

Interaction of Some Dihalide Esters with Thiourea

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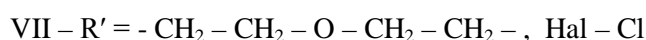
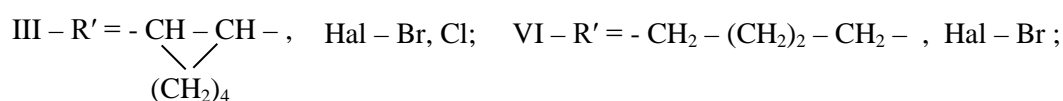
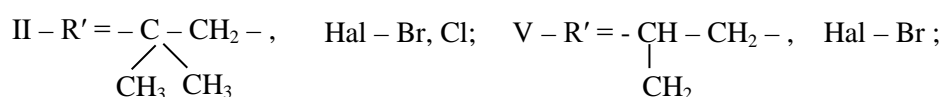
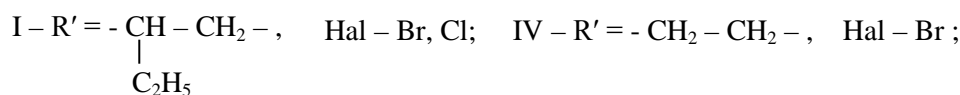
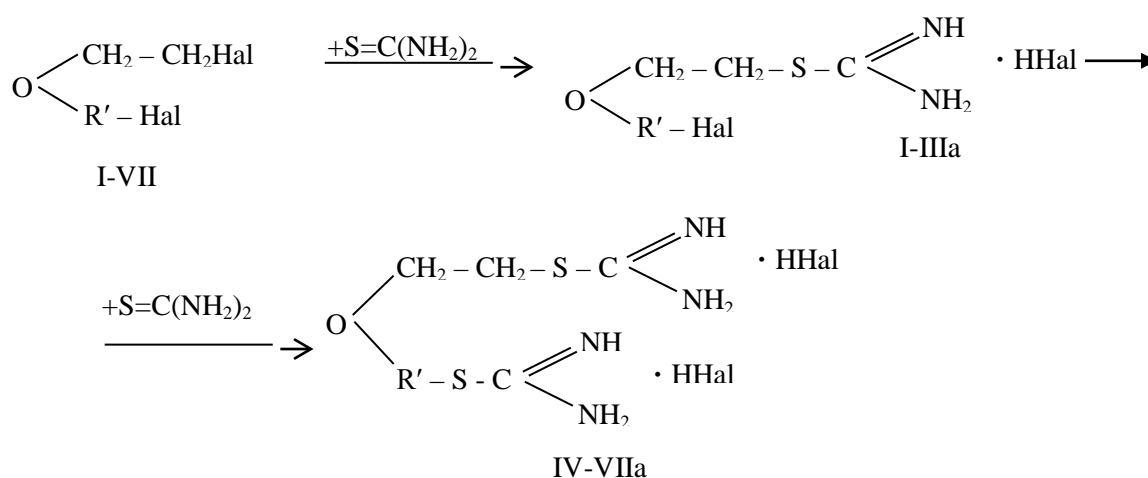
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Abstract: It has been established that depending on a structure of starting esters the mono- or dithiuronic salts are formed due to interaction of a series of dihalide esters with thiourea. Kinetics of interaction of bromex, dimethyl bromex and ethyl bromex has been studied and shown by thin thin-layer radiochromatography that the halogens' substitution occurs at the unsubstituted chain of dihalide esters. The corresponding oxathiols are obtained by the alkaline breaking of the thiuronic salts.

Key words: dihalide esters; thiourea.; alkyl bromexes; oxathiols.

Smart synthesis procedures to obtain dihalide esters were previously described, and their reactions with some nucleophilic agents were studied [1- 3].

Investigation of the interaction of these compounds with thiourea was undertaken to elucidate an influence of ester structure on composition and rate of formation for reaction products and further studying biological properties of new thiuronic compounds. All reactions were carried out in ethanol at 78°C and proceed according to the following plausible scheme:



When Esters I-III are introduced in the reaction zone the mono-thiuronic derivatives are formed that indicate an importance of steric factors at the nucleophilic substitution of bromine atom. While in the case of esters IVa - VIIa di-thiuronic derivatives are preferably obtained

The interaction of esters I with thiourea (^{35}S) taken in equimolar ratios ($C_0 = 0.1\text{M}$) has been studied by thin layer radiochromatography to determine a composition mixture and reaction rate depending on the structure of starting esters and reaction time.

