Russian Journal of Applied Chemistry, Vol. 75, No. 10, 2002, pp. 1660–1664. Translated from Zhurnal Prikladnoi Khimii, Vol. 75, No. 10, 2002, pp. 1694–1698.

ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis and Antioxidant Properties of Unsymmetrical Sulfides Based on ω-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)alkanethiols

P. I. Pinko, E. I. Terakh, E. A. Gorokh, V. V. Nikulina, A. E. Prosenko, and I. A. Grigor'ev

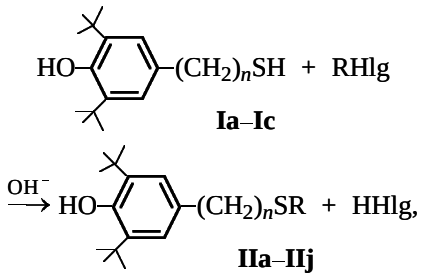
Novosibirsk State Pedagogical Institute, Novosibirsk, Russia

Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Division, Russian Academy of Sciences, Novosibirsk, Russia

Received January 10, 2002

Abstract—Unsymmetrical sulfides were prepared by reactions of ω-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-alkanethiols with various alkyl halides, and their antioxidant activity with respect to thermal autooxidation of lard was studied in relation to their structure.

SO-3 antioxidant {bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl] sulfide} is a well-known high-performance versatile inhibitor of oxidative degradation of organic and bioorganic substrates [1–4]. It is a bifunctional antioxidant; its molecule contains two phenolic moieties exhibiting antiradical activity and one sulfide moiety with antiperoxide activity. It has been shown previously that, with respect to some model systems, the antioxidant activity (AOA) of SO-3 is lower than that of its structural analogs containing the same number of sulfide and phenolic fragments [4–6]. In this connection, we prepared from ω-(3,5-di-*tert*-butyl-4-hydroxyphenyl)alkanethiols **I** and alkyl halides a series of unsymmetrical sulfides **II** and compared their antioxidant power with respect to oxidation of lard as a model reaction:



where n = 2 (**Ia**), 3 (**Ib**), 4 (**Ic**); n = 2, R = Bu (**IIa**); n = 3, R = Me (**IIb**); n = 3, R = Et (**IIc**); n = 3, R = Pr (IId); n = 3, R = Bu (**IIe**); n = 3, R = *s*-Bu (**IIf**); n = 3, R = *t*-Bu (**IIg**); n = 3, R = $C_{18}H_{37}$ (**IIh**); n = 3, R = CH_2Ph (**IIi**); n = 4, R = Bu (**IIj**).

The initial thiols **Ia**–**Ic** were prepared from the corresponding alkyl halides as described in [7]. The reactions of thiols **I** with primary and secondary alkyl halides were performed in ethanol in the presence of NaOH at approximately equimolar ratio of the reactants. The yields of sulfides **IIa**–**IIf** and **IIh**–**IIj** were 72–86%.

There were certain problems with synthesis of the *tert*-butyl sulfide **IIg**. This compound could not be prepared from **Ib** and 2-chloro- or 2-bromo-2-methylpropane under the above-described conditions because of vigorous dehydrohalogenation and evolution of 2-methylpropene. Sulfide **IIg** could be prepared in 43% yield only in the absence of bases at 150°C and elevated pressure (sealed ampules).

The composition and structure of all the compounds **II** were confirmed by elemental analysis and spectroscopy.

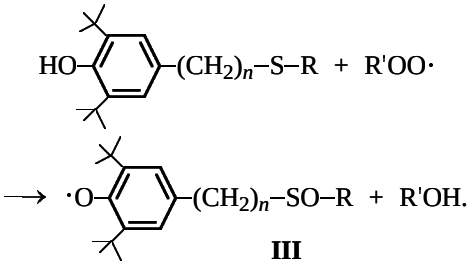
The relationship between the structure and the antioxidant power was studied for sulfides **II** with thermal autooxidation of lard as a model reaction. As references we used SO-3, Ionol (2,6-di-*tert*-butyl-4-methylphenol), and a 1 : 1 mixture of Ionol with didodecyl sulfide. The rate of lard oxidation was monitored by accumulation of primary oxidation products (hydroperoxides), and the AOA was judged from the induction period τ (time in which the lard was oxidized to a peroxide number of 0.1). The results are obtained listed in the table.

