A New Property of Geminal Bishydroperoxides: Hydrolysis with the Removal of Hydroperoxide Groups to Form a Ketone

A. O. Terent'ev, O. B. Krivykh, I. B. Krylov, Yu. N. Ogibin, and G. I. Nikishin

Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Leninskii pr. 47, Moscow, 119991 Russia e-mail: terentev@ioc.ac.ru

Received October 5, 2009

Abstract—A new property of geminal bishydroperoxide was discovered: the ability to hydrolyze in acid medium in the presence of hydrogen peroxide with the formation of ketones. The most resistant to hydrolysis are the cyclic C₆-bishydroperoxydes: at room temperature within one day they are practically not hydrolyzed; less stable is bishydroperoxycycloheptane (C₇): in a day its one fifth part is hydrolyzed. Bishydroperoxydes with the cycles of C₈ and C₁₂ for the same time hydrolyzed to 80 and 90% respectively. Of the two linear bishydroperoxydes, 2,2-dihydroperoxydecane, with sterically unhindered center, is more resistant to hydrolysis than 6,6-dihydroperoxyundecane.

DOI: 10.1134/S1070363210080165

In recent decades, a new wave of interest emerged in the chemistry of organic peroxides, caused by the discovery that these compounds have a high malaricidal activity [1]. In the world this disease affects about 500 million people [2]. The search for peroxides with high antitumor [3] and antihelminthic [4] activity is also promising. In industry, organic peroxides are traditionally used as oxidants and initiators of radical polymerization [5].

Currently among the various classes of organic bishydroperoxydes peroxides geminal **(I)** are highlighted. Synthesis and application of such compounds attracts the most attention. A half-century ago, when the related peroxides obtained from ketones have been known and used, the geminal bishydroperoxydes considered as unstable and hypothetical compounds. More recently methods were developed for the synthesis of such peroxides in preparative amounts [6a-6k], based on the reaction of ketones and aldehydes with H_2O_2 catalyzed with I_2 [6a], H_2SO_4 [6b, 6c], Re₂O₇ [6d], MeReO₃ [6e], camphorsulfonic acid (CSA) [6f], F₃CCO₂H [6g], as well as on the reaction of acetals and enol ethers with H₂O₂ catalyzed by BF₃ [6h], H_2WO_4 [6i] and phosphomolybdic acid, $H_{3}Mo_{12}O_{40}P \cdot x H_{2}O[6j]$

A specific interest to this class of peroxides is due to the presence in their molecule of two OOH groups, which makes it possible to use these compounds as intermediates in the synthesis of peroxides of more complex structure with malaricidal and antitumor activity [7], as well as initiators of radical polymerization [8]. The high content of active oxygen allows regarding them as promising oxidants [9].

Despite increased attention to the geminal bishydroperoxydes, their thermal and hydrolytic stability remain poorly studied. These characteristics are necessary for a broader synthetic and practical use of peroxides.

We discovered a previously unknown feature of the geminal bishydroperoxydes: their ability to hydrolysis with the loss of hydroperoxide groups, leading to the formation of ketones. Analyzing the results of the work on the synthesis of geminal bishydroperoxydes by means of the reaction of ketones with aqueous solution of hydrogen peroxide in THF [6b] and alcohols [6c] catalyzed by sulfuric acid as well as the research data of the iodine-catalyzed reaction of ketones with aqueous solution of hydrogen peroxide in acetonitrile [6a], we noted that the use of hydrogen peroxide in the amount of 4-10 mol per 1 mol of ketone, that is, much higher than the stoichiometric $(2 \text{ mol } H_2O_2)$, some ketones did not transform completely into the target bishydroperoxydes. Perhaps this is due to the existence of equilibrium with gem-

