ISSN 1070-4280, Russian Journal of Organic Chemistry, 2015, Vol. 51, No. 5, pp. 610–614. © Pleiades Publishing, Ltd., 2015.
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Transformations of Peroxide Products of Oleic Acid Ozonolysis at Treatment with Hydroxylamine and Semicarbazide Hydrochlorides

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Received February 16, 2015

Abstract—Peroxide products of oleic acid ozonolysis treated with semicarbazide and hydroxylamine hydrochlorides in methanol are predominantly converted into methyl nonanoate and dimethyl nonanedioate, in 2-propanol, into isopropyl nonanoate and monoisopropyl ester of nonanedioic acid, and also into nonanenitrile, in tetrahydrofuran and in a mixture of acetic acid with dichloromethane, into nonanoic and nonanedioc acids, and also in nonanal oxime and 9-(hydroxyimino)nonanoic acid.

DOI: 10.1134/S1070428015050036

Oleic [(9*Z*)-octadec-9-enoic] acid **1** is present in the composition of nearly all natural fats and oils. One of its main sources is olive (~80%), and also sunflower (39%) and cottonseed (35%) oils, in animal fats it constitutes 36–45% of the overall amount of fatty acids [1].

Main ozonolysis transformations of *Z*-unsaturated acid **1** resulting from the oxidation of peroxide ozonolysis products with H_2O_2 [2], a mixture H_2O_2–HCO_2H [3], or by oxygen in the presence of transition metal salts and oxides, e.g., $Mn(OAc)_2$ [4] lead to the formation of azelaic (nonanedioic) **2** and nonanoic **3** acids. The reduction with dimethyl sulfide [5, 6], potassium iodide [7], hydrogen on palladium black [4] or on catalyst $Pd/CaCO_3$ [8] provides 9-oxononanoic acid and nonanal. A preparation was described of 9-(hydroxyimino)nonanoic acid **4** from sodium oleate at the use of hydroxylamine in water [9, 10].

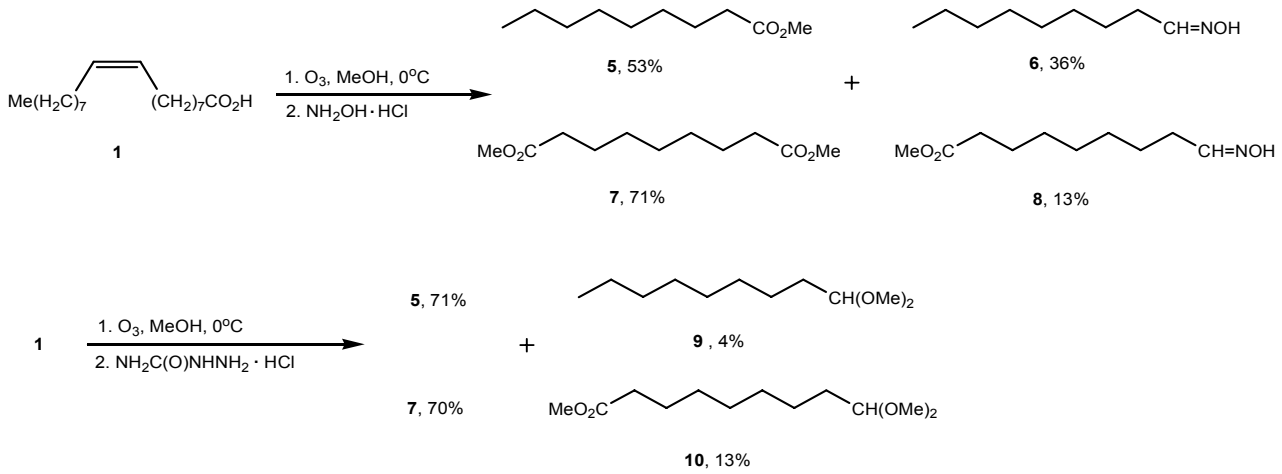
In this work results are reported of the study of ozonolysis transformations of oleic acid **1**; in the reduction of the peroxide ozonolysis products hydroxylamine and semicarbazide hydrochlorides were utilized in various organic solvents.

