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REACTIONS OF 1,3-ISOTHIOCYANATO KETONES WITH MINERAL ACIDS. SYNTHESIS OF 3,4-DIHYDRO-2H,1,3-THIAZIN-2-ONES

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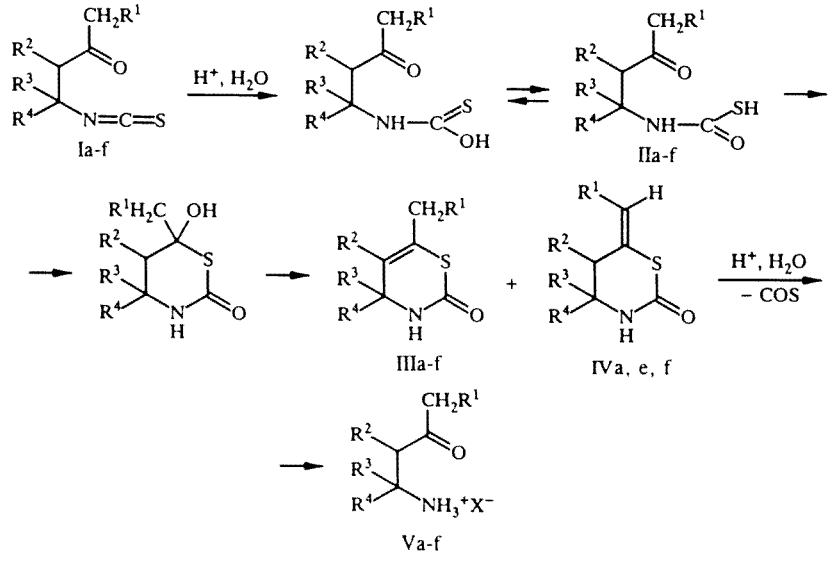
Reactions of 1,3-isothiocyanato ketones with mineral acids formed 3,4-dihydro-2H,1,3-thiazin-2-ones or their mixtures with 6-alkylidenetetrahydro-1,3-thiazin-2-ones. Subsequent acid hydrolysis of the thiazines obtained formed salts of 1,3-amino ketones. The direction and extent of the transformation depend on the nature of the acid, reaction temperature, and structure of the 1,3-isothiocyanato ketones.

It is well known that 1,2- and 1,3-isocyanato ketones undergo cyclization, spontaneously or in the presence of acid catalysts, to 4-oxazolin-2-ones [1] and 3,4-dihydro-2H-1,3-oxazin-2-ones [2], respectively. Similarly, 1,2-isothiocyanato ketones undergo cyclization to 4-oxazoline-2-thiones [3]. As for the intramolecular cyclization of 1,3-isothiocyanato ketones, the data reported in the literature are contradictory. It was reported in [2] that 4,4,6-trimethyl-3,4-dihydro-2H-1,3-oxazine-2-thione can be obtained by heating the corresponding 1,3-isothiocyanato ketone. At the same time, it is known that heating of 1,3-isothiocyanato ketones with hydrochloric acid forms hydrochlorides of the corresponding 1,3-amino ketones [4, 5]. Therefore, the reaction of 1,3-isothiocyanato ketones with mineral acids requires further study.

It was reasonable to assume that in the hydrolysis of 1,3-isothiocyanato ketones (Ia-f) to 1,3-amino ketones, the intermediate



I—V a $R^3 - R^4 - CH_3$, $R^1 - R^2 - H$; b $R^1 - H$, $R^2 - R^3 - R^4 - CH_3$; c $R^2 - R^3 - CH_3$, $R^1 - R^4 - H$; d $R^2, R^3 - (CH_2)_4$, $R^1 - R^4 - H$; e $R^1, R^2 - (CH_2)_3$, $R^3, R^4 - (CH_2)_5$; f $R^1, R^2 - (CH_2)_3$, $R^3 - R^4 - CH_3$

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TABLE 1. Quantitative Ratio of Products of the Reaction of 1,3-Isothiocyanato Ketones Ia-f with Acids

IIIa/IVa	IIIb / IVb	IIIc / IVc	IIId / IVd	IIIe / IVe	IIIf / IVf
85/15	100/0	100/0	100/0	70/30	85/15

