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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Antioxidant Properties of Some 5-Ethoxycarbonyl-Substituted 3,4-Dihydropyrimidin-2(1*H*)-ones (-thiones) and Their Derivatives

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Abstract—Inhibiting properties of some synthesized 5-ethoxycarbonyl-substituted 3,4-dihydropyrimidin-2(1*H*)-ones (-thiones) and their derivatives in model reactions were studied.

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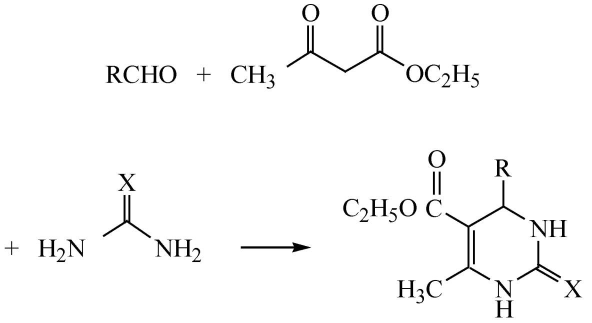
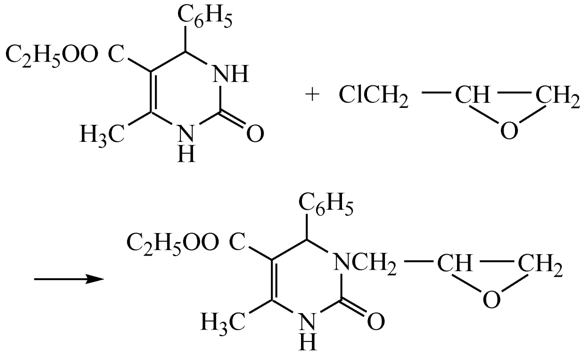
It is known that 3,4-dihydropyrimidin-2(1*H*)-ones (-thiones) and their derivatives exhibit a wide spectrum of biological activity. In addition, they are powerful calcium channel blockers, antihypertensive drugs, and neutopeptide antagonists [1].

In this study we examined the antioxidant properties of some ethoxycarbonyl-substituted 3,4-dihydropyrimidin-2(1*H*)-ones (-thiones) and their derivatives **I–V**. Compounds **I–III** were synthesized by ternary condensation [2]:



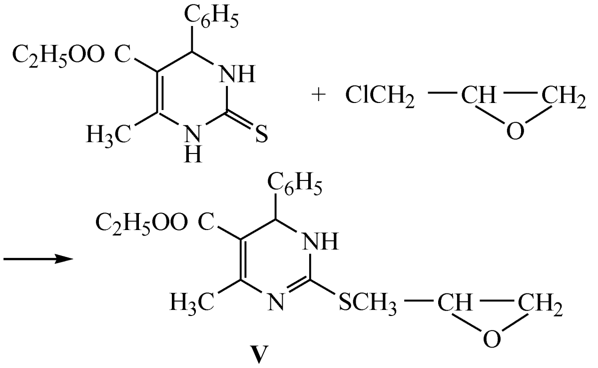
where X = O, R = CH_3 (**I**); X = O, R = C_6H_5 (**II**); X = S, R = C_6H_5 (**III**).

3-(2',3'-Epoxypropyl)-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **IV** was synthesized by the reaction of 5-exthoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one with epichlorohydrin [3]:



IV

2-(2',3'-Epoxypropylthio)-6-methyl-4-phenyl-3,4-dihydropyrimidine-5-carboxylate **V** was synthesized by the reaction of 5-exthoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione with epichlorohydrin [3]:



V

Table 1. Physicochemical characteristics of **I–V**

Compound	Yield, %	T_m, °C	R_f	Empirical formula	Found, %/Calculated, %			
					C	H	N	S
I	65	194–196	0.72	$C_9H_{14}N_2O_3$	54.50	7.02	14.22	–
					54.54	7.07	14.14	
II	80	202	0.17	$C_{14}H_{16}N_2O_3$	64.72	6.09	10.81	–
					64.61	6.15	10.76	
III	75	209	0.63	$C_{14}H_6N_2O_2S$	60.75	5.82	10.09	11.63
					60.86	5.79	10.14	11.59
IV	65	205–206	0.50	$C_{17}H_{20}N_2O_4$	64.61	6.29	8.90	–
					64.55	6.32	8.86	
V	60	160	0.54	$C_{17}H_{20}N_2O_3S$	61.56	6.17	8.57	9.75
					61.44	6.02	8.43	9.63

The structures of the compounds synthesized were confirmed by IR and ^{1}H and ^{13}C NMR spectroscopy, and the purity, by TLC. The physicochemical characteristics of the compounds synthesized are given in Table 1.

To evaluate the antioxidant activity of **I**, **IV**, and **V** in elementary steps of cumene oxidation, we studied the reactions of these compounds with cumylperoxy radicals (CPRs) and cumyl hydroperoxide (CHP).