All the sulfides **II** synthesized exhibited pronounced AOA, surpassing that of both Ionol and its mixture with didodecyl sulfide. The striking lack of synergistic effect in this mixture is most probably due to specific features of lard as oxidation substrate.

1070-4272/02/7510-1660 $27.00 © 2002 MAIK "Nauka/Interperiodica"

It is known [9] that lard contains a large amount of unsaturated fatty acid residues [in particular, oleic (41–54%), linoleic (5–16%), and linolenic and arachidonic (up to 2%)] whose hydroperoxide derivatives are thermally unstable. Because of the relatively high oxidation temperature in our model system, the rate of decomposition of hydroperoxides appears to be considerably higher than the rate of their reaction with didodecyl sulfide; as a result, the antioxidant effect of didodecyl sulfide is not manifested, and AOA of the synergistic mixture of Ionol and dodecyl sulfide is determined essentially by the antiradical activity of Ionol. Since neither SO-3 nor its structural analogs surpass Ionol in the antiradical activity [10], their high AOA can be accounted for only by the internal synergism (bifunctional antioxidant activity).

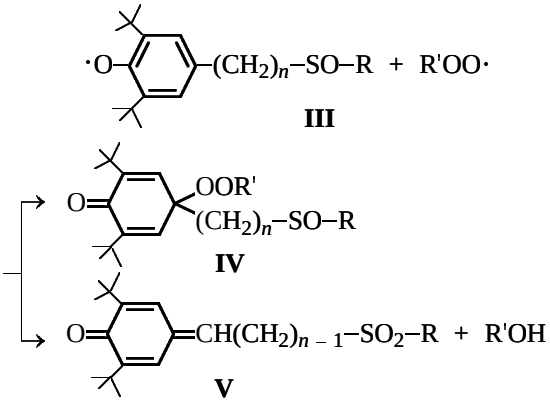
The internal synergism of SO-3, sulfides **II**, and their structural analogs [11, 12] is probably due to the favorable steric arrangement of the phenolic and sulfide moieties, owing to which the hydroperoxide molecule formed by reaction of the generated radical with the phenolic group of the inhibitor is activated by the sulfide moiety, having no time to escape to the bulk of the substrate:



III

Thus, the reaction of the antioxidant with an active radical yields a thermally stable alkanol instead of hydroperoxide acting as a chain-branching agent.

According to the generally accepted mechanism of the effect of phenolic antioxidants, phenoxyl **III** can react with peroxy radical to form quinoid peroxide **IV** or quinone **V**, with the former pathway presumably being preferable [13]:



III

IV

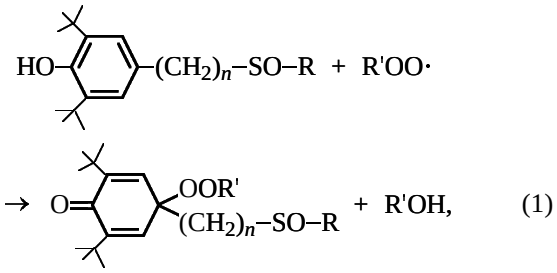
V

Induction period in lard oxidation inhibited with phenolic antioxidants (1 μmol per gram of lard, 130°C)

