ISSN 1070-4272, Russian Journal of Applied Chemistry, 2010, Vol. 83, No. 4, pp. 707−711. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © E.N. Garibov, I.A. Rzaeva, N.G. Shykhaliev, A.I. Kuliev, V.M. Farzaliev, M.A. Allakhverdiev, 2010, published in Zhurnal Prikladnoi Khimii, 2010, Vol. 83, No. 4, pp. 655−659.

ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Cyclic Thioureas as Cumene Oxidation Inhibitors

E. N. Garibov[a], I. A. Rzaeva[a], N. G. Shykhaliev[b], A. I. Kuliev[a], V. M. Farzaliev[a], and M. A. Allakhverdiev[a]

[a] *Kuliev Institute of Chemistry of Additives, National Academy of Sciences of Azerbaijan, Baku, Azerbaijan*
[b] *Baku State University, Baku, Azerbaijan*

Received August 4, 2009

Abstract—Hexahydro-1,3,5-triazine-4-thiones were synthesized by ternary condensation of thiourea with various aldehydes and amines. The products were characterized by IR and NMR spectroscopy, and their inhibiting effect on cumene oxidation was examined.

DOI: 10.1134/S1070427210040245

Thiourea and its derivatives are convenient starting compounds for preparing various heterocyclic systems [1]. Also, N-substituted thioureas exhibit a wide spectrum of physiological activity. Some of these compounds show antitumor, antiviral, antibacterial, and therapeutic activity [2]. The chemistry of heterocyclic compounds synthesized from thiourea and its derivatives is one of the most interesting and rapidly developing fields of the modern organic chemistry. Such heterocycles are used as pharmaceuticals, chemical agents for plant protection, bioprotectors for fuels and lubricating oils, antioxidants, fireproofing agents, and additives to polymeric materials for imparting to them special properties [3–6]. Thietanyl derivatives and other substituted thioureas show high antioxidant activity [7, 8].

We synthesized cyclic thioureas by ternary condensation of thiourea, various aldehydes, and primary amines [7–10] and examined the correlation between their structure and antioxidant properties (see the scheme)

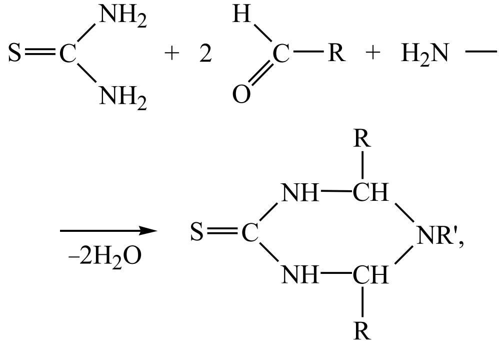
With aqueous ammonia used in the ternary condensation, the reaction is usually performed at room temperature for 20–40 h. With amines, the reaction is performed at 60–70°C for 3 h in benzene. The formation of cyclic thioureas **I–VI** is monitored by thin-layer chromatography. Cyclic thioureas **I–VI** are white finely crystalline substances. They are readily soluble in acetone, ethanol, and dimethyl sulfoxide.

The physicochemical constants, yields, and other parameters are given in Table 1.

The structure of the synthesized cyclic thioureas **I–VI** was proved by IR and ^{1}H, ^{13}C NMR spectroscopy, and the purity, by elemental analysis and thin-layer chromatography.

