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Complete Ozonolysis of 3-Methyl-4-(prop-1-en-1-yl)cyclohexene

O. S. Kukovinets[a, b], T. I. Zvereva[b], A. G. Kukovinets[b], M. I. Abdullin[b], and F. Z. Galin[a, b]

[a] *Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia*

[b] *Bashkir State University, ul. Mingazheva 100, Ufa, 450014 Bashkortostan, Russia*
e-mail: PMSV@bsu.bashedu.ru

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Abstract—Complete ozonolysis of the thermal dimer of piperylene, 3-methyl-4-(prop-1-en-1-yl)cyclohexene, followed by reduction of primary peroxy compounds with dimethyl sulfide, gave 2-methyl-3-formyl-1,6-hexanedial as the major product and five- and six-membered hydroxy lactones which were formed via intramolecular cyclization of peroxides with participation of oxygen-containing functional groups.

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A convenient synthetic approach to biologically active substances is based on the ozonolysis of cyclic olefins and cyclic polyenes [1–3]; it ensures purposeful preparation of α,ω-difunctional oxygen containing synthons. We previously showed that ozonolysis of the thermal dimer of piperylene, 3-methyl-4-(prop-1-en-1-yl)cyclohexene (**I**) with an equimolar amount of ozone gives 2-methyl-3-formyl-1,6-hexanedial (**II**) as minor product; compound **II** is a precursor of dienoates having a heterocyclic fragment, which are promising as substances possessing a juvenile hormone activity [4]. In the present work we studied the complete ozonolysis of diene **I** with a view to improve the yield of trialdehyde **II**.

The ozonolysis of compound **I** with 2 equiv of ozone in anhydrous methanol, followed by reduction of the peroxide products with dimethyl sulfide, gave trialdehyde **II** as the major product (yield 42%); it was isolated by column chromatography on silica gel using petroleum ether–ethyl acetate (85:15) as eluent. The yield of **II** was raised to 62% when the primary peroxide products were hydrogenated over Pd–$CaCO_3$–PbO. However, the IR spectrum of the reaction mixture, apart from the absorption band at 1725 cm^{-1} typical of trialdehyde **II**, contained bands at 1745 and 1780 cm^{-1} and at 3460 cm^{-1} (hydroxy group).

