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TRANSFORMATIONS OF PEROXIDE OZONOLYSIS PRODUCTS OF NATURAL OLEFINS BY *N*-CONTAINING ORGANIC COMPOUNDS IN METHANOL

G. Yu. Ishmuratov,* Yu. V. Legostaeva, L. P. Botsman, M. P. Yakovleva, O. O. Shakhanova, R. R. Muslukhov, and G. A. Tolstikov

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Transformations of peroxide ozonolysis products of cyclic and acyclic natural olefins with different degrees of saturation by hydroxylamine and semicarbazide hydrochlorides were investigated.

Key words: ozonolysis–reduction, (+)-α-pinene, Δ^3-carene, castor oil, hydroxylamine hydrochloride, semicarbazide hydrochloride.

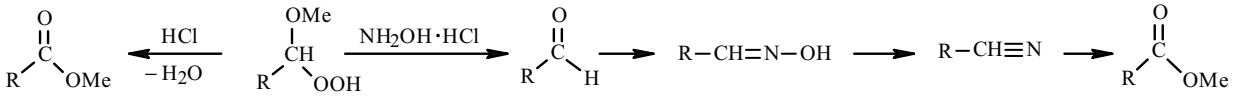
Ozonolytic cleavage of olefins is a convenient method of functionalizing compounds containing multiple bonds. Therefore, transformations of peroxide products of olefin ozonolysis are broadly used in preparative organic synthesis. They can be divided into two types, i.e., those occurring with retention of an oxidation level that is intermediate between a carbonyl and carboxylic acid (cleavage reaction) and with its transformation (reduction and oxidation reactions). In the middle of the twentieth century all these types of transformations of peroxide ozonolysis products were actively studied using a variety of reagents and thermal and photochemical degradation. However, in our opinion, *N*-containing organic compounds have seen limited use for these purposes and are represented in ozonolysis–reduction reactions by thiourea [1], tetracyanoethylene [2, 3], pyridine [4], tertiary amines [5], and amino-*N*-oxides [6]; in ozonolysis–cleavage reactions by triethylamine in combination with water [3] or acetic anhydride [7-9].

The goal of our work was to study the reduction of peroxide ozonolysis products of cyclic and acyclic natural olefins with different levels of substitution by organic *N*-containing compounds of various nature in methanol and the isolation and identification of reduction products and subsequent transformations to *N*- and carboxyl-containing compounds that are promising for rational organic synthesis of α,ω-bifunctional synthons and compounds with potential pharmacological and biological activity.

We studied di-[triglyceride of ricinic acid (**1**)]- and tri-[Δ^3-carene (**2**) and (+)-α-pinene (**3**)]-substituted olefins using hydroxylamine and semicarbazide hydrochlorides as reagents.

The use of hydroxylamine hydrochloride for transformation of peroxide products of olefin ozonolysis is limited to several examples. They were all carried out in methanol and resulted in the formation of aldehydes [10], an aldoxime [11, 12], and an ester [13], depending on the nature of the substrates.

Based on these examples, we proposed two probable schemes for forming an ester by treatment of peroxide ozonolysis products with hydroxylamine hydrochloride. The first pathway was aldehyde → aldoxime → nitrile → ester. An alternate pathway assuming dehydration of the methoxyhydroperoxide using an acid catalyst was also possible:



Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, Russian Federation, 450054, Ufa, prosp. Oktyabrya, 71, fax: (3472) 35 60 66, e-mail: insect@anrb.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 272-275, May-June, 2009. Original article submitted January 16, 2009.