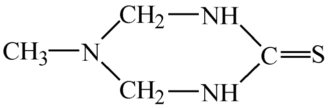
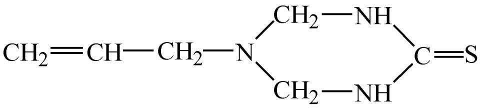
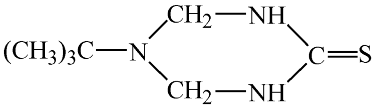
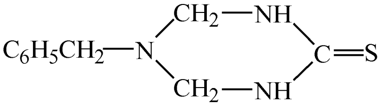
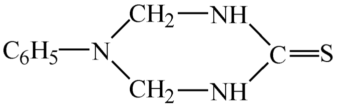
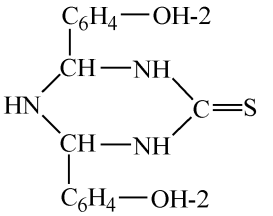
In the IR spectra of **I–VI**, the absorption band at 1215–1185 cm^{-1} corresponds to stretching vibrations of the C=S bond. It should be noted that the C=S band, in contrast to the C=O band, is not always readily revealed. The C(S)N vibrations are observed at 1340–1245 cm^{-1} [11]. Generally the C(S)N stretching vibrations are

Scheme.



R = H, R' = CH$_3$ (**I**); R = H, R' = CH$_2$=CH–CH$_2$ (**II**); R = H, R' = (CH$_3$)$_3$C (**III**); R = H, R' = C$_6$H$_5$CH$_2$ (**IV**); R = H, R' = C$_6$H$_5$ (**V**); R = C$_6$H$_4$–OH-2, R' = H (**VI**).

Table 1. Yields and some physicochemical constants of **I–VI**

Compound	Yield, %	T_m, °C	Found, %/Calculated, %				Empirical formula	R_f
			C	H	N	S		
 **(I)**	37	178–179	36.43 36.62	6.78 6.91	32.15 32.03	24.12 24.44	$C_4H_9N_3S$	0.42
 **(II)**	41	167	45.69 45.83	6.83 7.05	26.87 26.72	20.08 20.39	$C_6H_{11}N_3S$	0.57
 **(III)**	29	176–177	48.78 48.52	8.45 8.73	24.06 24.25	18.75 18.51	$C_7H_{15}N_3S$	0.49
 **(IV)**	35	164–165	57.64 57.94	6.58 6.32	20.08 20.27	15.61 15.47	$C_{10}H_{13}N_3S$	0.62
 **(V)**	30	155–156	55.64 55.93	5.93 5.74	21.54 21.74	16.32 16.59	$C_9H_{11}N_3S$	0.51
 **(VI)**	39	132–133	59.93 59.78	5.76 5.62	13.82 13.94	10.79 10.64		0.66

manifested at 1525, 1508, 1200, 1030, 919, and 625 cm^{-1} [12]. The stretching vibrations of the nonassociated NH bond are revealed at 3445–3465 cm^{-1}, and those of associated NH bonds, at 3215–3225 cm^{-1}.

In the ^{1}H NMR spectrum of 2,6-bis(2-hydroxyphenyl)-hexahydro-1,3,5-triazine-4-thione **VI**, the CH protons give a singlet at 3.1 ppm. Aromatic ring protons give doublets at 6.8, 7.2, and 7.4 ppm. The NH proton signal is observed at 7.8 ppm. The two OH protons give a singlet at 8.5 ppm.

The ^{1}H NMR spectra of the other compounds are similar to that of **VI** and differ only in the signals of substituents. For example, the CH_3N protons give a singlet at 2.60 ppm, and nine protons of the *tert*-butylamino group, a singlet at 1.25 ppm.

The ^{13}C NMR spectra of the substances prepared contain signals from carbon atoms of the benzene ring (121, 126, 129, 131 ppm) and methine group (39.40 ppm).

Antioxidant properties of the synthesized cyclic thioureas **I–VI** were studied in model reactions of cumene autooxidation. Experiments showed that all the compounds studied have pronounced antioxidant properties and efficiently inhibit cumene oxidation.

