-cis} = 8.0$ ,  $J_{1,4-trans} = J_{3,4-trans} = 11.0$  Hz), 3.88 d (2H, CH<sub>2</sub>O), 5.31 br.s (1H, OH). <sup>13</sup>C NMR spectrum,  $\delta_{C}$ , ppm: 17.82 q and 29.80 q (CH<sub>3</sub>), 18.23 t  $(CH_2)$ , 30.18 g  $(CH_3)$ , 44.73 s  $(C^2)$ , 45.15 d  $(C^1)$ , 52.35 d (C<sup>3</sup>), 56.42 t (OCH<sub>2</sub>), 201.18 s and 207.33 s (C=O). Found, %: C 65.23; H 8.70. C<sub>10</sub>H<sub>16</sub>O<sub>3</sub>. Calculated, %: C 65.21; H 8.69.

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