

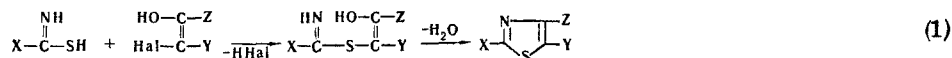
MECHANISM OF THE FORMATION OF 2-AMINOTHIAZOLE
IN THE REACTION OF CHLOROACETALDEHYDE
WITH THIOUREA *

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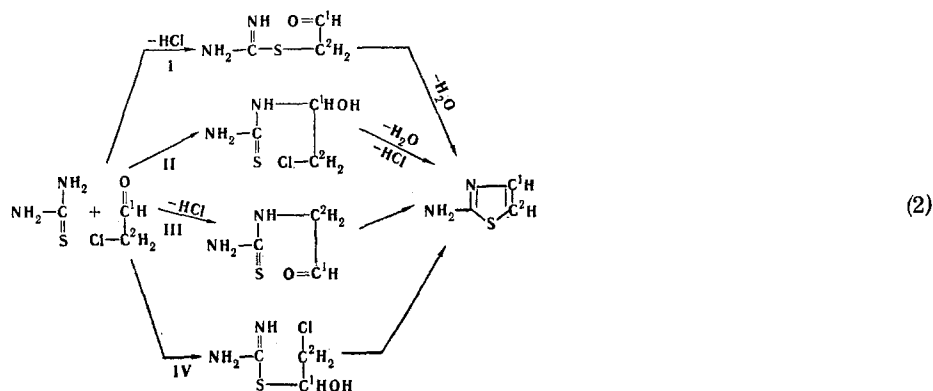
The kinetics of the reaction of chloroacetaldehyde with thiourea in water at the C=O and C-Cl bonds were studied. The first step of the formation of the 2-aminothiazole is the reaction of the NH₂ group of thiourea with the C=O group of chloroacetaldehyde. Hydrogen chloride evolution and the formation of a thiazole ring are secondary processes that occur simultaneously.

It is generally accepted that the first step in the Hantzsch-Traumann reaction [1] of α -halocarbonyl compounds with thioamides consists in condensation with the formation of a C-S bond through HHal evolution, and the second step reduces to ring closure of the enol form of the carbonyl compound, which is accompanied by the cleavage of water (see, for example, [2]):



A similar scheme is also acknowledged for the formation of 2-aminothiazoles [3]. Moreover, it is assumed that the thiourea reacts as the iso form, although the existence of isothiurea has not been proved. The results of our investigations do not agree with the proposed reaction scheme (1).

In principle, it is possible that the reaction proceeds via one of the following schemes:



From the available data regarding the synthesis of thiazole derivatives by the condensation of thioamides with α -halocarbonyl compounds (see, for example [6-20]) it follows that, in all cases, the C-S and C-NH₂ groups of the thioamides react with the C-Cl and C=O groups of the halocarbonyl compounds, respectively, i.e., paths III and IV in scheme (2) are less likely than paths I and II.

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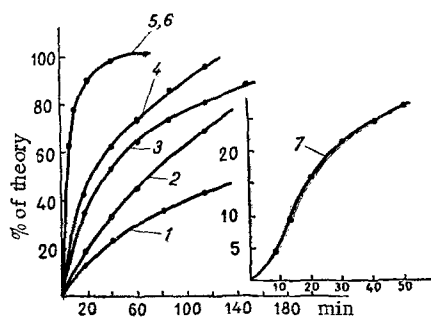


Fig. 1. Kinetics of the reaction of chloroacetaldehyde with thiourea at a molar ratio of 1 : 1 in water at various temperatures: 1,3,5) yield of aminothiazole (with respect to bonded hydrochloric acid); 2,4,6,7) consumption of chloroacetaldehyde with respect to the C = O group; 1,2) at 0°; 3,4) at 40°; 5,6) at 70°; 7) at -5°.