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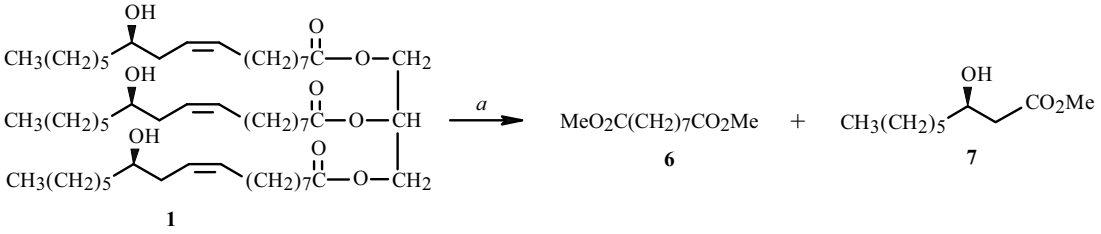
The first pathway assumes formation of nitrile derivatives, which were first identified by us during ozonolysis of cyclooctene, castor oil, and its acetate [14]. Furthermore, treatment of peroxide ozonolysis products of (*R*)-*p*-menth-3-ene confirmed the low reactivity of the ketone compared with an aldehyde toward hydroxylamine hydrochloride [15]. However, the corresponding ketoxime esters **4** and **5**, the structures of which were elucidated by ^{13}C NMR and PMR spectroscopy, were obtained on going to cycloolefins of more complicated structure, Δ^3-carene (**2**) and (+)-α-pinene (**3**). The ^{13}C NMR spectra contained singlets (157-158 ppm) and a strong-field quartet (12.9 ppm), indicating formation of oximes with the *trans*-configuration of the double bonds [16].

2 **4, 8** **3** **5, 9**

A: 1. O_3/MeOH, –5°C, 2. NH_2OH·HCl; B: 1. O_3/MeOH, –5°C, 2. $NH_2C(O)NHNH_2$·HCl
4, 5 (A): R = N-OH; **8, 9** (B): R = O

We used semicarbazide hydrochloride as another *N*-containing compound for transformation of peroxide ozonolysis products. Ozonolysis of castor oil [content of (*R*)-ricinic acid 85%] with subsequent treatment of the peroxides by this reagent produced a mixture (45:55) of diester **6** and hydroxyester **7** in high yields. Use of semicarbazide hydrochloride increased the chemical selectivity of the process compared with the use of hydroxylamine hydrochloride [14]. Hydroxyester **7** can be readily converted to the corresponding acid, which is a microcomponent of human blood plasma [17]:



1 **6** **7**

a. 1. O_3/MeOH, 0°C; 2. $NH_2C(O)NHNH_2$·HCl

Treatment of peroxide ozonolysis products of trisubstituted monoterpenoids **2** and **3** by the same reagent produced the corresponding ketoesters **8** and **9** in high yields.

Analysis of the NMR spectra of **4**, **5**, **8**, and **9** showed that use of hydroxylamine and semicarbazide hydrochlorides produced single stereoisomers with retention of the cyclobutane and cyclopropane rings. This was consistent with the characteristic SSCC values ^1J (^{13}C–^1H): (161-162 Hz) for C-3 and C-4 in **4** and **8** and (133-135 Hz) for C-1 and C-3 in **5** and **9**. The large difference in the chemical shifts of C atoms in the *trans*- and *cis*-*gem*-dimethyls (29.31 and 16.75 ppm for **5** and **9**; 28.31 and 14.80 ppm for **4** and **8**) indicated the *cis*-orientation of both substituents in all synthesized compounds without a change of configuration of the two optically active centers.

Thus, semicarbazide and hydroxylamine hydrochlorides are effective reagents for transforming peroxide products of olefin ozonolysis in methanol into carbonyl compounds, their *N*-containing derivatives, and methyl esters. A proposed effective synthetic scheme of a microcomponent of human blood plasma [3-(*R*)-hydroxynonanoic acid] was based on treatment of peroxide ozonolysis products of castor oil by semicarbazide hydrochloride.

EXPERIMENTAL

IR spectra in thin layers were recorded on a UR-20 instrument. NMR spectra in $CDCl_3$ were recorded on a Bruker AM-300 spectrometer (operating frequency 300.13 MHz for PMR and 75.47 MHz for ^{13}C NMR) with TMS internal standard.

GC was carried out on Chrom-5 [column length 1.2 m, stationary phase Silicone SE-30 (5%) on Chromaton N-AW-DMCS (0.16-0.20 mm), operating temperature 50-300°C] and Chrom-41 (column length 2.4 m, stationary phase PEG-6000, operating temperature 50-200°C) instruments with He carrier gas. Column chromatography was performed over silica gel (Lancaster, England, 60-200 μm); TLC, on Sorbfil plates (Krasnodar). Optical rotation was measured on a Perkin–Elmer 241-MS polarimeter. Elemental analyses of all compounds agreed with those calculated. We used *t*-butylmethylether (MTBE) and petroleum ether (bp 40-70°C, PE) for isolation and chromatographic purification.