Geminal bishydroperoxyde (Ia–Ig)	Time of hydrolysis, h	Value geminal bishydro– peroxide I: ketone II	Geminal bishydroperoxyde (Ia–Ig)	Time of hydrolysis, h	Value geminal bishydro– peroxide I: ketone II
ООН ООН Іа	24	> 95:5	НОО ООН	20	10:90
НОО ООН	24	92:8	Ie HOO OOH If	3.5 25 23 ^b 73	72:28 64:36 58:42 61:39
HOO OOH	20 0.5	81:19 88:12	HOO OOH	4 25	60:40 27:73
HOO OOH	22	20:80			

The results of hydrolysis of gem-bishydroperoxyde (Ia-Ig)^a

^a General conditions: To a mixture of bishydroperoxyde I (0.43–0.62 mmol, 100 mg), THF (6.6 ml/mmol of bishydroperoxyde), and 37% aqueous solution of H_2O_2 (5 mol/mol of bishydroperoxyde) was added 3.5 M (28.7%) aqueous solution of H_2SO_4 (0.5 mol/mol of bishydroperoxyde). Stirred for 0.5–73 h at 20–25°C. ^b To the decan-2-one (IIe), 76 mg (0.49 mmol), dissolved in 4 ml of THF was added 312 mg of 37% aqueous solution of H_2O_2 (3.43 mmol, 7 mol/mol of decan-2-one) and 83 mg 29% aqueous H_2SO_4 (0.25 mmol, 0.5 mol/mol of decan-2-one).

bishydroperoxyde I and ketone II as the boundary structures (Scheme 1).



In order to confirm this scheme, we synthesized a series of geminal bishydroperoxydes with the ring size C_6 - C_8 and C_{12} , as well as bishydroperoxydes from two linear ketones, decan-2-one and undecan-6-one. These bishydroperoxydes were hydrolyzed in the presence of hydrogen peroxide in the THF–water solvent system

acidified with sulfuric acid (see the table). Hydrogen peroxide was used to simulate the conditions of synthesis of geminal bishydroperoxyde I from ketones II. Under these conditions (as already mentioned [6b, 6c]) was not always possible to achieve high yields of target bishydroperoxyde I, despite the excess of hydrogen peroxide.

Based on the results of the experiments we can conclude that the most resistant to hydrolysis are bishydroperoxydes **Ia**, **Ib** with a six-membered ring, which in a day at 20–25°C practically are not hydrolyzed. The bishydroperoxycycloheptane **Ic** is less stable. Bishydroperoxydes with the rings C_8 (**Ig**) and C_{12} (**Id**) hydrolyzed to a much greater extent. Among the geminal bishydroperoxydes obtained from linear ketones the more stable is peroxide **Ic** with sterically less hindered reaction center. The geminal bishydroperoxyde **Ig** hydrolyzed much more readily than peroxide **Ic**. By an example of the peroxides **Ic** and **Ig** it is seen that their hydrolysis is not a fast process, for in 3.5–4 h the hydrolysis was not completed, the equilibrium was established over 23–25 h only. The synthesis of peroxide **Ic** was carried out using the ketone **IIf** under the same conditions (see the table, footnote b) as its hydrolysis. As a result, in 1 day the equilibrium was reached with the content 58% of **Ic** and 42% of **IIf** in the reaction mixture.

The molar ratio of hydrolysis products was determined by comparing the intensity of the characteristic signals in the ¹H NMR spectra, which for

the geminal bishydroperoxyde lie in the region 8–10 ppm (OOH), and for ketones at 2.1–2.4 ppm (CH₂CO). Experiments on the hydrolysis of peroxides **Ia**, **Ib** were performed with isolation of the products **I** and **II**. The yields corresponded to the estimates obtained by NMR spectroscopy without isolation of the products.

Probably the hydrolysis of geminal bishydroperoxyde **Ia–Ig** proceeds along the following mechanism. After the protonation (formation of the intermediate **A**) and removal of hydrogen peroxide hydroperoxycarbenium ion **B** is produced, which is hydroxylated to form hydroxyhydroperoxyde **C** and, after removal of the second hydrogen peroxide molecule, it is transformed into ketone **II** (Scheme 2).



