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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis and Antioxidative Properties of New Sulfur-Containing Derivatives of Sterically Hindered Phenols

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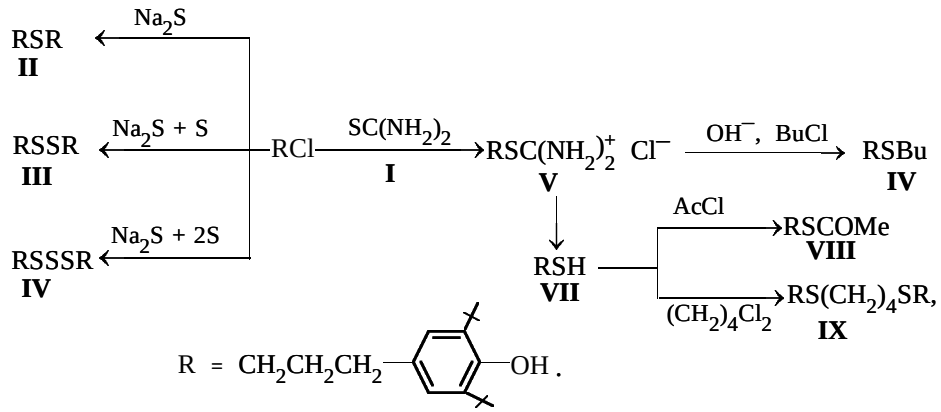
Abstract—3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1-chloropropane was converted into derivatives containing S(II) in various functional groups. The inhibiting power of the compounds with respect to thermal autooxidation of animal fat was evaluated.

Among inhibitors of free-radical oxidation of hydrocarbon substrates, a particular place is occupied by sulfur-containing derivatives of sterically hindered phenols, whose high antioxidative activity is due to the bifunctional mechanism of the antioxidative effect [1] and to internal synergism [2, 3]. Among such antioxidants is bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propyl] sulfide (SO-3), which shows a high performance as thermal stabilizer of polymer compounds based on polyethylene and polypropylene [4, 5]. As SO-3 is nontoxic, it can be used in production of household goods [6, 7]; also, the possibility was examined of its use as an antioxidant for fat-containing foodstuffs and fat-soluble drugs [8–10]. With the aim of searching for new high-performance inhibitors, we prepared in this work a series of structural analogs of SO-3 containing S(II) atoms in various functional groups and compared the antioxidative properties of these compounds with respect to thermal autooxidation of animal fat.

From 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-chloropropane **I**, we prepared sulfur-containing derivatives **II**–**IX** by the following scheme:



The compositions and structures of **II**–**IX** were proved by elemental analysis and spectroscopy.

The antioxidative properties of **II**–**IX** were studied with respect to thermal autooxidation of animal fat. The reference compound was 2,6-di-*tert*-butyl-4-methylphenol (Ionol), a commercial product used in food industry as an antioxidant for fat-containing foodstuffs [11]. As oxidation substrate we used lard; its oxidation was monitored by accumulation of hydroperoxides. The concentration of peroxides in a sample was

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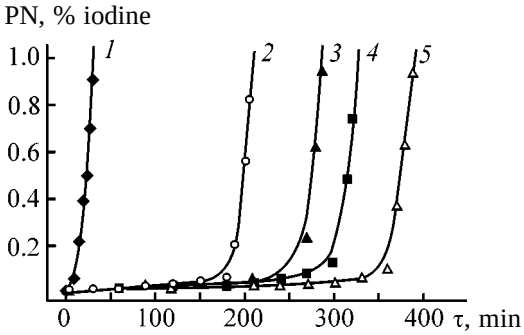

Fig. 1. Kinetic curves of lard oxidation in the presence of phenolic antioxidants. Antioxidant: (*1*) none, (*2*) Ionol, (*3*) **III**, (*4*) SO-3, and (*5*) **IX**. (PN) Peroxide number and (τ) time.

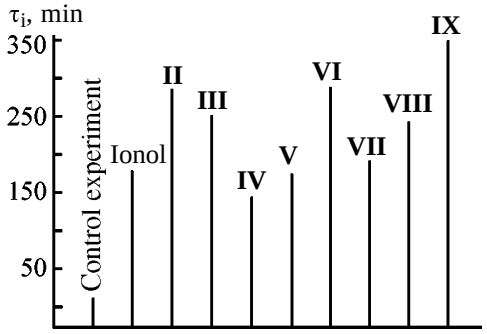

Fig. 2. Diagram of induction periods τ_i of lard oxidation inhibited with phenolic antioxidants (2.5 μmol g^{-1} fat, 130°C).

determined by Zinov'ev's version of the iodometric procedure [12]. The kinetic curves were plotted; they had similar shape for oxidation of the straight fat and the fat containing inhibitors (Fig. 1). The antioxidative activity (AOA) of inhibitors was judged from the duration of the induction period, defined as the time in which the peroxide number reaches 0.1 (the initial peroxide number was 0.003). The results are shown in Fig. 2.