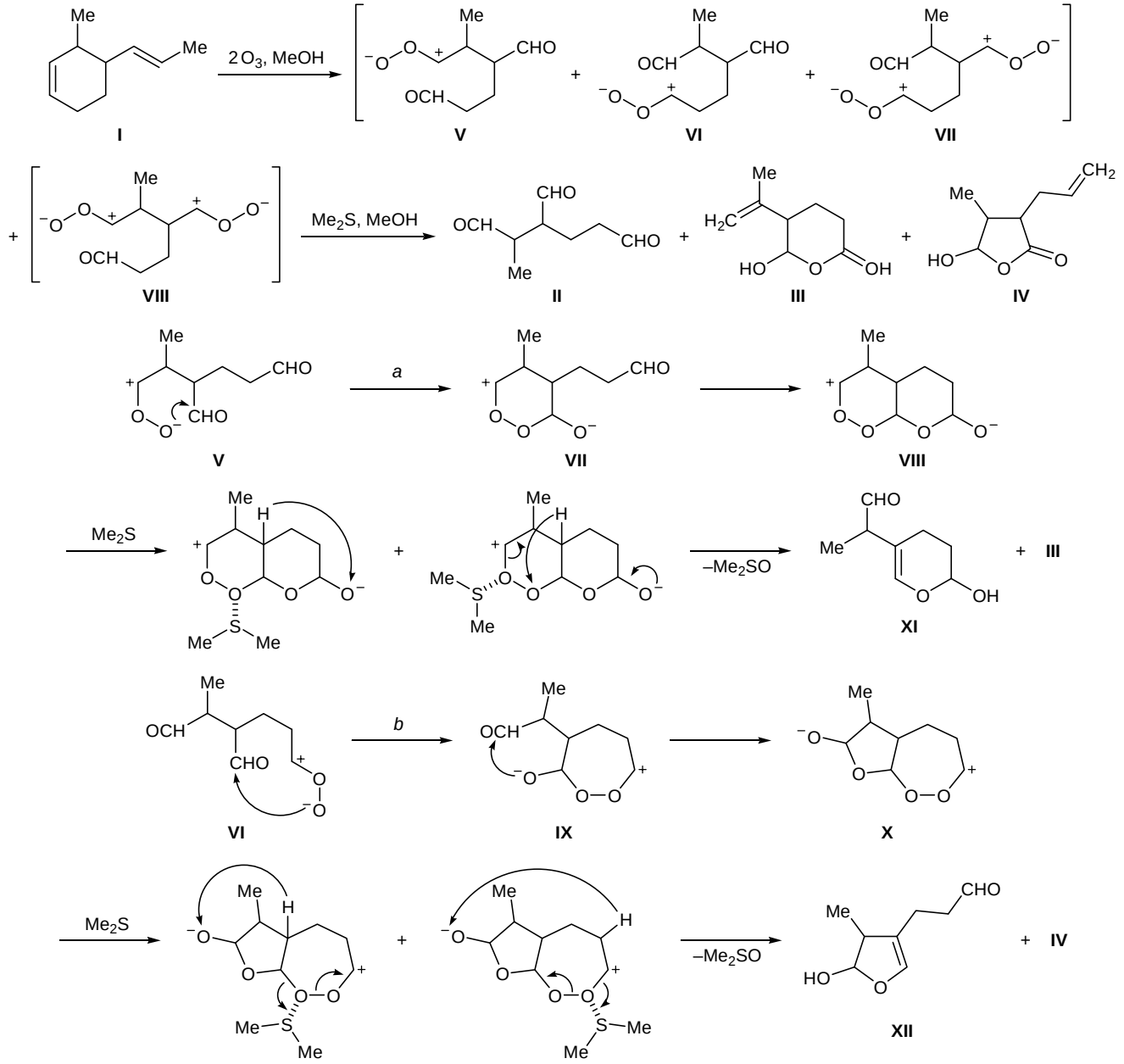
By column chromatography on silica gel (petroleum ether–ethyl acetate; gradient elution starting from a ratio of 85:15) we isolated two minor fractions. The first fraction showed in the IR spectrum absorption bands at 3460 and 1745 cm^{-1} and a shoulder at 1725 cm^{-1}, the latter corresponding to trialdehyde **II**. The ^1H NMR spectrum of that fraction contained a singlet at δ 1.72 ppm, which was assigned to methyl protons in isopropenyl fragment, a triplet at δ 2.4 ppm, a doublet at δ 5.58 ppm, and multiplet signals at δ 1.24–1.56 and 5.85 ppm. Taking into account the presence of absorption bands at 1745 and 3460 cm^{-1} in the IR spectrum and of signals at δ_C 101.18 and 173.70 ppm in the ^{13}C NMR spectrum, the main component of the first fraction was assigned the structure of 2-hydroxy-3-isopropenyltetrahydropyran-6-one (**III**); according to the GLC data, its fraction was 84%.

In the ^1H NMR spectrum of the second fraction we observed doublets at δ 1.09 and 5.49 ppm, a broadened singlet at 5.17 ppm, and a multiplet centered at δ 5.86 ppm. Its IR spectrum also contained absorption bands at 1780 (with a shoulder at 1745 cm^{-1}) and 3450 cm^{-1}. On the basis of these data, we presumed that the main component of the second fraction is 2-hydroxy-3-methyl-4-(prop-2-en-1-yl)tetrahydrofuran-5-one (**IV**); its fraction was 75% (GLC).

Presumably, the process includes not only conventional reaction of primary peroxides with the solvent (methanol) but also their stabilization with participation of the aldehyde group emerging in the ozonolysis of dimer **I**. The possibility for the reaction to take this pathway is consistent with published data [5–8].

Fairly high reactivity of the exocyclic double bond [9] toward ozonation (due to the presence of a methyl

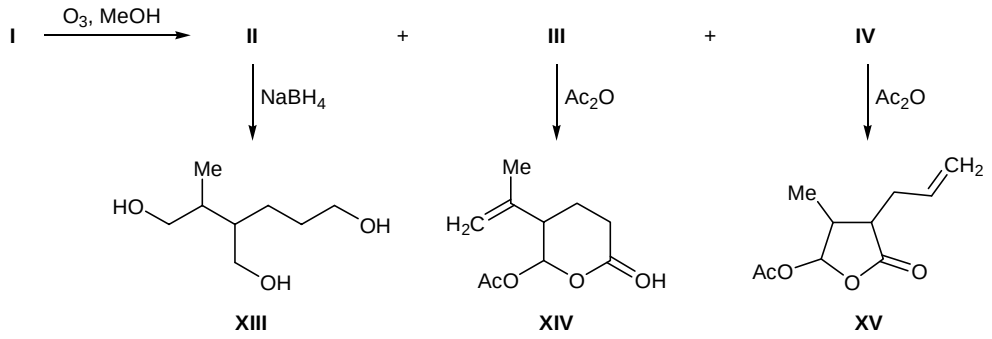
Scheme 1.