Results shown in Table.1 are giving a quantitative proof that existing steric hindrance makes virtually impossible generation of the di-thiuronic derivatives. If the steric hindrance is absent the gradual increase of concentration of the di-thiuronic derivatives is observed.

Table 1. Quantitative estimation of the reaction mixture composition for an interaction of some dihalogen ethers with thiourea ($C_0 = 0,1\text{M}$, abs. $\text{C}_2\text{H}_5\text{OH}$)

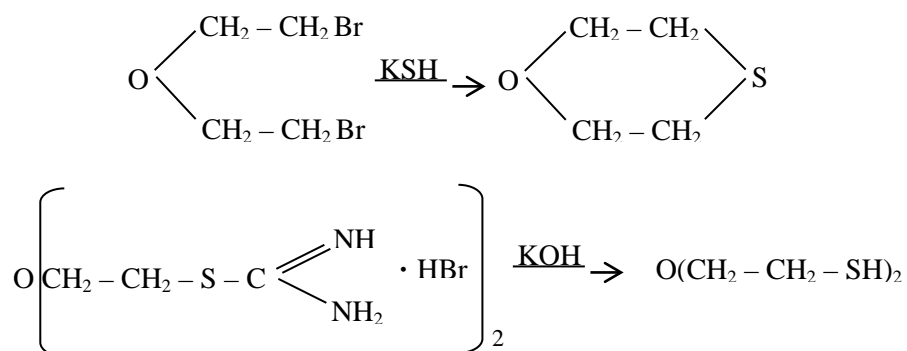
Time, hrs.	Ether $\text{Br}-\text{CH}_2-\text{CH}_2-\text{O}-\underset{\begin{array}{l} \text{R} \\ \text{R}' \end{array}}{\text{C}}-\text{CH}_2-\text{Br}$								
	Ia. $\text{R}=\text{H}, \text{R}'=\text{C}_2\text{H}_5$			Ib. $\text{R}=\text{R}'=\text{CH}_3$			Ic. $\text{R}=\text{R}'=\text{H}$		
	Thiourea (Thu)	Mono-ester (ME)	Diester (DE)	Thiourea	Mono-ester	Diester	Thiourea	Mono-ester	Diester
0.10	96.1	3.5	0.4	95.3	4,2	0,5	94.8	4.6	0.6
0,50	84.1	15.3	0.6	82.2	17.4	0.4	80.6	18.5	0.9
1.10	65.2	34.0	0.8	68.3	30.4	1.3	69.1	29.4	1.5
2.60	42.6	55.9	1.5	47.5	51.4	1.4	47.6	49.9	2.5
4.35	33.1	65.6	1.3	36.4	61.7	1.9	32.8	63.1	4.1
5.85	30.9	67.4	1.7	31.9	66.4	1.7	22.6	69.5	7.9
7.35	29.1	69.3	1.6	30.1	68.6	1.3	12.6	76.7	10.7

The interaction of the ethers with thiourea (^{35}S) at the same condition was studied in the presence of 15^{th} fold excess of di-bromides. Rate constants of the pseudomonomolecular reactions have been calculated on changing thiourea concentration ($C_{\text{OThu}} = 0.1\text{M}$, $C_{\text{OME/DE}} = 1.5\text{M}$, abs. $\text{C}_2\text{H}_5\text{OH}$):

Ia	$\text{R} = \text{R}' = \text{CH}_3$	$0,153 \pm 0,003$
Ib	$\text{R} = \text{H}, \text{R}' = \text{C}_2\text{H}_5$	$0,155 \pm 0,002$
Ic	$\text{R} = \text{R}' = \text{H}$	$0,153 \pm 0,002$

It can be seen that the rate constants are practically coincided that implies that the nucleophilic substitution of bromine takes place at the carbon atoms not having alkyl substituents at α - position.

The synthesized mono- and – dithiuronic derivatives can be used for further obtaining of corresponding thiols under the influence of alcoholic alkali. This reaction is of particular interest since the direct interaction dihalo - alkyl esters with potassium hydrosulfide as a main product are mainly formed corresponding cyclic products - 1 - oxa - 4 – thiocyclohexanes:



EXPERIMENTAL PART

1. ***Di-hydrobromide s,s-3-oxapentane-1,4-diizothiurea (IVa)***. A mixture of 29.6 g (0.39 mol) thiourea and 46.4 g (0.2 mol) bromex in absolute ethanol was heated at reflux for 6 hours. The solution was concentrated in vacuum, the precipitated crystals were filtered, washed acetone and ether and recrystallized from ethanol. Compounds IIa, IIIa, Va, VIa. were synthesized similarly. The yields, properties and results of elemental analysis of the obtained thiuronic salts IIa - VIa are shown in Table. 2.