At the ozonolysis of oleic acid **1** in methanol at 0°C followed by the treatment with hydroxylamine hydrochloride a mixture of compounds was obtained that was subjected to chromatography to isolate methyl nonanoate **5**, nonanal oxime **6**, dimethyl 1,9-nonanedioate **7**, and methyl 9-(hydroxyimino)nonanoate **8**. At the reduction with semicarbazide hydrochloride a mixture formed of the same methyl esters **5** and **7**, and also 1,1-dimethoxynonane **9** and methyl 9,9-dimethoxynonanoate **10** (Scheme 1). The latter is an intermediate product in the synthesis of biologically and pharmacologically active (2*E*)-9-oxo- and 10-hydroxydec-2-enoic acids, components of royal jelly of honeybees *Apis mellifera* L. [6].

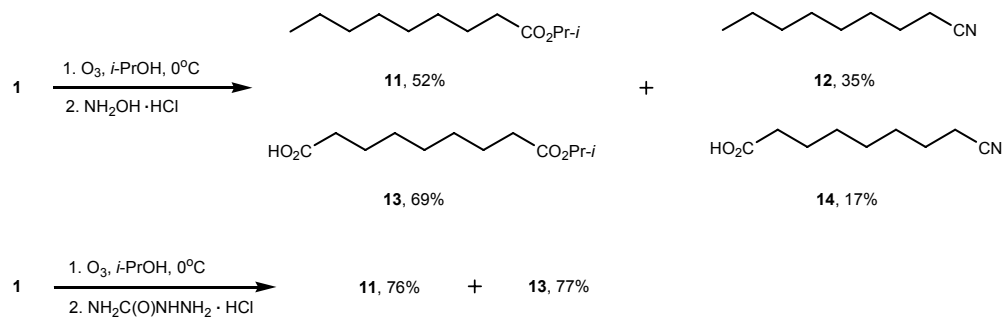
The treatment of peroxide products of oleic acid **1** ozonolysis in 2-propanol at 0°C with hydroxylamine hydrochloride provides a mixture of isopropyl nonanoate **11**, nitrile **12**, monoisopropyl ester of 1,9-nonandioic acid **13**, and 8-cyanooctanoic acid **14**. Under the action of semicarbazide hydrochloride a mixture was obtained of isopropyl nonanoate **11** and monoisopropyl ester of nonanedioic acid **13** in 76 and 77% respectively (Scheme 2). The formation of monoisopropyl ester **13** is apparently due to the lower reactivity of 2-propanol in the esterification compared with methanol. Ester **13** is contained in a composition used in dermatology in the treatment of freckles, liver spots, and acne [11].

The findings obtained are well consistent with the previous data on the transformation of peroxides from the ozonolysis of 10-undecenoic acid in MeOH and *i*-

Scheme 1.



Scheme 2.

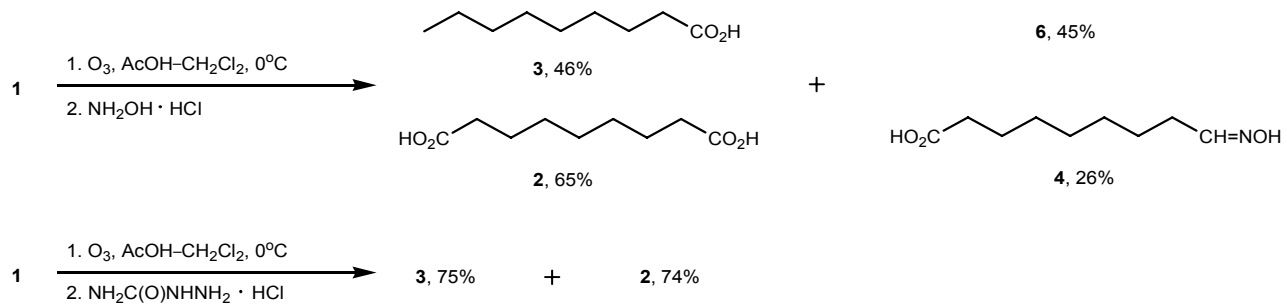


PrOH [12] in the reactions with hydroxylamine and semicarbazide hydrochlorides.