group) is likely to favor simultaneous attack by ozone on the endo- and exocyclic double bonds rather than their stepwise cleavage. The aldehyde group thus formed (dipolar ions **V** and **VI**; Scheme 1) reacts with the zwitterionic fragment along two possible pathways (*a* or *b*). Reduction of secondary peroxides **VIII** and **X** with dimethyl sulfide leads to heterocyclic compounds **III**, **IV**, **XI**, and **XII**; among these, compounds **III** and **IV** are the major products (as follows from the spectral data). Enhanced reactivity of the exocyclic double bond (in our case, due to methyl substitution) is a necessary condition for the formation of compounds **III** and **IV**. No analogous structures were detected among the products of ozonolysis of vinylcyclohexene under similar conditions.

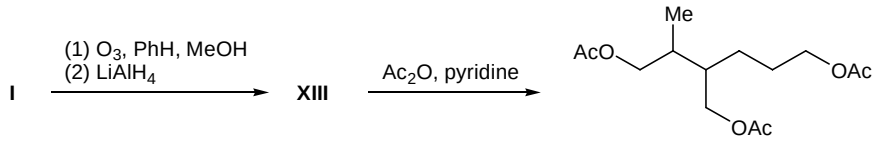
After reduction of the fractions containing tetrahydropyran and tetrahydrofuran derivatives **III** and **IV** and a minor amount of compound **II** with sodium tetrahydridoborate, the carbonyl region of the IR spectra lacked absorption band at 1725 cm^{-1}, while the bands assigned to cyclic lactones **III** and **IV** remained in the spectrum. 2-Methyl-3-hydroxymethylhexane-1,6-diol (**XIII**), obtained by reduction of the ozonolysis products with $NaBH_4$ (Scheme 2) is readily sol-

Scheme 2.



XIII XIV XV

Scheme 3.



XVI

uble in water, and it is transferred into the aqueous phase upon washing with water of a solution of the reduction products in methylene chloride. From the organic phase we isolated a mixture of compounds **III** and **IV**; it was subjected to acetylation, and subsequent chromatographic separation gave pure 3-methyl-5-oxo-4-(prop-2-en-1-yl)tetrahydrofuran-2-yl acetate (**XV**). Compound **XV** displayed in the ^{1}H NMR spectrum a signal at δ 2.03 ppm from the acetoxy group, a doublet at δ 1.09 ppm from the 3-methyl group, a doublet at δ 5.41 ppm from 2-H, and signals at δ 5.24 and 5.83 ppm from protons in the terminal vinyl group. Acetoxy derivative **XIV** was isolated as a mixture with **XV** (~5%). The ^{1}H NMR spectrum of compound **XIV** contained a singlet at δ 1.67 ppm from the methyl protons in the isopropenyl fragment, a doublet at δ 5.45 ppm, and a multiplet centered at δ 5.24 ppm.

The product composition also depends on the solvent used in the ozonolysis stage. When the ozonolysis of compound **I** was performed in benzene in the presence of 2 equiv of methanol, the subsequent reduction with $LiAlH_4$ and acetylation gave (after chromatographic purification) 76% of triacetate **XVI** as the only product (Scheme 3).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples prepared as thin films or dispersed in Nujol. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer (300.13 and 75.25 MHz, respectively) using $CDCl_3$ as solvent and TMS as internal reference. GLC analysis was performed on a Chrom-5 chromatograph equipped with a 1200×3-mm column; stationary phase 5% of SE-30 on Chromaton N-AW-DMCS (0.16–0.20 mm); oven temperature programming from 50 to 300°C at a rate of 12 deg/min; carrier gas helium.

3-Methyl-4-(prop-1-en-1-yl)cyclohexene (**I**) was obtained by thermal dimerization of *trans*-piperylene [9] and was isolated by distillation through a 1.2-m column; according to the GLC data, it contained 95% of the main substance.