2. ***Dihydrochloride s,s-3-3,6-dioxaoctane-1,8-diizothiurea (VIIa)***. 13.5 g (0.18 mol) thiourea. was added to a solution 1,8-dichloro-3,6-dioxactane in absolute ethanol. After boiling the mixture for 70 hours it was evaporated in vacuum to dryness and the residue was dissolved in a minimum amount of water. After, an excess of a saturated aqueous solution of picric acid was added and formed picrate was precipitated. The precipitate was filtered off and treated with 20% hydrochloric acid. After filtration picric acid, the solution was evaporated in vacuum and the residue was treated with ether and acetone. In a result a white crystalline compound had been obtained with properties shown in Table. 2.

3. ***3-oxa-1,5-pentandithiol (IVb)***. Solution of 11.2 g (0.2 mol) of KOH in ethanol was added to an alcohol solution of 20.6 g (0.05 mol) dihydrobromide s,s-oxapentane-1.5-diizothiurea. The precipitate of KBr was filtered off, the solution was concentrated in vacuum and distilled under nitrogen, collecting the fraction boiling at 82-84°C / 6 mmHg.

The yields, some properties and elemental analysis results obtained oxathiols IIb, IVb, Vb, VIb are shown in Table. 3.

4. 3-oxa-1-bromo-2-ethylpentantiol (Ib). 4.56 g (0.06 mol) thiourea was added to 12 g (0.06 mol) of 3-oxa-1,5-dibromo-2-ethylpentane in ethyl alcohol, and the mixture was heated for 20 hours. Upon completion of the reaction (absence of thiourea band in the chromatogram) solution was evaporated, and a solution of 6.7 g (0.12mol) of KOH in 20 ml of ethanol. Was added to the residue. After separating the sediments of KBr, the solution was concentrated in vacuum, saturated with NaCl and extracted with thiol-ether. The extract was dried, the solvent was removed and the residue was distilled under nitrogen, collecting the fraction boiling at 84-85 °C / 2 mmHg.

The properties and elemental analysis of the resulting product are shown in Table.3. Similarly, the corresponding thiol Ib was obtained from 3-oxa-1,5-dichloro-2-ethylpentane.

5. Chromatographic control and conducting of radiochromatographic research. Quality control of the reaction mixture composition was carried out by thin layer chromatography on the plates Silufol. The plates were developed in the chosen system, and the fixation of products was carried out by Grotto reagent [5]. For the radiochromatographic research 0.1M of thiourea (³⁵S) in absolute ethanol was used. Radioactivity was measured by using a scintillation counter, Mark-II (Nuclear-Chirago, USA) with 90% efficiency of accounting for ³⁵S_m.

In order to prepare scintillation fluid 5g of 2,5-diphenyloxazole (PPO) and 0.1g of 1,4-di (2,5-phenyl) oxazalybenzene (POPOP) was dissolved in 1 liter of scintillation toluene.

The reaction rate constant was determined from the known Equation for calculating the reaction rate constant of the first order $k = \frac{1}{t} \ln \frac{\alpha}{\alpha - x}$, where α - initial concentration of thiourea, $\alpha(\alpha-x)$ - concentration at an instant time t.

For specific calculation the Equation may be converted to:

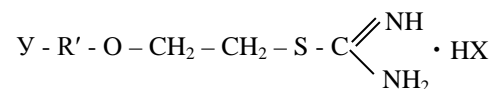
$$k = \frac{1}{t} 2,31g \frac{1}{\nu TM}$$

The purity of isolated thiols was monitored by gas-liquid chromatography using 7A - LCM apparatus; detector - katharometer, 200⁰C , column of 6 m length of 6mm diameter; filler was apiezon- L, deposited on an inert support TND-TC-M , the carrier gas was hydrogen.

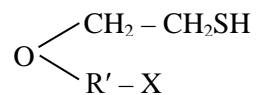
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Table 2. Products of interaction of dihalide esters with thiourea