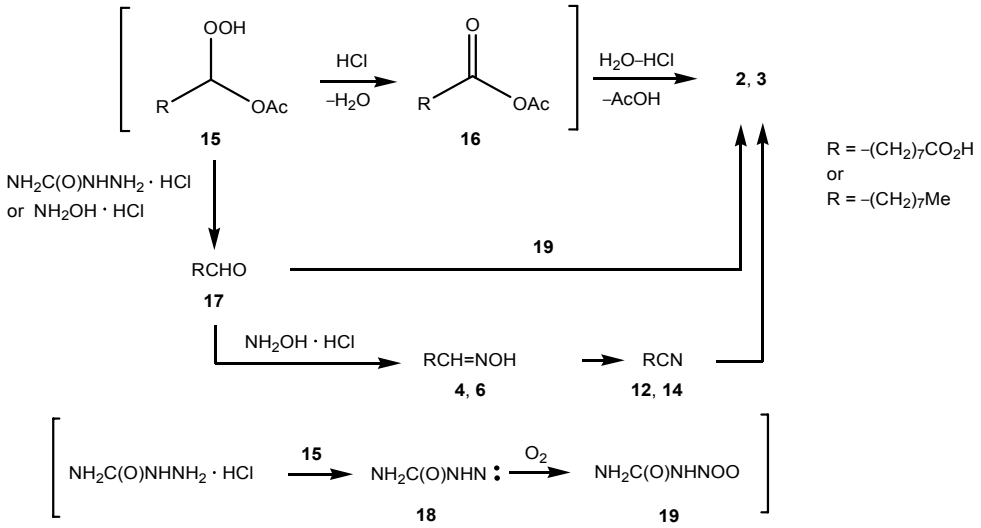
The ozonolysis of oleic acid **1** in a mixture of acetic acid and dichloromethane, 1 : 5, followed by the treatment with hydroxylamine hydrochloride afforded a mixture of nonanoic acid **3**, oxime **6**, azelaic acid **2**, and 9-hydroxyiminononanoic acid **4**. The mixture was separated by chromatography. The treatment of peroxide ozonolysis products with semicarbazide hydrochloride led to the formation of a mixture of nonanoic **3** and azelaic **2** acids (Scheme 3). The latter is a natural antioxidant, exhibits antibacterial and antiphlogistic actions, and is widely used in cosmetics [13]. Nonanal oxime **6** was employed in the synthesis of the analog of *N*-acyl homoserine lactone, PAI-1, the activator of transcription factor of *Pseudomonas aeruginosa* [14].

In the presence of semicarbazide hydrochloride acid **2** and **3** are obtained evidently from the readily hydrolysable mixed anhydrides **16**, which in their turn form from the intermediate acetoxyhydroperoxides **15** in the presence of HCl. Anhydrides **15** can as well be reduced to aldehydes **17** that are further oxidized into the corresponding acids **2** and **3** with nitroso oxide **19** formed by the oxidation of semicarbazide hydro-

Scheme 3.



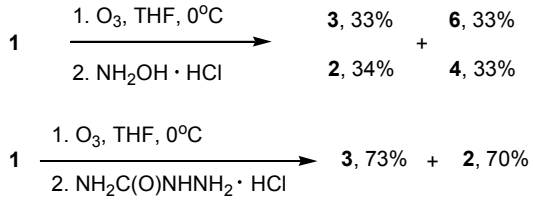
Scheme 4.



chloride first with peroxide **15**, and then with oxygen through an intermediate stage of nitrene **18** formation [15].

Compounds **2**, **3** and **6** at the use of hydroxylamine hydrochloride form evidently along the previously suggested route [16]: aldehyde **17** → aldoximes **4**, **6** → nitriles **12**, **14** → acids **2**, **3** (Scheme 4).