The capability of **I**, **IV**, and **V** to terminate oxidation chains by the reaction with CPRs was evaluated using as example the cumene oxidation at 60°C, initiated by azobis(isobutyronitrile) (AIBN) taken in a concentration of 2×10^{-2} M. We found that compounds **I**, **IV**, and **V** actively terminate oxidation chains by reacting with CPRs (Fig. 1).

From the duration of the induction period τ_{ind} we calculated the stoichiometric coefficient of the inhibition *f*, equal to the number of oxidation chains terminated on one inhibitor molecule and its transformation products:

$$f = \frac{\tau_{\text{ind}} W_i}{[\text{InH}]_0},$$

where W_i is the initiation rate and $[\text{InH}]_0$ is the initial inhibitor concentration.

From the kinetics of oxygen uptake we calculated the rate constants of the reactions of the compounds in question with CPRs, k_7 [4, 5]. To this end, the kinetic curves of the oxygen uptake were transformed from the $[O_2]–\tau$ coordinates to the $[O_2]^{-1}–\tau^{-1}$ coordinates, and from the slope of the straight line [5, 6]

$$\tan\alpha = \frac{f k_7 [\text{InH}]_0}{k_2 [\text{RH}] W_i},$$

the quantity k_7 was determined:

$$k_7 = \frac{\tan\alpha k_2 [\text{RH}] W_i}{f [\text{InH}]_0},$$

where k_2 is the rate constant of chain initiation [4, 5], equal to 1.51 l mol^{-1} s; [RH] = 7.17 M.

High antioxidant activity of **I**, **IV**, and **V** was also confirmed in experiments on cumene autooxidation at 110°C, and the kinetic parameters of the reactions were determined (Fig. 2).

As seen from Table 2, the coefficients *f* for **I**, **IV**, and **V** vary from 0.5 to 1.58, and the constant of the reaction of the inhibitors with CPRs, k_7, varies from 2.01×10^4 to 2.60×10^4 l mol^{-1} s^{-1}. The products formed in reactions

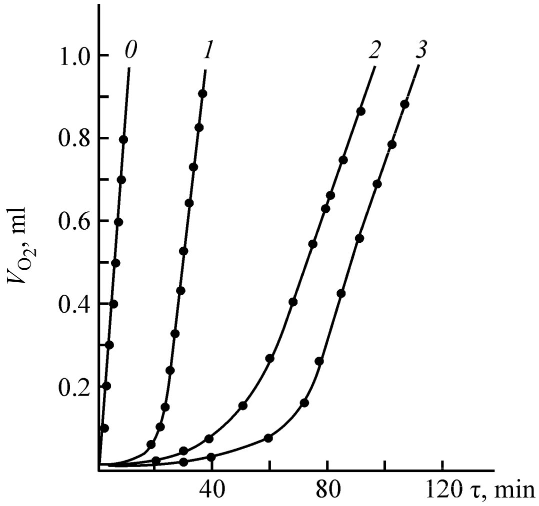


Fig. 1. Kinetic curves of initiated oxidation of cumene in the presence of **I**, **IV**, and **V**. T = 60°C, [AIBN] = 2×10^{-2} M, [InH] = 5×10^{-4} M. (V_{O_2}) Oxygen volume and (τ) time; the same for Fig. 2. Inhibitor: (*0*) none, (*1*) **I**, (*2*) **IV**, and (*3*) **V**; the same for Fig. 2.

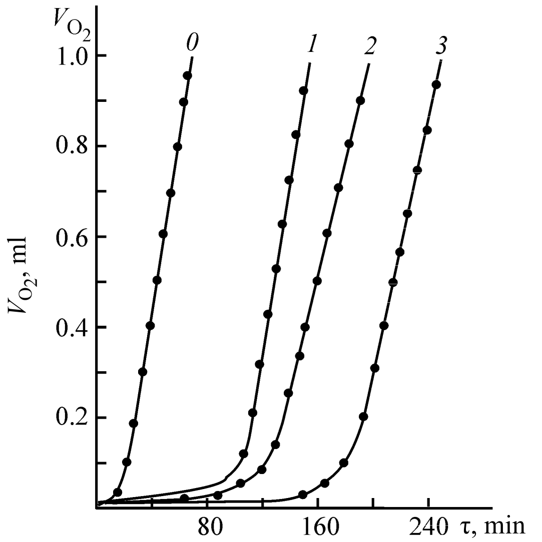


Fig. 2. Kinetic curves of cumene autooxidation in the presence of **I**, **IV**, and **V**. T = 110°C.