Methyl{(1*R*,3*S*)-3-[(2*E*)-2-(hydroxyimino)propyl]-2,2-dimethylcyclopropyl}-acetate (4). An O_2–O_3 mixture was bubbled through a solution of Δ^3-carene (**2**, 2.00 g, 14.7 mmol) in anhydrous MeOH (50 mL) at –5°C until 14.7 mmol of O_3 was absorbed. The mixture was purged with Ar, treated at –5°C with $NH_2OH{\cdot}HCl$ (3.58 g, 51.5 mmol), stirred at room temperature for 60 h, and evaporated. The solid was dissolved in CH_2Cl_2 (100 mL), washed with H_2O (4 × 25 mL), dried over $MgSO_4$, and evaporated. The solid was chromatographed (SiO_2, PE:MTBE, 5:1, R_f 0.29) to afford ketoxime **4** (2.40 g, 78%), $[\alpha]_D^{23}$ –0.3° (*c* 0.49, CH_2Cl_2). IR spectrum (ν, cm^{-1}): 1610 (C=N), 1735 (CO_2Me), 3275 (OH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.78 (1H, ddd, ^3J = 9.1, 7.2, 1.8, H-1), 0.93 (1H, ddd, ^3J = 9.1, 7.7, 2.2, H-3), 1.09, 0.94 (3H, each s, $2CH_3$), 1.89 (3H, s, CH_3), 2.21 (1H, dd, ^2J = -13.3, ^3J = 7.3, H′-4), 2.30 (1H, dd, ^2J = -15.7, ^3J = 6.0, $CH_2CO_2CH_3$, H″), 2.32 (1H, dd, ^2J = -13.3, ^3J = 5.2, H″-4), 2.48 (1H, dd, ^2J = -15.7, ^3J = 7.1, $CH_2CO_2CH_3$, H′), 3.70 (3H, s, OCH_3), 8.0 (1H, br.s, NOH).

^{13}C NMR spectrum [$CDCl_3$, δ, ppm, $^1J(^{13}C–^1H)$, Hz]: 12.88 [q, $CH_2C(NOH)CH_3$], 17.04 (s, C-2), 14.49, 28.21 (each q, $2CH_3$), 21.54 (d, J = 161.2, C-3), 22.51 (d, J = 161.4, C-1), 29.34 (t, J = 127.7, $CH_2CO_2CH_3$), 30.55 [t, J = 126.3, $CH_2C(NOH)CH_3$], 51.50 (q, OCH_3), 157.82 [s, $CH_2C(NOH)CH_3$], 173.85 (s, $CH_2CO_2CH_3$).

Methyl{(1*S*,3*S*)-3-[(1*E*)-*N*-hydroxyethanimidoyl]-2,2-dimethylcyclobutyl}-acetate (5). An O_2–O_3 mixture was bubbled through a solution of (+)-α-pinene (**3**, 2.00 g, 14.7 mmol, $[\alpha]_D^{20}$ +34.1°) in anhydrous MeOH (50 mL) at –5°C until 14.7 mmol of O_3 was absorbed. The mixture was worked up as above for **4**. Chromatography (SiO_2, PE:MTBE, 5:1, R_f 0.33) afforded oximeester **5** (2.62 g, 85%), $[\alpha]_D^{23}$ +1.1° (*c* 2.42, CH_2Cl_2). IR spectrum (ν, cm^{-1}): 1610 (C=N), 1734 (CO_2Me), 3309 (OH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.21, 0.85 (3H, each s, $2CH_3$), 1.79 (3H, s, CH_3), 1.84 (1H, dd, ^2J = -10.2, ^3J = 10.5, H′-4), 2.03 (1H, dd, ^2J = -10.2, ^3J = 7.3, H″-4), 2.20-2.37 (3H, m, H-1, CH_2), 2.60 (1H, dd, ^3J = 10.5, 7.3, H-3), 3.64 (3H, s, OCH_3), 8.3 (1H, br.s, NOH).

^{13}C NMR spectrum [$CDCl_3$, δ, ppm, $^1J(^{13}C–^1H)$, Hz]: 14.26 [q, $CH_2C(NOH)CH_3$], 16.75, 29.89 (each q, $2CH_2$), 24.55 (t, J = 135.5, C-4), 34.62 (t, $CH_2CO_2CH_3$), 38.06 (d, J = 134.1, C-1), 42.49 (s, C-2), 47.91 (d, J = 133.0, C-3), 51.25 (q, OCH_3), 157.12 [s, $CH_2C(NOH)CH_3$], 173.19 (s, $CH_2CO_2CH_3$).