Scheme 5.



The treatment of the products of oleic acid **1** ozonolysis in tetrahydrofuran with hydroxylamine hydrochloride provided a similar mixture of compounds, but the yields of substances **2**–**4** and **6** are somewhat smaller (Scheme 5).

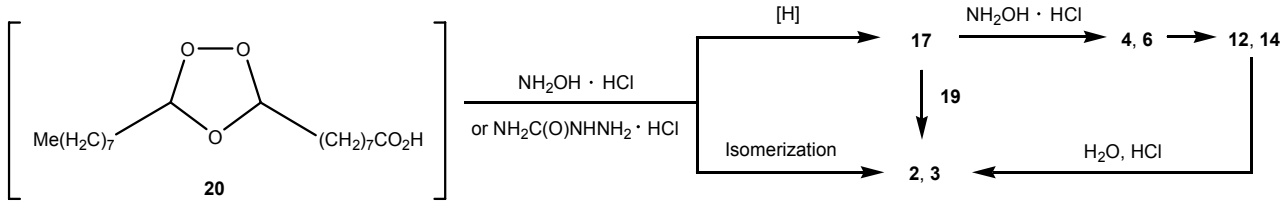
Presumably the peroxide product of oleic acid **1** ozonolysis in THF is ozonide **20**, and the hydroxylamine and semicarbazide hydrochlorides either reduce it to aldehydes **17**, or isomerize it into acids **2** and **3** (Scheme 6). In their turn aldehydes **17** can be converted into acids **2** and **3** through the transformations described in Scheme 4.

Thus as a result of a systematic investigation of the transformations of peroxide products of oleic acid ozonolysis procedures were developed of the preparative production of a number of nonanoic and azelaic acids derivatives widely used in medicine, perfumery and cosmetics, in technology and chemical industry.

EXPERIMENTAL

In the study the equipment of the Center of shared usage "Chemistry" of Ufa Institute of Chemistry, Russian Academy of Sciences, was used. IR spectra were recorded on a Fourier Transform Spectrophotometer IR Prestige-21 (Shimadzu) from thin films. NMR spectra were registered on a spectrometer Bruker AM-300 [operating frequencies 300 (^{1}H), 75.47 (^{13}C) MHz] in $CDCl_3$, internal reference TMS. GLC analysis were carried out on a chromatograph Chrom-5 [column 1.2 m, stationary phase silicone SE-30 (5%) on the carrier Chromaton N-AW-DMCS (0.16–0.20 mm), ramp 50–

Scheme 6.



300°C], carrier gas helium. TLC was performed on Sorbfil plates (Russia). For column chromatography silica gel was used of Lancaster (England) (70–230). The elemental analyses of all compounds were in agreement with calculated values.

Ozonolysis of oleic acid (1). General procedure. At ozone generator output 40 mmol O_3/h through a solution of 1.41 g (5.0 mmol) of oleic acid **1** in 25 mL of anhydrous alcohol or 20 mL of anhydrous THF or 25 mL of a mixture AcOH–CH_2Cl_2, 1 : 5, at 0°C was bubbled ozone-oxygen mixture till 5.5 mmol of ozone was consumed. The reaction mixture was flushed with argon and then it was treated by two procedures.

a. At 0°C 1.20 g (17.3 mmol) of $NH_2OH·HCl$ was added, the mixture was stirred at room temperature till disappearance of peroxides (iodine-starch test). The solvent was distilled off, the residue was dissolved in $CHCl_3$ (50 mL), the obtained solution was washed with H_2O (2 × 15 mL), dried over Na_2SO_4, and evaporated.

b. At 0°C 1.90 g (17.0 mmol) of $NH_2C(O)·NHNH_2·HCl$, was added, the mixture was stirred at room temperature till disappearance of peroxides (iodine-starch test). The solvent was distilled off, the residue was dissolved in $CHCl_3$ (50 mL), the obtained solution was washed with H_2O (2 × 15 mL), dried over Na_2SO_4, and evaporated.