3-Formyl-2-methylhexane-1,6-dial (II), 6-hydroxy-5-isopropenyltetrahydropyran-2-one (III), and 5-hydroxy-4-methyl-3-(prop-2-en-1-yl)tetrahydrofuran-2-one (IV). *a*. A solution of 4 g (29.4 mmol) of cyclic diene **I** in 45 ml of anhydrous methanol was cooled to –10°C, and 58.8 mmol of ozone was passed through the solution until the initial diene disappeared (TLC, silica gel, petroleum ether–ethyl acetate, 85:15). The mixture was purged with a stream of nitrogen, and 6.5 ml of dimethyl sulfide was added. The solvent was distilled off, 40 ml of chloroform was added to the residue, the solution was quickly washed with a saturated solution of sodium chloride and dried over $MgSO_4$, the solvent was distilled off, and the residue (4.3 g) was subjected to chromatography on silica gel (petroleum ether–ethyl acetate, 85:15) to isolate (in the order of elution) 1.81 g (42%) of trialdehyde **II**, 0.37 g of a mixture of compounds **III** and **IV** enriched in the former (84%, according to the GLC data), and 0.55 g of mixture **III**/**IV** enriched in the latter (75%, GLC).

b. A solution of 2.00 g (14.7 mmol) of compound **I** in 25 ml of anhydrous methanol was cooled to –10°C, and 29.40 mmol of ozone was passed through the solution until diene **I** disappeared completely. Excess ozone was removed by purging with a stream of nitrogen, 0.2 g of the Lindlar catalyst (Pd–$CaCO_3$–PbO) was added, and the mixture was stirred under hydrogen until peroxy compounds were no longer detected (test with an acidified aqueous solution of KI). The catalyst was filtered off, the solvent was distilled off, and the residue (1.24 g) was subjected by column chromatography to isolate 0.77 g (62%) of compound **II** which was identical to a sample of **II** obtained as described above in *a*.

3-Formyl-2-methylhexane-1,6-dial (II). Yellow oily substance. IR spectrum, ν, cm^{-1}: 1725, 2750 (CHO). ^{1}H NMR spectrum, δ, ppm: 1.16 d (3H, CH_3, J = 6.5 Hz), 1.64 m (2H, CH_2), 1.95–2.06 m (4H, HCCO), 9.6 s (3H, CHO). Found, %: C 61.84; H 7.65. $C_8H_{12}O_3$. Calculated, %: C 61.54; H 7.69.

6-Hydroxy-5-isopropenyltetrahydropyran-2-one (III). IR spectrum, ν, cm^{-1}: 940 m, 1640 m, 1745 s, 3080 w, 3460 s, br. ^{1}H NMR spectrum, δ, ppm: 1.24–1.56 m (2H, CH_2), 1.72 s (3H, CH_3), 2.4 t (2H, CH_2CO, J = 7.5 Hz), 2.56 m (1H, 5-H), 5.58 d (1H, 6-H, J = 6.0 Hz), 5.85 m (3H, CH_2=C, OH). ^{13}C NMR spectrum, δ_C, ppm: 19.57 q (CH_3), 24.85 t (C^4), 31.63 d (C^5), 34.05 t (C^3), 101.18 d (C^6), 113.30 d (CH=), 138.40 s (CH_3**C**=), 173.70 s (C=O).

5-Hydroxy-4-methyl-3-(prop-2-en-1-yl)tetrahydrofuran-2-one (IV). IR spectrum, ν, cm^{-1}: 910 s, 1640 m, 1780 s, 3080 w, 3450 s, br. ^{1}H NMR spectrum, δ, ppm: 1.09 d (3H, CH_3, J = 7.0 Hz), 2.13 m (2H, CH_2), 2.81 d (1H, 3-H, J = 7.0 Hz), 2.94 m (1H, 4-H), 5.17 br.s (2H, H_2C=), 5.49 d (1H, 5-H, J = 6.0 Hz), 5.86 m (1H, 2'-H). ^{13}C NMR spectrum, δ_C, ppm: 9.15 q (CH_3), 35.41 t (CH_2), 40.96 d (C^3), 42.38 d (C^4), 102. 80 d (C^5), 116.31 t (CH_2=), 135.48 d ($C^{2'}$), 178.16 s (C=O).

3-Isopropenyl-6-oxotetrahydropyran-2-yl acetate (XIV) and 3-methyl-5-oxo-4-(prop-2-en-1-yl)-tetrahydrofuran-2-yl acetate (XV). A mixture of the ozonolysis products, enriched in compounds **III** and **IV**, 2.00 g, was dissolved in 40 ml of distilled methanol, 1.44 g (38.92 mmol) of sodium tetrahydridoborate was added in portions, the mixture was stirred for 3 h and left to stand for 12 h at room temperature, 32 ml of 7% aqueous acetic acid was added under stirring, and the mixture was stirred for 3 h. Methanol was distilled off, 40 ml of methylene chloride was added to the residue, and the solution was washed in succession with a saturated solution of sodium hydrogen carbonate and water and dried over $MgSO_4$. Removal of the solvent left 0.54 g of the crude product which was treated with 4.90 g (48.04 mmol) of acetic anhydride and 4.5 ml of anhydrous pyridine. The mixture was stirred for 2.5 h at 0°C and was left to stand for 12 h in a refrigerator. It was then diluted with methylene chloride, washed in succession with 1 N hydrochloric acid and a saturated solution of sodium hydrogen carbonate, and dried over $MgSO_4$. The solvent was distilled off, and the residue was subjected to chromatography on silica gel using hexane–diethyl ether as eluent (95 : 5, with gradual increase of the fraction of the latter) to isolate 0.11 g (3.8%) of compound **XIV** and 0.16 g (5.5%) of **XV**.