To evaluate the capability of cyclic thioureas **I–VI** to terminate oxidation chains in reactions with peroxy radicals, we performed cumene oxidation in the presence of **I–VI**, initiated with azobis(isobutyronitrile) (AIBN), at 60°C. The initiator concentration was 2 × 10^{-2} M in all the experiments. All the cyclic thioureas studied inhibit the cumene oxidation. From the induction period τ, we calculated the stoichiometric inhibition coefficient f equal to the number of oxidation chains terminated on one inhibitor molecule and its transformation products:

$$f = \frac{\tau W_i}{[\mathrm{InH}]_0},$$

where W_i is the initiation rate equal to 2×10^{-7} mol l^{-1} s^{-1} [13]; $[InH]_0$, initial antioxidant concentration (M); and τ, induction period (s).

From the kinetics of the oxygen uptake, we calculated the rate constant of the reaction of the antioxidants with peroxy radicals K_7. To this end, the kinetic curves of the oxygen uptake were transformed from the coordinates $\Delta[O_2]–t$ into the coordinates $\Delta[O_2]^{-1}–t^{-1}$. From the slope, equal to [14]

$$\tan\alpha = \frac{fK_7[\mathrm{InH}]_0}{K_2[\mathrm{RH}]\,W_\mathrm{i}},$$

we found

$$K_7 = \frac{\tan\alpha K_2[\mathrm{RH}]\,W_\mathrm{i}}{f[\mathrm{InH}]_0},$$

where $K_2 = 1.51$ l mol^{-1} s^{-1} [15], [RH] = 6.9 M.

Figure 1 shows the kinetic curve of initiated oxidation of cumene in the presence of cyclic thiourea **VI** taken as example. As can be seen, compound **VI** inhibits the oxidation by reacting with cumylperoxy radicals. It is seen from the kinetic curve of initiated cumene oxidation that the reaction rate in the presence of the cyclic thiourea after the end of the induction period is lower than the oxidation rate without inhibitor. This fact indicates that the products formed from **VI** in reaction with cumylperoxy radicals also exhibit antioxidant properties. The kinetic parameters of the reactions of **I–VI** with cumylperoxy radicals are given in Table 2.

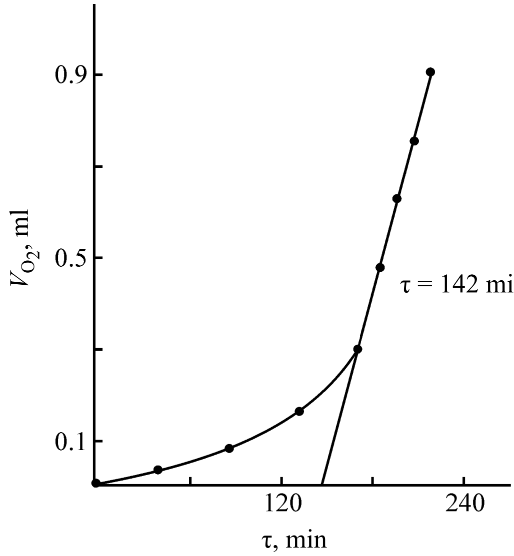


Fig. 1. Kinetic curve of initiated oxidation of cumene in the presence of **VI**. [AIBN] = 2×10^{-2} M, T = 60°C, [InH] = 5×10^{-4} M. (V_{O2}) Oxygen uptake and (τ) time.

As can be seen, the values of f for **I–VI** vary within 2.42–3.42. The rate constant of the reaction of the antioxidants with cumylperoxy radicals varies from 2.10×10^4 to 4.75×10^4 l mol^{-1} s^{-1}.

Analysis of the kinetic parameters of the reactions of **I–VI** with cumylperoxy radicals shows that the substituents at the triazine ring strongly affect the reactivity of the compounds. For example, compound **VI**, in contrast to the other antioxidants, repeatedly terminates oxidation chains (f = 3.42) and exhibits vary high reactivity toward cumylperoxy radicals ($K_7 = 4.75 \times 10^4$ l mol^{-1} s^{-1}).

The reactions of **I–VI** with cumene hydroperoxide (CHP) were performed in chlorobenzene in a nitrogen atmosphere at 110°C. All the compounds catalytically decompose CHP. As seen from Fig. 2 showing data for **VI** as example, the kinetic curve of the CHP decomposition under the action of **I–VI** is S-shaped, which is characteristic of an autocatalytic process (Fig. 2).