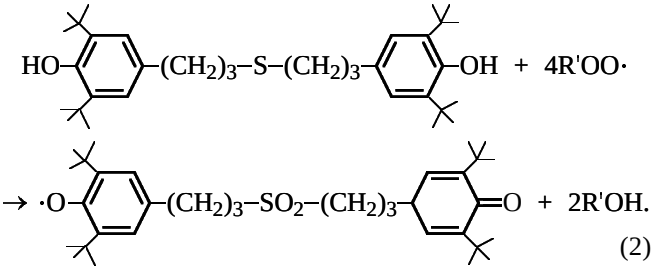
Antioxidant*	τ, min
$R(CH_2)_2SC_4H_9$ (**IIa**)	254
$R(CH_2)_3SCH_3$ (**IIb**)	271
$R(CH_2)_3SC_2H_5$ (**IIc**)	296
$R(CH_2)_3SC_3H_7$ (**IId**)	290
$R(CH_2)_3SC_4H_9$ (**IIe**)	282
$R(CH_2)_3SCH(CH_3)C_2H_5$ (**IIf**)	297
$R(CH_2)_3SC(CH_3)_3$ (**IIg**)	321
$R(CH_2)_3SC_{18}H_{37}$ (**IIh**)	284
$R(CH_2)_3SCH_2C_6H_5$ (**IIi**)	266
$R(CH_2)_4SC_4H_9$ (**IIj**)	350
RCH_3 (Ionol)	169
$C_{12}H_{25}SC_{12}H_{25}$	34
$RCH_3 + C_{12}H_{25}SC_{12}H_{25}$ (synergistic mixture)	169
$R(CH_2)_3S(CH_2)_3R$ (CO-3)	290
Control	34

* R = 3,5-di-*tert*-butyl-4-hydroxyphenyl.

In this connection, the oxidative transformations of sulfides **II** and SO-3 in reactions with peroxy radicals can be represented by schemes (1) and (2), respectively:



(1)



(2)

Under the conditions chosen by us for oxidation of lard, the antioxidant activities of SO-3 and sulfides **II** are similar (the induction periods differ by no more than 20%), which is quite consistent with the assumed mechanism [reactions (1), (2)]. Despite the lower sulfur content in SO-3, its sulfide moiety, similar to

that in unsymmetrical sulfides **II**, is capable of deactivating all the hydroperoxide molecules formed with the participation of the phenolic groups of the antioxidant. Therefore, SO-3 and sulfides **II** exhibit similar degrees of internal synergism. The capability of sulfoxide **IV** to reduce a second hydroperoxide molecule formed in the substrate without participation of the antioxidant does not contribute noticeably to the inhibiting effect, as shown by data on the antioxidant activity of didodecyl sulfide (see table).

Among sulfides **II**, sulfide **IIj** appeared to be the most effective as inhibitor of lard oxidation; AOA grew in the order **IIa**–**IIe**–**IIj**, i.e., with increasing number of methylene units linking phenolic and sulfide moieties [10]. The effect of alkyl substituent R on AOA of sulfides **II** is most probably determined by its electron-donor power. For example, there is a reliably detected trend toward an increase in the antioxidant activity in the order **IIe**–**IIf**–**IIg** and in going from **IIb** to **IIc**, i.e., with an increase in the electron density on the sulfur atom and, hence, in the reactivity of the sulfide moiety toward hydroperoxides.

On the whole, sulfides **IIa**–**IIj** can be considered effective polyfunctional antioxidants.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker spectrometer (500 MHz, $CDCl_3$, external reference TMS), and the IR spectra, on a Vektor 22 Fourier spectrometer [neat samples, CCl_4 solutions, or KBr pellets (150 : 1).

The melting points were determined with a PTP device.

Butyl 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethyl sulfide IIa. 1-Chlorobutane (1.9 ml, 18.3 mmol) was added dropwise at room temperature to a solution of 4.5 g (16.9 mmol) of thiol **Ia** and 0.71 g (17.7 mmol) of NaOH in 25 ml of ethanol. The mixture was refluxed for 2 h, cooled, and treated with toluene. The extract was washed with water and dried over Na_2SO_4; the solvent was distilled off, and the residue was vacuum-distilled. Yield of sulfide **IIa** 4.03 g (74%), bp 159–161°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.01–1.04 t (3H, $CH_2\underline{Me}$), 1.51–1.53 m (2H, $C\underline{H}_2Me$), 1.55 s (18H, *t*-Bu), 1.68–1.69 m (2H, $C\underline{H}_2Et$), 2.63–2.66 t (2H, $SC\underline{H}_2Pr$), 2.87–2.90 m [4H, $Ar(C\underline{H}_2)_2S$], 5.17 s (1H, OH), 7.12 s (2H, Ar–H). IR spectrum (KBr), ν_{max}, cm^{-1}: 3646 (PhOH).

Found, %: C 74.63, H 10.78, S 10.17.
$C_{20}H_{34}OS$.
Calculated, %: C 74.47, H 10.62, S 9.94.

Methyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl sulfide IIb was prepared similarly to **IIa** from 5 g (17.8 mmol) of thiol **Ib** and 1.2 ml (19.2 mmol) of iodomethane; yield 4.11 g (78%), bp 145°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40–1.43 s (18H, *t*-Bu), 1.89–1.90 m (2H, $ArCH_2C\underline{H}_2$), 2.10 s (3H, S–Me), 2.51–2.54 t (2H, $CH_2S\underline{Me}$), 2.61–2.64 t (2H, $ArC\underline{H}_2$), 5.04 s (1H, OH), 6.98 s (2H, Ar–H). IR spectrum (KBr), ν_{max}, cm^{-1}: 3644 (PhOH).

Found, %: C 73.47, H 10.32, S 11.06.
$C_{18}H_{30}OS$.
Calculated, %: C 73.41, H 10.27, S 10.89.

Ethyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl sulfide IIc was prepared similarly to **IIa** from 5 g (17.8 mmol) of **Ib** and 1.5 ml (18.5 mmol) of iodoethane; yield 4.0 g (73%), bp 150–151°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.23–1.26 t (3H, $CH_2\underline{Me}$), 1.43 s (18H, *t*-Bu), 1.85–1.91 m (2H, $ArCH_2C\underline{H}_2$), 2.53–2.57 m (4H, CH_2SCH_2), 2.61–2.63 t (2H, $ArC\underline{H}_2$), 5.03 s (1H, OH), 6.98 s (2H, Ar–H). IR spectrum (thin film), ν_{max}, cm^{-1}: 3645 (PhOH).

Found, %: C 73.84, H 10.51, S 10.55.
$C_{19}H_{32}OS$.
Calculated, %: C 73.97, H 10.45, S 10.39.

Propyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl sulfide IId was prepared similarly to **IIa** from 5 g (17.8 mmol) of thiol **Ib** and 2 ml (22.6 mmol) 1-chloropropane; yield 4.32 g (75%), bp 155–157°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.96–0.99 t (3H, $CH_2\underline{Me}$), 1.39–1.47 s (18H, *t*-Bu), 1.58–1.62 m (2H, $C\underline{H}_2Me$), 1.86–1.89 m (2H, $ArCH_2C\underline{H}_2$), 2.47–2.55 m (4H, CH_2SCH_2), 2.61–2.64 t (2H, $ArC\underline{H}_2$), 5.03 s (1H, OH), 6.98 s (2H, Ar–H). IR spectrum (thin film), ν_{max}, cm^{-1}: 3645 (PhOH).

Found, %: C 74.61, H 10.78, S 9.83.
$C_{20}H_{34}OS$.
Calculated, %: C 74.47, H 10.62, S 9.94.

Butyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl sulfide IIe was prepared similarly to **IIa** from 5 g (17.8 mmol) of thiol **Ib** and 1.9 ml (18 mmol) of 1-chlorobutane; yield 4.68 g (78%), bp 165°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.89–0.92 t (3H, $CH_2\underline{Me}$), 1.38–1.42 m (2H, CH_2Me), 1.43 s (18H, *t*-Bu), 1.53–1.59 m (2H, CH_2Et), 1.86–1.91 m (2H, $ArCH_2C\underline{H}_2$), 2.50–2.52 t (2H, $SC\underline{H}_2Pr$), 2.53–2.55 t (2H, $C\underline{H}_2SBu$), 2.61–2.64 t (2H, $ArCH_2$), 5.03 s (1H, OH); 6.98 s (2H, Ar–H). IR spectrum (thin film), ν_{max}, cm^{-1}: 3646 (PhOH).

Found, %: C 75.08, H 10.85, S 9.69.
$C_{21}H_{36}OS$.
Calculated, %: C 74.94, H 10.78, S 9.53.