Our results show that compounds **II**–**IX** exhibit pronounced AOA: the induction period of lard oxidation increases by a factor of 12–30. All the compounds except trisulfide **IV** and isothiuronium chloride **V** surpass Ionol in performance, which suggests their bifunctional activity. The AOA decreases in the order **II** (SO-3) > **III** > **IV**, which may be due to thermal oxidative cleavage of the S–S bonds with generation of thiyl radicals [13], which can participate not only in chain termination, but also in chain propagation [14]:

$$RSSR \rightarrow 2RS^{\bullet},$$

$$RS^{\bullet} + {}^{\bullet}OH \rightarrow RSOH,$$

$$RS^{\bullet} + XH \rightarrow RSH + X^{\bullet}.$$

Apparently, the possible formation of thiyl radicals is responsible for the relatively low inhibiting power of thiol **VII**:

$$RSH + {}^{\bullet}OH \rightarrow RS^{\bullet} + H_2O,$$

$$RSH + X^{\bullet} \rightarrow RS^{\bullet} + XH.$$

Among the new compounds, the most effective antioxidants are sulfide analogs of SO-3: unsymmetrical sulfide **VI** and bissulfide **IX**, with the latter appreciably surpassing SO-3 in the antioxidative effect under the experimental conditions. Our results show that compounds **II**, **III**, **VI**, **VIII**, and **IX** deserve further study as antioxidants for fat-containing foodstuffs.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded with a Bruker spectrometer (500 MHz, external reference TMS). The IR spectra were taken with a Vektor-22 Fourier spectrometer (CCl_4 solutions or KBr pellets, 150 : 1). The melting points were determined with a PTP device.

Bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl] sulfide **II** and bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl disulfide **III** were prepared according to [15, 16].

Bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl] trisulfide IV. A mixture of 3.51 g (45 mmol) of sodium sulfide, 2.88 g (90 mmol) of sulfur, and 80 ml of 2-propanol was refluxed for 2 h. After cooling to 50–60°C, 20 g (69 mmol) of **I** was added, and the mixture was refluxed for 4 h. The reaction mass was cooled and treated with toluene (80 ml). The extract was washed with water and dried over Na_2SO_4; the solvent was distilled off. The reaction product was purified by chromatography on silica gel, eluent hexane–diethyl ether (5 : 1). Yield of **IV** 17.3 g (84%); resinous yellow substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.430 s (36H, *t*-Bu), 1.970–2.000 m (4H, $ArCH_2CH_2$), 2.612–2.642 t (4H, $ArCH_2$), 2.715–2.742 t (4H, CH_2S), 5.034 s (2H, OH), 6.971 s (4H, H_{arom}). IR spectrum (CCl_4), ν, cm^{-1}: 3640 (OH). UV spectrum (EtOH), λ_{max}, nm (log ε): 220 (4.20), 278 (3.57).

Found, %: C 69.11, H 9.13, S 17.44.
$C_{34}H_{54}O_2S_3$.
Calculated, %: C 69.09, H 9.21, S 16.27.

***S*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl]-thiuronium chloride V.** A mixture of 4.24 g (15 mmol) of **I**, 0.95 g (12.5 mmol) of thiourea, and

30 ml of 1-butanol was refluxed for 5 h, after which the solvent was distilled off, and the product was washed with warm pentane, filtered off, and dried. Yield of **V** 4.13 g (92%); colorless crystalline substance, mp 165°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.430 s (18H, *t*-Bu), 2.048 m (2H, $ArCH_2CH_2$), 2.726 t (2H, $ArCH_2$), 3.123 t (2H, CH_2S), 7.146 s (2H, H_{arom}). IR spectrum (KBr), ν, cm^{-1}: 3644 (OH), 3263 and 3062 (NH_2^+), 1650 (NH_2^+). UV spectrum (EtOH), λ_{max}, nm (log ε): 209 (1.84), 276 (0.16).

Found, %: C 59.89, H 8.92, Cl 9.74, N 7.52, S 8.71.
$C_{18}H_{31}ClN_2OS$.
Calculated, %: C 60.22, H 8.70, Cl 9.88, N 7.80, S 8.93.

Butyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl sulfide VI. A mixture of 7 g (19.5 mmol) of isothiuronium chloride **V**, 1.72 g (43 mmol) of NaOH, 3.04 ml (29.3 mmol) of 1-chlorobutane, and 20 ml of ethanol was stirred for 1 h at 20°C under argon and then heated at 50–60°C for 2 h. The mixture was treated with toluene. The extract was washed with water and dried over Na_2SO_4, the solvent was distilled off, and the product was vacuum-distilled. Yield of **VI** 4.59 g (70%); bp 165°C (1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.892–0.921 t (3H, CH_2Me), 1.380–1.416 m (2H, CH_2Me), 1.430 s (18H, *t*-Bu), 1.532–1.591 m (2H, CH_2Et), 1.862–1.908 m (2H, $ArCH_2CH_2$), 2.498–2.524 t (2H, SCH_2Pr), 2.528–2.553 t (2H, CH_2SBu), 2.610–2.641 t (2H, $ArCH_2$), 5.030 s (1H, OH), 6.977 s (2H, H_{arom}). IR spectrum (CCl_4), ν, cm^{-1}: 3646 (OH). UV spectrum (EtOH), λ_{max}, nm (log ε): 208 (1.56), 277 (0.19).