Ozonolysis in methanol. By method *a* after chromatographing 1.89 g of residue (SiO_2, eluent petroleum ether–*tert*-butyl methyl ether, 2 : 1) we obtained 0.46 g (53%) of methyl nonanoate **5**, 0.28 g (36%) of nonanal oxime **6**, 0.77 g (71%) of dimethyl nonanedioate **7**, and 0.18 g (18%) of methyl 9-hydroxyiminononanoate **8**.

By method *b* after chromatographing 1.85 g of residue (SiO_2, petroleum ether–*tert*-butyl methyl ether, 2 : 1) we obtained 0.61 g (71%) of methyl nonanoate **5**, 0.13 g (14%) of 1,1-dimethoxynonane **9**, 0.76 g (70%) of dimethyl nonanedioate **7**, and 0.16 g (13%) of methyl 9,9-dimethoxynonanoate **10**.

Methyl nonanoate (5). R_f 0.59 (petroleum ether–*tert*-butyl methyl ether, 2 : 1). IR, ^{1}H and ^{13}C NMR spectra are identic to those previously described [16, 17].

***N*-Hydroxynonan-1-imine (nonanal oxime) (6)**. R_f 0.26 (petroleum ether–*tert*-butyl methyl ether, 2 : 1), mp 63–64°C (mp 63.5°C [18]). IR spectrum, ν, cm^{-1}: 3335 (NOH), 1660 (CH=N). ^{1}H NMR spectrum, δ, ppm: 0.87 t (3H, CH_3, *J* 5.7 Hz), 1.24–1.31 m (2H, C^8H_2), 1.48–1.61 m (10H, $C^{3-7}H_2$), 2.20–2.35 m (2H, C^2H_2), 7.27 s (1H, CH), 7.40 br.s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 14.12 q (CH_3), 22.69 t (C^8H_2), 24.89 t (C^2H_2), 25.93 t, 26.46 t, 29.19 t, 29.47 t, 31.74 t ($C^{3-7}H_2$), 152.15 d (C^1H).

Dimethyl nonanedioate (7). R_f 0.45 (petroleum ether–*tert*-butyl methyl ether, 2 : 1). IR, ^{1}H and ^{13}C NMR spectra are identic to those previously described [17].

Methyl 9-hydroxyiminononanoate (8). R_f 0.24 (petroleum ether–*tert*-butyl methyl ether, 2 : 1). IR spectrum, ν, cm^{-1}: 3335 (NOH), 1734 (CO_2Me), 1662 (CH=N). ^{1}H NMR spectrum, δ, ppm: 1.48–1.61 m (10H, $C^{3-7}H_2$), 2.20–2.35 m (2H, C^2H_2), 2.32 t (2H, C^8H_2, *J* 7.4 Hz), 3.65 s (3H, OCH_3), 7.27 s (1H, CH), 7.40 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 24.99 t (C^2H_2), 26.25 t, 26.58 t, 28.95 t, 29.30 t, 29.72 t ($C^{3-7}H_2$), 34.08 t (C^8H_2), 51.52 q (OCH_3), 152.31 d (CNOH), 174.36 s ($\underline{C}O_2CH_3$).

1,1-Dimethoxynonane (9). R_f 0.62 (petroleum ether–*tert*-butyl methyl ether, 2 : 1). ^{1}H NMR spectrum is identic to that previously described [19].

Methyl 9,9-dimethoxynonanoate (10). R_f 0.47 (petroleum ether–*tert*-butyl methyl ether, 2 : 1). IR, ^{1}H and ^{13}C NMR spectra are identic to those previously described [20].

Ozonolysis in 2-propanol. By method *a* after chromatographing 1.88 g of residue (SiO_2, petroleum ether–*tert*-butyl methyl ether, 2 : 1) we obtained 0.52 g (52%) of isopropyl nonanoate **11**, 0.24 g (35%) of nonanenitrile **12**, 0.79 g (69%) of monoisopropyl ester of nonanedioic acid **13**, and 0.14 g (17%) of 8-cyanooctanoic acid **14**.