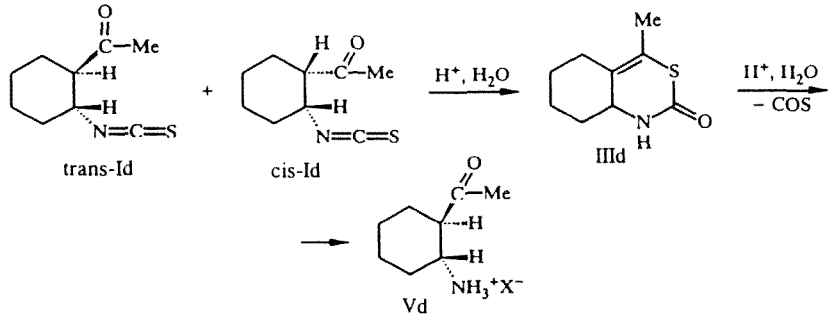
products would be N-3-oxoalkylthiocarbamic acids IIa-f, capable of undergoing cyclization to 6-hydroxytetrahydro-1,3-thiazin-2-ones, which under the reaction conditions can undergo dehydration, forming 3,4-dihydro-1,3-thiazin-2-ones IIIa-f. Analogous transformations are known for N-3-oxoalkyldithiocarbamic acids [6, 7].

To confirm this course of the reaction, we studied the reactions of 1,3-isothiocyanato ketones Ia-e with concentrated sulfuric acid at temperatures of (−10)-25°C, and Ie,f with hydrochloric acid at 20-25°C. The products of these reactions were found to be the previously unknown 3,4-dihydro-2H-1,3-thiazin-2-ones IIIa-f [8].

Compounds IIIb-d, which in the 5 position contain an alkyl group that stabilizes the double bond in the heterocyclic ring, are formed in the pure state. Compound IIIa, which does not contain an alkyl substituent in the 5 position, and compound IIIe,f, which has a fused carbon ring in the 5, 6 positions, are formed in a mixture with 1,3-thiazines isomeric with them, with an exocyclic double bond, IVa, e, f (Table 1).

Under the conditions of hydrolysis of isothiocyanato ketones [4, 5], with heating in the presence of hydrochloric acid, compounds IIIa-e and IVa, e, f form the corresponding hydrochlorides of 1,3-amino ketones Va-f [4, 5] in quantitative yields.

Acid hydrolysis of the mixture of the diastereoisomers of isothiocyanato ketone Id (cis/trans, 2/3) results in the formation of 2-amino-1-acetylcyclohexane hydrochloride Vd, which has the trans configuration exclusively. In [5], this fact was explained by the reversibility of the reaction between the thiocyanic acid and α,β-unsaturated ketone which are produced during the hydrolysis, with the formation of a more stable trans isomer of isothiocyanato ketone Id, which then converted into the salt of trans-2-amino-1-acetylcyclohexane Vd. In light of the new data, this fact can be explained by the intermediate formation, from the mixture of diastereoisomers Id, of 3,4-dihydro-1,3-thiazin-2-one IIId, accompanied by the loss of the chirality of the carbon atom in the α position with respect to the carbonyl group of compound Id. Subsequent hydrolysis of IIId leads to the formation of a more stable trans isomer of Vd.



The transformation of the diastereomeric mixture of acyclic isothiocyanato ketones Ic as well as of the corresponding thiazines IIIc to amino ketones Vc (erythro/threo, 2.3) is practically devoid of regioselectivity (Table 3).

The structure of the synthesized compounds was confirmed by data on their IR, ^1H and ^{13}C NMR spectra and ultimate analysis (Table 2). The IR spectrum of compounds IIIa-e at 1630-1655 cm^{-1} contains an absorption band characteristic of the NHC=O group of thiocarbamate. In the ^{13}C NMR spectrum of compound IIIa, b, d, e and IVa, e, the most characteristic signals are those of the carbon nuclei of the C=O group at 165.3-167.4 ppm and of the sp^2 hybridized carbon atoms of the double bond at 111.2-130.1 ppm.

The study thus leads to the conclusion that the reaction of 1,3-isothiocyanato ketones with mineral acids may occur via the stage of formation of 3,4-dihydro-1,3-thiazin-2-ones, the subsequent acid hydrolysis of which forms salts of 1,3-amino ketones, and the diastereoselectivity of the reaction being evidently controlled at this stage. The direction of the reaction and its extent depend on the acid employed, reaction temperature, and structure of the initial 1,3-isothiocyanato ketone.