3-Isopropenyl-6-oxotetrahydropyran-2-yl acetate (XIV). IR spectrum, ν, cm^{-1}: 940 m, 1640 m, 1745 s, 3080 w. ^{1}H NMR spectrum, δ, ppm: 1.24–1.56 m (2H, CH_2), 1.67 s (3H, CH_3), 2.03 s (3H, CH_3CO), 2.43 t (2H, CH_2CO, J = 7.5 Hz), 2.54 m (1H, 3-H), 5.24 m (2H, CH_2=C), 5.45 d (1H, 2-H, J = 6.0 Hz).

3-Methyl-5-oxo-4-(prop-2-en-1-yl)tetrahydrofuran-2-yl acetate (XV). IR spectrum, ν, cm^{-1}: 910 m, 1640 m, 1745 s, 1780 s, 3080 w. ^{1}H NMR spectrum, δ, ppm: 1.09 d (3H, CH_3, J = 7.0 Hz), 2.03 s (3H, CH_3CO), 2.16 m (2H, CH_2), 2.47 m (1H, 3-H), 2.99 m (1H, 4-H), 5.41 d (1H, 2-H, J = 5.5 Hz), 5.24 br.s (2H, H_2C=), 5.83 m (1H, HC=). Found, %: C 60.88; H 7.94. $C_{10}H_{14}O_4$. Calculated, %: C 60.61; H 7.07.

3-Acetoxymethyl-2-methylhexane-1,6-diyl diacetate (XVI). *a*. A solution of 2.00 g (14.70 mmol) of compound **I** in 25 ml of anhydrous methanol was cooled to –10°C, and 29.40 mmol of ozone was passed through the solution until the initial diene disappeared completely. After removal of excess ozone, peroxide compounds were reduced by adding 6.5 ml of dimethyl sulfide, the solvent was distilled off, the residue was dissolved in 35 ml of chloroform, the solution was washed with a cold saturated solution of sodium chloride and dried over $MgSO_4$, and the solvent was distilled off under reduced pressure (water-jet pump). Anhydrous benzene, 40 ml, was added to the residue, 1.67 g (0.044 mol) of lithium tetrahydridoaluminate was added in portions under stirring, maintaining the temperature below 40–50°C, and the mixture was stirred for 0.5 h and was then heated for 1 h under reflux with stirring. The mixture was cooled, 0.8 ml of water was carefully added under vigorous stirring, the

mixture was stirred for an additional 1 h, the solution was separated from the precipitate by decanting, the residue was treated with 40 ml of benzene, the mixture was stirred for 10 min, the solution was separated by decanting, and this procedure was repeated two times more. The benzene extracts were combined and dried over $MgSO_4$, the solution was filtered and evaporated, 26.30 g (0.25 mol) of acetic anhydride and 24.4 ml of anhydrous pyridine were added to the residue at 0°C, and the mixture was stirred for 2.5 h at 0°C and was left to stand for 12 h in a refrigerator. The product was isolated as described above for compound **XV**. Yield of **XVI** 1.78 g (43%). IR spectrum, ν, cm^{-1}: 1745 s. ^1H NMR spectrum, δ, ppm: 0.96 d (3H, CH_3, J = 7.0 Hz), 1.54 m (4H, CH_2), 1.79 m (2H, CH), 2.03 br.s (9H, CH_3CO), 4.29 m (6H, CH_2O). Found, %: C 58.41; H 8.27. $C_{14}H_{24}O_6$. Calculated, %: C 58.33; H 8.33.

b. A solution of 1.0 g (7.35 mmol) of cyclic diene **I** in 30 ml of anhydrous benzene containing 0.6 ml (14.7 mmol) of methanol was cooled to 5°C, and 14.70 mmol of ozone was passed through the solution until the initial compound disappeared. The mixture was purged with argon, 1.67 g (0.044 mol) of $LiAlH_4$ was added, and the mixture was stirred for 0.5 h and then heated for 1 h under reflux with stirring. The reduction product was isolated and converted into triacetate **XVI** as described above in *a*. Yield 1.57 g (76.0%); the product was identical to a sample obtained according to method *a*.

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