***sec*-Butyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl sulfide IIf** was prepared similarly to **IIa** from 5 g (17.8 mmol) of thiol **Ib** and 2 ml (18.3 mmol) of 2-bromobutane; yield 4.33 g (72%), bp 151°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.96–0.99 t (3H, $CH_2\underline{Me}$), 1.24–1.26 d (3H, $SC\underline{H}Me$), 1.43 s (18H, *t*-Bu), 1.51–1.61 m (2H, $C\underline{H}_2Me$), 1.87– 1.89 m (2H, $ArCH_2C\underline{H}_2$), 2.53–2.56 t (2H, $C\underline{H}_2S$), 2.61–2.63 t (2H, $ArC\underline{H}_2$), 2.68–2.69 m (1H, $SC\underline{H}$), 5.03 s (1H, OH), 6.98 s (2H, Ar–H). IR spectrum (thin film), ν_{max}, cm^{-1}: 3647 (PhOH).

Found, %: C 74.98, H 10.89, S 9.72.
$C_{21}H_{36}OS$.
Calculated, %: C 74.94, H 10.78, S 9.53.

***tert*-Butyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl sulfide IIg.** A 120-ml ampule was charged with 5 g (17.8 mmol) of thiol **Ib** and 30 ml (270 mmol) of 2-bromo-2-methylpropane and kept at 150°C for 3 h in a thermostat equipped with a shaker, after which it was cooled. The reaction mixture was treated with benzene. The extract was washed with water and dried over Na_2SO_4; the solvent was distilled off. The product was purified by column chromatography (silica gel, hexane). Yield 2.60 g (43%), bp 157–160°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 s (9H, S–*t*-Bu), 1.43 s (18H, Ar–*t*-Bu), 1.87 m (2H, $ArCH_2C\underline{H}_2$), 2.57 t (2H, $C\underline{H}_2S$), 2.66 t (2H, $ArC\underline{H}_2$), 5.03 s (1H, OH), 6.98 s (2H, Ar–H). IR spectrum (KBr), ν_{max}, cm^{-1}: 3632 (PhOH).

Found, %: C 74.87, H 10.91, S 9.94.
$C_{21}H_{36}OS$.
Calculated, %: C 74.94, H 10.78, S 9.53.

Octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl sulfide IIh was prepared similarly to **IIa** from 5 g (17.8 mmol) of thiol **Ib** and 6.16 g (18.5 mmol) of 1-bromooctadecane (synthesis time 8 h); yield 7.45 g (78%), mp 48–50°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.87–0.89 t (3H, $(CH_2)_{17}\underline{Me}$), 1.26–1.30 s [30H, $(CH_2)_{15}\underline{Me}$], 1.43 s (18H, *t*-Bu), 1.57 m (2H, $C\underline{H}_2C_{16}H_{33}$), 1.88 m (2H, $ArCH_2C\underline{H}_2$), 2.50–2.56 m (4H, CH_2SCH_2), 2.61–2.69 t (2H, $ArC\underline{H}_2$), 5.03 s (1H, OH), 6.98 s (2H, Ar–H). IR spectrum (KBr), ν_{max}, cm^{-1}: 3645 (PhOH).

Found, %: C 78.84, H 12.23, S 6.21.
$C_{35}H_{64}OS$.
Calculated, %: C 78.88, H 12.10, S 6.02.

Benzyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl sulfide IIi was prepared similarly to **IIa** from 5 g (17.8 mmol) of thiol **Ib** and 2.15 ml (18.7 mmol) of benzyl chloride (synthesis time 0.5 h); yield 5.73 g (86%), mp 75–76°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.42 s (18H, *t*-Bu), 1.85 m (2H, $ArCH_2C\underline{H}_2$), 2.42–2.45 t (2H, CH_2S), 2.57–2.60 t (2H, $ArC\underline{H}_2$), 3.69 s (2H, $C\underline{H}_2Ph$), 5.03 s (1H, OH); 6.94 s (2H, Ar–H); 7.26–7.28 m (5H, Ph). IR spectrum (KBr), ν_{max}, cm^{-1}: 3574 (PhOH).

Found, %: C 77.91, H 9.19, S 8.79.
$C_{24}H_{34}OS$.
Calculated, %: C 77.78, H 9.25, S 8.65.