Ozonolysis of Castor Oil (1). An O_2–O_3 mixture was bubbled through a solution of castor oil (4.00 g, 4.3 mmol) in anhydrous MeOH (25 mL) at 0°C until 13.0 mmol of O_3 was absorbed. The mixture was purged with Ar at 0°C with stirring, treated with $NH_2C(O)NHNH_2{\cdot}HCl$ (5.02 g, 45.1 mmol), stirred at room temperature for 21 h, and evaporated. The solid was dissolved in CH_2Cl_2 (100 mL), washed with H_2O (4 × 25 mL), dried over $MgSO_4$, and evaporated to afford a mixture (45:55, 4.97 g) containing according to GC the methyl ester (**7**) and the dimethyl derivative (**6**) of 3*R*-hydroxynonanoic acid, the GC and ^{13}C NMR spectra of which were identical to those reported [14].

Methyl[(1*R*,3*S*)-2,2-dimethyl-3-(2-oxopropyl)cyclopropyl]-acetate (8). An O_2–O_3 mixture was bubbled through a solution of Δ^3-carene (**2**, 2.00 g, 14.7 mmol) in anhydrous MeOH (50 mL) at -5°C until 14.7 mmol of O_3 was absorbed. The mixture was purged with Ar, stirred at -5°C, treated with $NH_2(O)CNHNH_2{\cdot}HCl$ (5.70 g, 51.5 mol), stirred at room temperature for 60 h, and evaporated. The solid was dissolved in CH_2Cl_2 (100 mL), washed with H_2O (4 × 25 mL), dried over $MgSO_4$, and evaporated. The solid was chromatographed (SiO_2, PE:MTBE, 5:1, R_f 0.36) to afford ketoester **8** (2.47 g, 85%), $[\alpha]_D^{20}$ –19.9° (*c* 16.5, $CHCl_3$) [18].

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.97 (1H, ddd, ^3J = 10.2, 6.3, 1.2, H-1), 1.12, 0.91 (3H, each s, $2CH_3$), 1.05 (1H, ddd, ^3J = 10.2, 5.1, 1.2, H-2), 2.16 (3H, s, CH_3), 2.24 (1H, dd, ^2J = -11.5, ^3J = 7.2, $CH_2CO_2CH_3$, H″), 2.33 [1H, dd, ^2J = -15.9, ^3J = 6.8, $CH_2C(O)CH_2$, H″], 2.37 (1H, dd, ^2J = -11.5, ^3J = 6.8, $CH_2CO_2CH_3$, H′), 2.41 [1H, dd, ^2J = -15.9, ^3J = 5.1, $CH_2C(O)CH_3$, H′], 3.18 (3H, s, OCH_3).

^{13}C NMR spectrum [$CDCl_3$, δ, ppm, $^1J(^{13}C–^1H)$, Hz]: 14.82, 28.31 (each q, $2CH_3$), 17.07 (s, C-2), 21.02 (d, J = 161.1, C-1), 21.66 (d, J = 161.9, C-3), 29.45 [q, $CH_2C(O)CH_3$], 29.85 (t, J = 125.1, $CH_2CO_2CH_3$), 39.16 [t, J = 124.7, $CH_2C(O)CH_3$], 51.65 (q, OCH_3), 173.71 (s, $CH_2CO_2CH_3$), 208.45 (s, C=O).

Methyl[(1*S*,3*S*)-3-acetyl-2,2-dimethylcyclobutyl]-acetate (9). An O_2–O_3 mixture was bubbled through a solution of (+)-α-pinene (**3**, 2.00 g, 14.7 mmol, $[\alpha]_D^{20}$ +34.1°) in anhydrous MeOH (50 mL) at –5°C until 14.7 mmol of O_3 was absorbed and then worked up as described above for **8**. Chromatography (SiO_2, PE:MTBE, 5:1, R_f 0.44) afforded ketoester **9** (2.42 g, 83%), $[\alpha]_D^{23}$ +21.6° (*c* 2.07, CH_2Cl_2). IR spectrum (ν, cm^{-1}): 1705 (C=O), 1735 (CO_2Me).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.31, 0.83 (3H, each s, $2CH_3$), 1.88 (1H, dt, ^2J = -10.9, ^3J = 10.3, H′-4), 2.02 [3H, s, $C(O)CH_3$], 2.04 (dd, ^2J = -14.2, ^3J = 7.4, $CH_2CO_2CH_3$, H″), 2.29 (1H, dt, ^2J = -10.9, ^3J = 7.4, H″-4), 2.20-2.45 (2H, m, H-1, $CH_2CO_2CH_3$, H′), 2.60 (1H, dd, J = 10.3, 7.4, H-3), 3.63 (s, 3H, OCH_3).