Compound	R'	X	Y	Yield, %	Melting point, °C	Elemental analysis, found/calculated			
						C	H	Hal	S
Hydrobromide S-3-oxo-1-bromine-2,2-dimethylpentan-5-isothiourea	$\begin{array}{c} -C-CH_2- \\ \quad \\ CH_3 \quad CH_3 \end{array}$	Br	Br	91	143-144	$\frac{22,32}{22,70}$	$\frac{4,58}{4,91}$	$\frac{49,32}{49,08}$	$\frac{9,98}{9,52}$
Hydrobromide S-2-(2-isothiourea etoxy)-1-bromocyclohexane	$\begin{array}{c} -CH-CH- \\ \\ (CH_2)_4 \end{array}$	Br	Br	84	138-140	$\frac{29,14}{29,56}$	$\frac{5,21}{4,97}$	$\frac{44,67}{44,19}$	$\frac{9,01}{8,84}$
Hydrobromide S, S -3-oxa-pentan-1,5-diisothiourea	$-CH_2 - CH_2 -$	Br	$-S - C \begin{array}{l} \text{NH} \\ \text{NH}_2 \end{array} \cdot HBr$	73	153-155	$\frac{19,24}{18,75}$	$\frac{4,52}{4,16}$	$\frac{40,88}{41,66}$	$\frac{16,23}{16,66}$
Hydrobromide S, S -3-oxa-pentan-2-methyl-1,5-diisothiourea	$\begin{array}{c} -CH-CH_2- \\ \\ CH_3 \end{array}$	Br	$-S - C \begin{array}{l} \text{NH} \\ \text{NH}_2 \end{array} \cdot HBr$	65	91-93	$\frac{18,84}{19,07}$	$\frac{4,27}{4,64}$	$\frac{41,52}{21,24}$	$\frac{16,14}{16,08}$
Hydrobromide S, S -3-oxa-heptan-1,5-diisothiourea	$-CH_2 - (CH_2)_2 - CH_2 -$	Br	$-S - C \begin{array}{l} \text{NH} \\ \text{NH}_2 \end{array} \cdot HBr$	68	105-107	$\frac{23,11}{23,30}$	$\frac{4,98}{4,86}$	$\frac{39,12}{38,83}$	$\frac{15,01}{15,56}$
Hydrobromide S, S -3,6-dioxa-octan-1,8-diisothiourea	$-CH_2 - CH_2 - O - CH_2 - CH_2 -$	Cl	$-S - C \begin{array}{l} \text{NH} \\ \text{NH}_2 \end{array} \cdot HCl$	51	107-110	$\frac{28,16}{28,01}$	$\frac{6,01}{5,90}$	$\frac{20,56}{20,94}$	$\frac{18,36}{18,88}$


Table 3. The synthesized oxathiols

Compound	R	X	Yield, %	Boiling temperature, °C	n_D^{20}	d_4^{20}	Elemental analysis, found/calculated.			
							C	H	Hal	S
3-oxa-1-bromo-2-ethyl-5-pentanthiol	$\begin{array}{c} -\text{CH}-\text{CH}_2- \\ \\ \text{C}_2\text{H}_5 \end{array}$	Br	58	84-85/ 2 mmHg	1.5005	1.3614	$\frac{34,21}{33,80}$	$\frac{5,72}{6,10}$	$\frac{37,38}{37,56}$	$\frac{14,91}{15,02}$
3-oxa-1-chloro-2-ethyl-5-pentanthiol	$\begin{array}{c} -\text{CH}-\text{CH}_2- \\ \\ \text{C}_2\text{H}_5 \end{array}$	Cl	51	78-80 4 mmHg	1.4755	1.0756	$\frac{43,15}{42,86}$	$\frac{8,05}{7,74}$	$\frac{20,57}{20,83}$	$\frac{19,25}{19,05}$
3-oxa-1-bromo-2,2-dimethyl-5-pentanthiol	$\begin{array}{c} -\text{C}-\text{CH}_2- \\ / \quad \backslash \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$	Br	62	76-78 4 mmHg	1.5036	1.3530	$\frac{33,97}{33,80}$	$\frac{5,89}{6,10}$	$\frac{37,31}{37,56}$	$\frac{15,31}{15,02}$
3-oxa-1,5-pentandithiol	$-\text{CH}_2-\text{CH}-$	SH	52	82-84 6 mmHg	1.5205	1.1040	$\frac{35,16}{34,77}$	$\frac{6,96}{7,25}$	-	$\frac{46,12}{46,38}$
3-oxa-2-methyl-1,5-pentandithiol	$\begin{array}{c} -\text{CH}-\text{CH}_2- \\ \\ \text{CH}_3 \end{array}$	SH	60	71-72 2 mmHg	1.5085	1.0688	$\frac{39,11}{39,48}$	$\frac{7,53}{7,89}$	-	$\frac{41,86}{42,11}$
3-oxa-1,7-heptandithiol	$-\text{CH}_2-(\text{CH}_2)_2-\text{CH}_2-$	SH	44	102-104 5 mmHg	1.5075	1.0442	$\frac{43,04}{43,37}$	$\frac{8,22}{8,43}$	-	$\frac{38,16}{38,55}$