Butyl 4-(3,5-di-***tert*-butyl-4-hydroxyphenyl)butyl sulfide IIj** was prepared similarly to **IIa** from 5.7 g (19.3 mmol) of thiol **Ic** and 2.2 ml (21.3 mmol) of 1-chlorobutane (synthesis time 4 h); yield 4.88 g (72%), bp 168–170°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.92–0.95 t (3H, $CH_2\underline{Me}$), 1.42–1.42 m (2H, $C\underline{H}_2Me$), 1.46 s (18H, *t*-Bu), 1.56–1.62 m (2H, $C\underline{H}_2Et$), 1.71 m [4H, $ArCH_2(C\underline{H}_2)_2$], 2.55–2.56 m (4H, CH_2SCH_2), 2.64 t (2H, $ArC\underline{H}_2$), 5.03 s (1H, OH), 6.99 s (2H, Ar–H). IR spectrum (KBr), ν_{max}, cm^{-1}: 3645 (PhOH).

Found, %: C 75.61, H 11.09, S 9.32.
$C_{22}H_{38}OS$.
Calculated, %: C 75.36, H 10.92, S 9.15.

Lard was oxidized at 130°C in an oxidation cell with bubbling oxygen, as described in [14]. The amount of lard placed in the cell was 50 g, and the concentration of antioxidants, 1 μmol per gram of lard. The progress of oxidation was monitored

by accumulation of peroxide compounds whose concentration was determined iodometrically [15] and expressed in peroxide numbers. The initial peroxide number of the lard was 0.002% iodine. The induction periods were determined graphically from the kinetic curves.

CONCLUSIONS

(1) The alkyl ω-(3,5-di-*tert*-butyl-4-hydroxyphenyl)alkyl sulfides synthesized exhibit high inhibiting activity, which is due to the bifunctional mechanism of the antioxidant effect and to the internal synergism.

(2) Under the conditions of the model reaction used in this study, the antioxidant activity of the sulfides grows with increasing length of the hydrocarbon chain linking the phenolic and sulfide moieties and with increasing electron-donor power of the aliphatic substituent.

(3) The compounds synthesized are of interest as antioxidants preventing development of oxidation processes in fats.

ACKNOWLEDGMENTS

The authors are grateful to the Russian Foundation for Basic Research for the access to STN International data bases (project no. 00-03-32 721) via the Novosibirsk STN center at the Novosibirsk Institute of Organic Chemistry, Siberian Division, Russian Academy of Sciences.

REFERENCES

1. RF Patent 1 072 420.
2. RF Patent 1 007 405.
3. Rezvukhin, A.I., Krysin, A.P., and Shalaurova, I.Yu., *Vopr. Med. Khim.*, 1995, no. 3, pp. 37–39.
4. Prosenko, A.E., Terakh, E.I., Kandalintseva, N.V., *et al., Zh. Prikl. Khim.*, 2001, vol. 74, no. 11, pp. 1839–1843.
5. USSR Inventor's Certificate, no. 1 123 284.
6. USSR Inventor's Certificate, no. 1 154 296.
7. USSR Inventor's Certificate, no. 1 074 865.
8. US Patent 4 021 468.
9. Bezzubov, A.P., *Khimiya zhirov* (Chemistry of Fats), Moscow: Pishchevaya Prom–st., 1975.
10. Prosenko, A.E., Kandalintseva, N.V., and Tolstikov, G.A., *Kinet. Katal.*, 2002, vol. 43, no. 1, pp. 29–33.
11. Pinko, P.I., Terakh, E.I., Prosenko, A.E., and Grigor'ev, I.A., *Zh. Prikl. Khim.*, 2001, vol. 74, no. 11, pp. 1843–1847.
12. Prosenko, A.E., ω-(4-Hydroxyaryl)haloalkanes and Sulfur-Containing Antioxidants Derived from Them, *Cand. Sci. Dissertation*, Novosibirsk, 2000.
13. Roginskii, V.A., *Fenol'nye antioksidanty: Reaktsionnaya sposobnost' i effektivnost'* (Phenolic Antioxidants: Reactivity and Performance), Moscow: Nauka, 1988.
14. Shishkina, L.N., in *Issledovanie sinteticheskikh i prirodnykh antioksidantov in vivo i in vitro* (*In vivo* and *in vitro* study of Synthetic and Natural Antioxidants), Moscow: Nauka, 1992, pp. 26–30.
15. Zinov'ev, A.A., *Khimiya zhirov* (Chemistry of Fats), Moscow: Pishchepromizdat, 1952.