The kinetics of the acid-catalyzed hydrolysis of bistert-butylperoxide (derivatives of linear ketones) with similar structure, whose several homolog are produced industrially and used to initiate polymerization, was previously studied by spectrophotometry [10]. According to the kinetic measurements, the first rapid phase of hydrolysis is the protonation followed by the cleavage of *tert*-butylhydroperoxide and the formation of peroxycarbenium cation, then follows the addition of water and the cleavage of the second molecule of *tert*-butylhydroperoxide.

In contrast to the bis-*tert*-butylperoxide, hydrolysis of bishydroperoxyde **I** is more complex. It is accompanied by the cross-reactions of peroxides **I** and **C** with ketone **II** and cationic intermediate **B** with the formation of products with bisperoxide fragment, (1,1)-dihydroperoxyperoxides, 1,2,4,5- and 1,2,4,5-tetraoxanes, and 1,2,4,5,7,8-hexaoxanes), which were identified in trace amounts by the signals at 105–122 ppm in ¹³C NMR spectrum, characteristic of the

OO–C–OO fragment [1i, 6a, 11]. In this investigation these cross-reactions were suppressed by the use of bishydroperoxyde I in low concentration and by adding hydrogen peroxide to the reaction mixture.

Thus we found a new property of linear and cyclic geminal bishydroperoxydes: the hydrolysis in acid medium in the presence of H_2O_2 resulting in the formation of the corresponding ketones. The tendency to hydrolysis of cyclic peroxides increases from 6-membered to 8- and 12-membered ring; linear peroxides C_{10} and C_{12} by the ability to hydrolysis are in an intermediate position between these two groups of cyclic bishydroperoxydes.

The data obtained are important in predicting the results of synthesis of peroxides from ketones in aqueous solutions of hydrogen peroxide, and they explain the unsuccessful attempts to obtain cyclic peroxides from cyclic C_8 – C_{15} and linear ketones with sterically hindered reaction center in a high yield.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker AC-200 and a Bruker AM-300 instruments (solvent CDCl₃). For the TLC were used Silufol UV-254 plates, for column chromatography, silica gel 63–200 mesh (Acros). Ketones **IIa–IIf** are the products of Acros. Tetrahydrofuran, Et_2O , CHCl₃ (pure grade) and petroleum ether (40–70) (pure grade) were distilled before use. Geminal bishydroperoxydes **Ia–Id**, **If** are known compounds, and peroxide **Ic** was obtained in this study by the method [6h].

1,1-Dihydroperoxy-4-*tert*-butylcyclohexane **(Ia)** [6b]. Colorless crystals, mp 81–82.5°C (Et₂O). The ¹H NMR spectrum (250.13 MHz, δ , ppm): 0.85 s (9H, CH₃), 0.98–1.78 m (7H, CH, CH₂), 2.24–2.35 m (2H, CH₂), 9.25–9.40 br.s (2H, OOH).

1,1-Dihydroperoxy-3,3,5-trimethylcyclohexane (Ib). Colorless crystals, mp 56–57.5°C (Et₂O). ¹H NMR spectrum (300 MHz, CDCl₃), δ , ppm: 0.83–1.08 m (11H, CH₂, CH₃), 1.22–1.47 m (2H, CH₂), 1.73–2.26 m (5H , CH, CH₂), 9.45–9.55 br.s (2H, OOH). 13C NMR spectrum (75 MHz, CDCl₃), δ , ppm: 22.0, 25.4, 26.3, 31.5, 33.6, 37.6, 40.6, 48.2 (CH, CH₂, CH₃), 112.1 (C). Found, %: C, 57.03; H, 9.33. C₁₈O₉H₄. Calculated, %: C, 56.82; H, 9.54.

1,1-Dihydroperoxycycloheptane (Ic) [6b]. Colorless crystals, mp 19–21°C (Et₂O). ¹H NMR spectrum (300 MHz, CDCl₃), δ , ppm: 1.28–1.65 m (8H, CH₂), 1.70–2.03 m (4H, C–CH₂), 9.60–9.80 br.s (2H, OOH).