Found, %: C 75.13, H 10.62, S 9.50.
$C_{21}H_{36}OS$.
Calculated, %: C 74.94, H 10.78, S 9.53.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1-propanethiol VII. A mixture of 30 g (106 mmol) of **I**, 9.7 g (127 mmol) of thiourea, and 100 ml of DMF was heated at 130°C for 2 h. After cooling to 50°C, a solution of 0.92 g (23 mmol) of NaOH in 3 ml of water was added, and the mixture was stirred for 2 h at 50°C, acidified with HCl, and treated with toluene. The extract was washed with water and dried over Na_2SO_4, the solvent was distilled off, and the reaction product was vacuum-distilled. Yield of **VII** 25.3 g (85%); mp 48, bp 138–145°C (1–2 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.132 s (1H, SH), 1.430 s (18H, *t*-Bu), 1.912 m (2H, $ArCH_2CH_2$); 2.257–2.756 m (4H, $ArCH_2$, CH_2S), 4.852 s (1H, OH), 6.871 s (2H, H_{arom}). IR spectrum (KBr), ν, cm^{-1}: 3650 (OH). UV spectrum (EtOH), λ_{max}, nm (log ε): 207 (3.88), 278 (3.28).

Found, %: C 73.09, H 10.13, S 11.20.
$C_{17}H_{28}OS$.
Calculated, %: C 72.80, H 10.06, S 11.43.

***S*-[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)propyl] ethanethioate VIII.** To a mixture of 5 g (17.8 mmol) of **I**, 5 ml (35.6 mmol) of triethylamine, and 20 ml of benzene, we added dropwise 1.3 ml (18.2 mmol) of acetyl chloride. 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 reaction product was recrystallized from ethanol. Yield of **VIII** 5.12 g (89%), mp 57–58°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.428–1.446 s (18H, *t*-Bu), 1.851–1.881 m (2H, $ArCH_2CH_2$), 2.328 s (3H, COMe), 2.580–2.611 t (2H, $ArCH_2$), 2.893–2.921 t (2H, CH_2S), 5.040 s (1H, OH), 6.952 s (2H, H_{arom}). IR spectrum (CCl_4), ν, cm^{-1}: 3647 (OH), 1695 (C=O). UV spectrum (EtOH), λ_{max}, nm (log ε): 206 (2.18), 229 (0.94), 221 (0.92), 277 (0.18).

Found, %: C 70.82, H 9.36, S 9.77.
$C_{19}H_{30}O_2S$.
Calculated, %: C 70.76, H 9.38, S 9.94.

1,4-Bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl) propylthio]butane IX. A mixture of 5.05 g (18 mmol) od **I** and 1.3 g (19.7 mmol) of KOH was dissolved in 30 ml of ethanol, and 1.14 g (9 mmol) of 1,4-dichlorobutane was added. The mixture was refluxed for 2.5 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 product was recrystallized from ethanol. Yield of **IX** 4.0 g (72%), mp 64–65°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.430 s (36H, *t*-Bu), 1.691 m [4H, $SCH_2(CH_2)_2CH_2S$], 1.871 m (4H, $ArCH_2CH_2$), 2.526–2.556 m (8H, SCH_2), 2.603–2.635 t (4H, $ArCH_2$), 5.030 s (2H, OH), 6.970 s (4H, H_{arom}). IR spectrum (KBr), ν, cm^{-1}: 3643 (OH). UV spectrum (EtOH), λ_{max}, nm (log ε): 210 (1.84), 277 (0.36).

Found, %: C 74.47, H 10.31, S 10.65.
$C_{38}H_{62}O_2S_2$.
Calculated, %: C 74.21, H 10.16, S 10.43.

Oxidation of lard (50 g, Novosibirsk Meat Packing and Canning Plant) was performed at 130°C in an oxygen flow in an oxidation cell similar to that described in [17]. In the course of oxidation, 1-g sam-

ples were taken. The concentration of antioxidants (main substance content no less than 98–99%) was 2.5 μmol g^{-1} fat.

CONCLUSIONS

(1) The synthesized derivatives of 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-chloropropane containing sulfur atoms in various functional groups (sulfide, disulfide, thiol, thio ester) are effective inhibitors of animal fat oxidation.

(2) Symmetrical and unsymmetrical 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propyl sulfides considerably surpass in the antioxidative properties the commercial antioxidant Ionol used in food industry and deserve further study as promising antioxidants for fat-containing foodstuffs.

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