^{13}C NMR spectrum [$CDCl_3$, δ, ppm, $^1J(^{13}C–^1H)$, Hz]: 16.75, 24.31 (each q, $2CH_3$), 22.55 (t, J = 135.2, C-4), 29.67 [q, $C(O)CH_3$], 34.62 (t, $CH_2CO_2CH_3$), 37.51 (d, J = 134.1, C-1), 42.72 (s, C-2), 50.93 (q, OCH_3), 53.65 (d, J = 134.9, C-3), 172.61 (s, $CH_2CO_2CH_3$), 206.87 (s, C=O).

REFERENCES

1. D. Gupta, R. Soman, and S. Dev, *Tetrahedron*, **38**, 3013 (1982).
2. H. Kwart and D. M. Hoffman, *J. Org. Chem.*, **31**, 419 (1966).
3. R. Criegee and P. Gunther, *Chem. Ber.*, **96**, 1564 (1963).
4. V. N. Odinokov and G. A. Tolstikov, *Usp. Khim.*, **10**, 1207 (1981).
5. I. E. Pokrovskaya, A. K. Ryzhankova, A. T. Menyailo, and L. S. Mishina, *Neftekhimiya*, **1**, 873 (1971).
6. C. Schwartz, J. Raible, K. Mott, and P. H. Dussault, *Org. Lett.*, **8**, 3199 (2006).
7. S. L. Schreiber, R. E. Claus, and J. Reagan, *Tetrahedron Lett.*, **23**, 3867 (1982).
8. V. N. Odinokov, V. R. Akhmetova, Kh. D. Khasanov, A. A. Abduvakhabov, G. A. Tolstikov, and A. A. Panasenko, *Khim. Prir. Soedin.*, 276 (1989).
9. K. Prasad and O. Repic, *Tetrahedron Lett.*, **25**, 4889 (1984).
10. A. G. Mustafin, D. I. D′yachenko, R. R. Gataullin, G. Yu. Ishmuratov, R. Ya. Kharisov, I. B. Abdrakhmanov, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 937 (2003).
11. V. N. Odinokov, G. A. Tolstikov, G. Yu. Ishmuratov, R. Ya. Kharisov, R. M. Sadrislamov, R. G. Davletov, O. M. Nefedov, N. V. Volchkov, V. F. Zabolotskikh, L. Yu. Gubaidullin, and E. I. Dogunov, Pat. No. 1,622,366 (1990); *Byull. Izobret.*, No. 3 (1991).
12. V. N. Odinokov, G. Yu. Ishmuratov, O. S. Kukovinets, R. Ya. Kharisov, E. A. Lozhkina, A. G. Mustafin, I. B. Abdrakhmanov, and G. A. Tolstikov, *Zh. Org. Khim.*, **34**, 229 (1998).
13. R. R. Gataullin, Author's Abstract of a Doctoral Dissertation in Chemical Sciences, Inst. Org. Chem., Ufa Sci. Cent., RAS, Ufa, 2004.
14. G. Yu. Ishmuratov, A. Kh. Shayakhmetova, M. P. Yakovleva, O. V. Shitikova, E. G. Galkin, and G. A. Tolstikov, *Zh. Org. Khim.*, **43**, 1125 (2007).
15. G. Yu. Ishmuratov, M. P. Yakovleva, A. Kh. Shayakhmetova, L. P. Botsman, G. V. Nasibullina, R. R. Muslukhov, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 515 (2006).
16. E. Breitmaier and W. Voelter, *^{13}C NMR Spectroscopy*, Verlag Chemie GmbH, Weinheim, 1974.
17. P. S. S. Clerk, *Spectra Data for Structure Determination of Organic Compounds*, Springer-Verlag, New York, 1983.
18. R. Sobti and Sukh Dev, *Tetrahedron*, **30**, 2927 (1974).