1,1-Dihydroperoxycyclooctane (Ig) [6b]. Oil. ¹H NMR spectrum (300 MHz, CDCl₃), δ, ppm: 1.21–1.99 m (14H, CH₂), 9.59–9.70 br.s (2H, OOH).

1,1-Dihydroperoxycyclododecane (Id) [6b]. Colorless crystals, mp 138–140°C (Et₂O). ¹H NMR spectrum (300 MHz, CDCl₃), δ , ppm: 1.21–1.82 m (22H, CH₂), 9.98–10.04 br.s (2H, OOH).

2,2-Dihydroperoxydecane (Ic). ¹H NMR spectrum (300 MHz, CDCl₃), δ , ppm: 0.88 t (3H, CH₃, *J* 6.6 Hz), 1.17–1.50 m (15H, CH₂, CH₃), 1.67–1.79 m (2H, CH₂), 8.6–10.0 br.s (2H, OOH). ¹³C NMR spectrum (75 MHz, CDCl₃), δ , ppm: 14.1, 17.9 (CH₃), 22.7, 24.0, 29.3, 29.5, 29.8, 31.91, 31.93, 33.1 (CH₂), 112.7 (C). Found, %: C, 57.96; H, 11.23. C₁₀H₂₂O₄. Calculated, %: C, 58.23; H, 10.75.

6,6-Dihydroperoxyundecane (Ig) [6a]. ¹H NMR spectrum (300 MHz, CDCl₃), δ , ppm: 0.90 t (6H, CH₃,

J 7.0 Hz), 1.23–1.47 m (12H, CH₂), 1.62–1.78 m (4H, CH₂), 8.00–9.50 br.s (2H, OOH).

Hydrolysis of geminal bishydroperoxydes (Ia–Ig). To a mixture of geminal bishydroperoxyde Ia–Ig (0.43–0.62 mmol, 100 mg), THF (6.6 ml per 1 mmol of bishydroperoxyde) and 37% aqueous solution of H_2O_2 (5 mol per 1 mole of bishydroperoxyde) was added 3.5 M (28.7%) of the aqueous solution of H_2SO_4 (0.5 mol per 1 mol of bishydroperoxyde). After 0.5–73 h, 30 ml of CHCl₃ was added, the extract was washed with 5 ml of a saturated solution of NaHCO₃ and water (10 ml), dried over MgSO₄, the solvent was removed in a vacuum of water-jet pump (8–15 mm Hg). The ratio of geminal bishydroperoxyde Ia–Ig : ketone IIa–IIf was measured by ¹H NMR spectroscopy.

In experiments with bishydroperoxydes Ia, Ib the separation of hydrolysis product I and II was carried out using column chromatography with the gradient elution with a mixture petroleum ether– Et_2O at increasing the fraction of the latter from 5 to 20 vol %.

The reaction of the decan-2-one (IIe) with H_2O_2 (see Table, footnote b). To decan-2-one IIe, 76 mg, dissolved in 4 ml of THF was added 312 mg of 37% aqueous solution of H_2O_2 (3.43 mmol, 7 mol per 1 mol of decan-2-one) and 83 mg of 29% aqueous H_2SO_4 (0.25 mmol, 0.5 mol per 1 mol of decan-2-one). The reaction mixture was kept for 23 h, 30 ml of CHCl₃ was added and the extract was washed with 5 ml of a saturated solution of NaHCO₃ and water (10 ml), and dried over MgSO₄. The solvent was removed in a vacuum of a water-jet pump (8–15 mm Hg). The ratio of geminal bishydroperoxyde Ic : ketone IIe was determined by ¹H NMR spectroscopy.

ACKNOWLEDGMENTS

This work was supported financially by the Program of support of leading scientific schools of Russian Federation (VNSH 2942.2008.3).

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