The catalytic factor ν shows how many CHP molecules decompose under the action of one antioxidant molecule. This quantity is calculated by the formula

$$\nu = \frac{[\mathrm{ROOH}]_0 - [\mathrm{ROOH}]_\infty}{[\mathrm{InH}]_0},$$

where $[ROOH]_0$ and $[ROOH]_\infty$ are the initial and final CHP concentrations, respectively; $[InH]_0$ is the initial antioxidant concentration.

Our results show that one molecule of **I–VI** is capable to decompose up to several ten thousands of

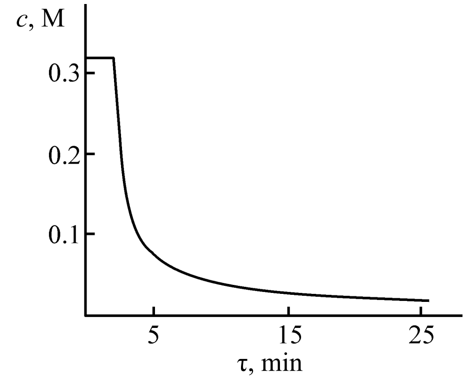


Fig. 2. Kinetic curve of CHP decomposition under the action of **VI**. T = 110°C, [InH] = 5×10^{-5} M. (c) CHP concentration and (τ) time.

Table 2. Kinetic parameters of reactions of **I–VI** with cumylperoxy radicals and of catalytic decomposition of cumene hydroperoxide. [AIBN] = 2×10^{-2} M

Compound	T 60°C		T 110°C		
	f	$K_7 \times 10^{-4}$, l mol^{-1} s^{-1}	ν	K, × 10^{-4}, l mol^{-1} s^{-1}	τ, min
I	2.42	2.10	25000	32	160
II	3.15	1.90	27000	29	175
III	2.90	3.10	32000	37	180
IV	2.75	3.50	45000	46	155
V	3.30	3.90	55000	55	170
VI	3.42	4.75	65000	63	190

CHP molecules. Cyclic thiourea **VI** containing two hydroxyphenyl fragments is the most active. For this compound, the catalytic factor ν and the rate constant K are equal to 65000 and 63 l mol^{-1} s^{-1}, respectively.

Thus, the compounds under consideration exert a combined effect as antioxidants: they terminate oxidation chains in reactions with cumylperoxy radicals and catalytically decompose cumene hydroperoxide.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 spectrometer (300 MHz) from solutions in DMSO-d_6, with HMDS as internal reference, and the IR spectra, on a Specord 75-IR spectrophotometer from mulls in mineral oil. Thin-layer chromatography of **I–VI** was performed on Silufol UV-254 plates, with isopropyl alcohol : hexane (1 : 3) mixture as eluent.

2,6-Bis(2-hydroxyphenyl)hexahydro-1,3,5-triazine-4-thione VI. A three-necked flask was charged with 52 g (0.1 mol) of 33.5% aqueous ammonia and 7.6 g (0.1 mol) of thiourea dissolved in 30 ml of distilled water. The mixture was vigorously stirred at 30–35°C. Then 24.5 g (0.2 mol) of salicylaldehyde was added dropwise, and the mixture was allowed to stand for 48 h at room temperature. The precipitate was filtered off and recrystallized from ethanol. Yield of **VI** 11.7 g (39%); mp 132–133°C. Found, %: C 59.93, H 5.76, N 13.82, S 10.79. $C_{15}H_{15}N_3O_2S$. Calculated, %: C 59.78, H 5.62, N 13.94, S 10.64; R_f 0.66.

The other cyclic thioureas **I–V** were prepared similarly. Their physicochemical constants are given in Table 1.