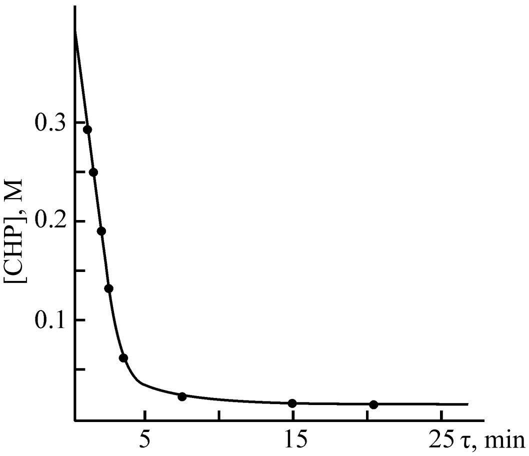


Fig. 3. Kinetic curve of CHP decomposition in the presence of **V**. T = 110°C, $[CHP]_0$ = 0.38 M, $[InH]_0 = 1 \times 10^{-4}$ M. (τ) Time.

of **I**, **IV**, and **V** with CPRs exhibit certain inhibiting effect: The oxidation rate after the induction period is somewhat lower than in the case of the uninhibited oxidation (Fig. 1).

The reactions of **I**, **IV**, and **V** with CHP were performed in chlorobenzene under nitrogen at 110°C. We found that, for all the compounds studied (Fig. 3), the kinetic curve of CHP decomposition under the action of compounds **I**, **IV**, and **V** is S-shaped, which is characteristic of an autocatalytic process. The reaction starts with a certain induction period when the CHP consumption is insignificant, which is followed by rapid catalytic decomposition of CHP, and then the reaction rate decreases owing to a decrease in the CHP concentration.

Apparently, the inhibitor first reacts with CHP, and then the resulting transformation product catalytically decomposes CHP. To determine the reaction stoichiometry, CHP was taken in an excess.

The catalytic factor is $\nu = [ROOH]_0 - [ROOH]_\infty/[In]_0$, where $[ROOH]_0$ and $[ROOH]_\infty$ are the initial and final CHP concentrations, respectively, and $[In]_0$ is the initial inhibitor concentration.

Experiments showed that one molecule of **I**, **IV**, and **V** can decompose up to several tens thousands (20000–25000) CHP molecules. It can be concluded that the compounds under consideration exert a combined inhibiting effect, terminating oxidation chains in reaction with CPRs and catalytically decomposing CHP.

EXPERIMENTAL

The purity of the compounds prepared and the reaction progress were monitored by TLC on Silufol UV-254 plates, with 2-propanol–hexane mixture (1 : 1) as eluent.

3,4-Dihydropyrimidin-2(1*H*)-ones (-thiones) were synthesized by the published procedure [2]. A round-bottomed flask equipped with a reflux condenser and a power-driven stirrer was charged with an aldehyde (1.25 mol), ethyl acetoacetate (1.90 mol), urea or thiourea (1.25 mol), CCl_3COOH (25 mg), and 95% ethanol

Table 2. Kinetic parameters of reactions of **I**, **IV**, and **V** with cumylperoxy radicals, k_7 and f (60°C, [AIBN] = 2×10^{-2} M), and of cumyl hydroperoxide decomposition, k and ν (110°C)

Compound	110°C			60°C	
	k, l mol^{-1} s^{-1}	ν	τ, min	f	k, l mol^{-1} s^{-1}
I	11	20000	100	0.5	2.01
IV	14.5	25000	180	1.58	2.6
V	13	22000	120	1.056	2.24

(10 ml). The reaction mixture was stirred for 2–4 h. The reaction progress was monitored by TLC. After the reaction completion, the mixture was cooled to room temperature, and the crystalline product was filtered off, washed with ethanol, dried, and recrystallized from aqueous ethanol (1 : 3).

General procedure for preparing IV and V [3]. A mixture of 0.1 mol of epichlorohydrin and 0.01 mol of 5-ethoxycarbonyl-substituted 3,4-dihydropyrimidin-2(1*H*)-one (-thione) **I–III** in 15 ml of dimethylformamide was refluxed for 3–4 h. After that, the reaction mixture was allowed to stand at room temperature and then cooled to 0°C. The precipitated crystals were filtered off, washed with cold ethanol, and recrystallized from ethanol. Cumyl hydroperoxide was purified according to [6] and then distilled.

Chlorobenzene and cumene were purified by the standard procedure based on sulfonation of impurities with concentrated sulfuric acid [7, 8]. The CHP concentration was determined by iodometric titration [6] with intermittent sampling.

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

Experiments on initiated oxidation of cumene were performed on a manometric unit [7]. The initiator was AIBN, for which the initiation rate constant at 60°C is 1×10^{-5} l^{-1} mol s^{-1} [9]. The initiator concentration in all the experiments was constant, 2×10^{-2} M, and the concentration of **I–V** was $(1–5) \times 10^{-4}$ M.

CONCLUSIONS

(1) The synthesized 5-ethoxycarbonyl-substituted 3,4-dihydropyrimidin-2(1*H*)-ones (-thiones) and their derivatives exhibit high antioxidant ability.

(2) They efficiently inhibit cumene oxidation and decompose the oxidation product, cumyl hydroperoxide.

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