By method *b* after chromatographing 2.17 g of residue (SiO_2, petroleum ether–*tert*-butyl methyl ether, 2 : 1) we obtained 0.76 g (76%) of isopropyl nonanoate **11** and 0.87 g (77%) of monoisopropyl ester of nonanedioic acid **13**.

Isopropyl nonanoate (11). R_f 0.60 (petroleum ether–*tert*-butyl methyl ether, 2 : 1). IR spectrum, ν, cm^{-1}: 1729 (C=O), 1181–1250 (C–O–C). ^{1}H and ^{13}C NMR spectra are identic to those previously described [21].

Nonanenitrile (12). R_f 0.25 (petroleum ether–*tert*-butyl methyl ether, 2 : 1). IR, ^{1}H and ^{13}C NMR spectra are identic to those previously described [16].

9-Oxo-9-(propan-2-yloxy)nonanoic acid (13). R_f 0.19 (petroleum ether–*tert*-butyl methyl ether, 2 : 1). IR spectrum, ν, cm^{-1}: 3200 (OH), 1730 (C=O in ester), 1709 (C=O in acid), 1082–1216 (C–O–C). ^{1}H NMR

spectrum, δ, ppm: 1.22 d [6H, CH(C<u>H</u>$_3$)$_2$, *J* 6.2 Hz], 1.26–1.66 m (10H, C$^{3-7}$H$_2$), 2.24 t (2H, C^{2}H$_2$, *J* 7.3 Hz), 2.32 t (2H, C^{8}H$_2$, *J* 6.6 Hz), 4.99 septet [1H, C<u>H</u>(CH$_3$)$_2$, *J* 6.4 Hz], 9.80 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 21.78 q [CH(<u>C</u>H$_3$)$_2$], 24.67 t, 24.88 t, 28.85 t, 29.06 t, 29.63 t (C$^{3-7}$H$_2$), 34.07 t, 34.58 t (C^{2}H$_2$, C^{8}H$_2$), 67.33 d [<u>C</u>H(CH$_3$)$_2$], 173.38 s (C^1), 178.60 s (C^9).

8-Cyanooctanoic acid (14). R_f 0.19 (petroleum ether–*tert*-butyl methyl ether, 2 : 1). IR and ^{1}H NMR spectrum are identic to those previously described [22].

Ozonolysis in a mixture of acetic acid and dichloromethane. By method *a* after chromatographing 1.62 g of residue (petroleum ether–*tert*-butyl methyl ether, 2 : 1) we obtained 0.36 g (46%) of nonanoic acid **3**, 0.36 g (45%) of nonanal oxime **6**, 0.61 g (65%) of nonanedioic acid **2**, and 0.25 g (26%) of 9-(hydroxyimino)nonanoic acid **4**.

By method *b* after chromatographing 1.86 g of residue (SiO_2, petroleum ether–*tert*-butyl methyl ether, 2 : 1) we obtained 0.60 g (75%) of nonanoic acid **3** and 0.64 g (74%) of nonanedioic acid **2**, whose IR, ^{1}H and ^{13}C NMR spectra were identic to those previously described [17].

Ozonolysis in THF. By method *a* after chromatographing 1.48 g of residue (SiO_2, petroleum ether–*tert*-butyl methyl ether, 2 : 1) we obtained 0.26 g (33%) of nonanoic acid **3**, 0.26 g (33%) of nonanal oxime **6**, 0.32 g (34%) of nonandioic acid **2**, and 0.31 g (33%) of 9-(hydroxyimino)nonanoic acid **4**.

By method *b* after chromatographing 1.92 g of residue (SiO_2, petroleum ether–*tert*-butyl methyl ether, 2 : 1) we obtained 0.57 g (73%) of nonanoic acid **3** and 0.66 g (70%) of nonanedioic acid **2**.

The study was carried out under the partial financial support of the Program of the President of the Russian Federation for supporting the leading scientific schools (grant NSh-2625.2014.3 “Synthetic transformations of substances obtained from domestic raw material as the basic principle of developing pharmaceuticals of high social importance”).

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