Cumene hydroperoxide was purified by the known procedure [16] with the subsequent distillation; chlorobenzene and cumene were purified by the common procedure based on sulfonation of impurities with concentrated sulfuric acid [17]. The CHP concentration was determined by iodometric titration [18], with intermittent sampling.

Experiments on CHP decomposition were performed in chlorobenzene at 110°C in a glass bubbler in a nitrogen atmosphere. The CHP concentration was varied in the range 0.16–0.64, and the concentration of **I–VI**, in the range $(1–5) \times 10^{-4}$ M.

Experiments on initiated oxidation of cumene were performed on a manometric unit [18]. The initiator was AIBN, for which at 60°C the initiation rate is 1×10^{-5} l mol^{-1} s^{-1}. The initiator concentration in all the experiments was constant (2×10^{-2} M), as well as the concentration of **I–VI,** equal to 5×10^{-4} M.

CONCLUSIONS

(1) Ternary condensation of thiourea with aldehydes and amines yields hexahydro-1,3,5-triazine-4-thiones.

(2) Cyclic thioureas exert a combined effect as antioxidants: they terminate oxidation chains in reactions with cumylperoxy radicals and catalytically decompose cumene hydroperoxide.

REFERENCES

1. *Heterocyclic Compounds*, Elderfield, R.C., Ed., New York: Wiley, 1957, vol. 5.
2. Walter, A.M. and Heilmayer, L., *Antibiotika Fibel*, Stuttgart: Thieme, 1965.

3. US Patent 3025295.
4. US Patent 3822262.
5. US Patent 3190887.
6. Hall, N.K. and Schneider, A.K., *J. Am. Chem. Soc.,* 1958, vol. 80, pp. 6409–6415.
7. Farzaliev, V.M., Allakhverdiev, M.A., Magerramov, A.M., et al*., Zh. Prikl. Khim*., 2001, vol. 74, no. 1, pp. 110–112.
8. Azerbaijan Patent I 20030078.
9. Magerramov, A.M., Abdinbekova, R.T., Kurbanova, M.M., et al., *Zh. Prikl. Khim*., 2004, vol. 77, no. 10, pp. 1681–1688.
10. Magerramov, A.M., Kurbanova, M.M., Abdinbekova, R.T., et al., *Zh. Prikl. Khim*., 2006, vol. 79, no. 5, pp. 795–800.
11. Lien, E.J. and Kumler, W.P.*, J. Med. Chem*., 1968, vol. 11, pp. 214–219.
12. Singh, B., Sharma, D.K., and Sharma, U.S., *J. Indian Chem. Soc*., 1979, vol. 56, pp. 764–771.
13. Denisov, E.T., Kharitonov, V.V., and Fedorov, V.V., *Transformation of Kinetic Curves as a Method for Evaluating the Performance of Oxidation Inhibitors*, Preprint of the Inst. of Chemical Physics, USSR Acad. Sci., Chernogolovka, 1973.
14. Emanuel', N.M., Denisov, E.T., and Maizus, Z.K., *Tsepnye reaktsii okisleniya uglevodorodov v zhidkoi faze* (Chain Reactions of Liquid-Phase Oxidation of Hydrocarbons), Moscow: Nauka, 1967.
15. Denisov, E.T., *Konstanty skorosti gomoliticheskikh zhidkofaznykh reaktsii* (Rate Constants of Homolytic Liquid-Phase Reactions), Moscow: Nauka, 1971.
16. Karnojitzki, V.*, Les Peroxides Prganiques*, Paris: Hermann, 1958.
17. Weissberger, A. and Proskauer, E.S., *Organic Solvents. Physical Properties and Methods of Purification*, Riddick, J.A. and Toops, E.E., Eds., New York: Interscience, 1955.
18. Emanuel', N.M., Gladyshov, G.P., and Denisov, E.T., *Order of Testing Chemical Compounds as Stabilizers*, Preprint of the Inst. of Chemical Physics, USSR Acad. Sci., Chernogolovka, 1976.