TABLE 2. Characteristics of Products (IIIa-f) Formed in Reactions of 1,3-Isothiocyanato Ketones Ia-f with Acids*

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (solvent)	IR spectrum, ν, cm^{-1}			Yield, %
		C	H	N	S		NHCO	C=C	NH	
IIIa	$C_7H_{11}NOS$	53.24 53,47	6.89 7,05	–	20.24 20,39	106...107 (hexane-$CHCl_3$)	1650	1670	3160	54,1 (from NMR data)
IIIb	$C_8H_{13}NOS$	56.40 56,11	7.49 7,65	–	18.62 18,72	157...158 (EtOH)	1630	1660	3160	73,3
IIIc	$C_7H_{11}NOS$	53.36 53,47	7.01 7,05	8.78 8,91	–	87...88 (hexane-$CHCl_3$)	1630	1660	3170	74,9
IIId	$C_9H_{13}NOS$	58.93 58,98	7.11 7,15	7.54 7,64	–	163...164 (EtOH)	1640	1670	3170	80,0
IIIe	$C_{13}H_{19}NOS$	65.98 65,78	7.88 8.07	–	13,10 13,51	193...194 (EtOH)	1650	1670	3190	56,0 (from NMR data)
IIIf	$C_{10}H_5NOS$	61.14 60,88	7.78 7,66	–	16.39 16,25	180...182 (*i*-PrOH)	1655	1670	3190	79,7 (from NMR data)

*Reaction conditions: IIIa) 16 ml 96% H_2SO_4, −5...−10°C; IIIb) 7 ml 96% H_2SO_4, 20...25°C; IIIc, d) 17 ml 96% H_2SO_4, 20...25°C; IIIe) 19 ml 96% H_2SO_4, −5...−10°C or 19 ml 36% HCl, 20...25°C (yield 56.6%); IIIf) 19 ml 36% HCl, 20...25°C.

TABLE 3. Proton Chemical Shifts of Compounds IIIa-f, IVa, e, f

Compound	C^6-R	C^5-R	C^3-R	C^4-R	NH
	$(-CH_2-)_n$				
IIIa	1,94	5,44	1,37	1,37	6,5
IIIb	1,81	1,68	1,30	1,30	7,1
IIIc	1,91	1,82	1,34	3,92	7,1
IIId	1,81	(2,75, 2,15...1,10)		4,03	6,4
IIIe	(2,08...1,10)				6,1
IIIf	(2,12...1,60)		1,34	1,33	6,9
IVa	5,12...5,15	1,46...1,48	1,29	1,29	
IVe	5,76	2,50			6,2
	(2,08...1,10)				
IVf	5,78	2,50	1,26	1,17	7,0
	(2,12...1,60)				

TABLE 4. PMR Spectra of Compounds Vc, d

Compound	C^1—CH_3	C^2—H	C^2—R	C^3—R	C^3—H	$(^3J_{2\text{-H},3\text{-H}})$
		$(^3J_{2\text{-H},2\text{-R}})$		$(^3J_{3\text{-H},3\text{-R}})$		
Vc*	2,25	2,92	1,27	1,32	3,60	
erythro		(7,5)		(6,8)		(5,3)
Vc	2,26	2,94	1,25	1,32	3,58	
threo		(7,2)		(6,8)		(7,2)
Vd	2,24	2,73	2,3...1,1		3,39	
trans		(3,5; 11,3)		(3,6; 11,3)		(11,3)

*The signal ratio is based on the PMR spectrum of tetrahydro-1,3-oxazin-2-one, obtained from Vc by the method of [10].

TABLE 5. Chemical Shifts of ^{13}C Nuclei of Compounds IIIa, b, d, e and IVa, e

Compound	C^2	C^4	C^5	C^6	4-R	4-R	5-R	6-R (C^6-C)
IIIa	165,7	55,4	122,6	126,4	28,4	28,4	—	20,9
IIIb	166,5	56,2	118,8	127,2	27,0	27,0	13,9	18,4
IIId	167,4	60,9	117,7	127,2	39,2, 31,5, 29,2, 27,1, 19,9			
IIIe	166,2	58,8	123,3	130,1	32,1, 32,1, 29,2, 25,2, 24,5, 22,4, 21,9, 20,5, 20,5			
IVa	165,7	57,8	40,2	122,6	28,1	18,0	—	(123,2)
IVe	165,3	56,6	45,1	128,9	33,2, 28,3, 25,4, 24,8, 24,4, 21,7, 20,3, 18,0			(123,7)

EXPERIMENTAL

Isothiocyanato ketones Ia-e are obtained by the method of [4, 9].

3,4-Dihydro-2H-1,3-thiazin-2-ones (IIIa-f). To a specified amount of acid is added, dropwise with stirring and cooling, 0.01 mole of 1,3-isothiocyanato ketone Ia-e. The reaction mixture is stirred at a specified temperature (Table 2) for 1 h, then poured into 100 g of crushed ice and extracted with chloroform (3 × 50 ml). The combined extract is washed with water until the wash waters give a neutral reaction, dried with anhydrous magnesium sulfate, the chloroform is distilled off, and the residue is recrystallized.

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