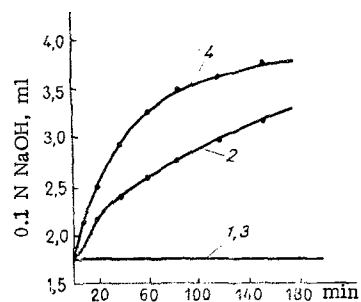


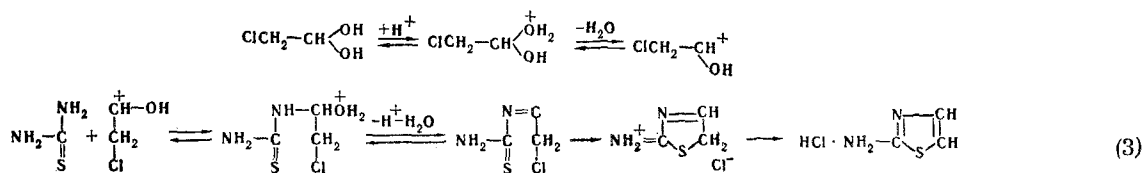
Fig. 2. Kinetics of the formation of HCl in the reaction of chloroacetaldehyde with thiourea (1 : 1) in the presence of free HCl: 1,3) consumption of 0.1 N NaOH in the titration of free HCl; 2,4) the same for the total amount of HCl; 1,2) at 0°; 3,4) at 30°.

In order to choose between I and II, we investigated the kinetics of the reaction of thiourea and chloroacetaldehyde in water at various temperatures. The reaction was followed from the decrease in the percentage of carbonyl groups (by means of dinitrophenylhydrazine) and the formation of 2-aminothiazole (with respect to the hydrochloric acid bonded to the aminothiazole by titration with alkali using phenolphthalein and methyl orange). It is apparent from Fig. 1 that in water at 0° at an equimolar ratio of the ingredients the decrease in the percentage of carbonyl group leads the production of Cl ions and the formation of 2-aminothiazole. At 40°, the difference in the rates of these processes becomes less, and no difference at all is noted at 70-80°.

Data on the change in the amount of hydrochloric acid in the reaction, into which hydrochloric acid was introduced before the process began, are presented in Fig. 2. It is apparent that the total amount of acid increases with time, while the amount of free acid remains constant. Consequently, HCl evolution and the formation of the 2-aminothiazole bonded to it occurs simultaneously. This provides a basis for supposing that the formation of the thiazole ring is actually a two-step process; in the first step chloroacetaldehyde reacts with thiourea at the C = O group, and in the second step the aldehyde reacts with thiourea at the CH₂Cl group; in the process, the ring is closed, and the amine, bonded to the evolved hydrogen chloride, is formed.

It is known [4] that alkyl halides react with thiourea to form S-alkylthiuronium salts, which are converted to bases by the action of alkalis.

The kinetic curve of the consumption of chloroacetaldehyde with respect to the C = O group (Fig. 1, curve 7) is S-shaped, which is characteristic for autocatalytic processes. The induction period of the reaction is eliminated when acid is added. The reaction of the carbonyl group of chloroacetaldehyde is apparently catalyzed by acid, as was noted also in other cases of the reaction of chloroacetaldehyde at the carbonyl group in polar solvents and in water, with which it forms hydrates [5]. 2-Aminothiazole is not formed in alkaline media, and chloroacetaldehyde undergoes aldol condensation. This once more confirms that the primary process is reaction at the C = O group of chloroacetaldehyde. Thus, path II of scheme (2) can be considered to be more likely than path I, and the mechanism of the formation of 2-aminothiazole in water can be represented by the following sequence of reactions:



On reaction with the acetals of bromoacetaldehyde and α,β -dibromoethyl ether in alkali, 2-mercaptoimidazole primarily forms products involving reaction at the S-H and C-Br bonds with subsequent closing

of the thiazole ring and water evolution [3]. Consequently, two paths for the formation of thiazole rings via the Hantzsch-Traumann reaction are possible. The first path involves primary reaction at the C-S bond of the thioamide compound and the C-Hal bond of the α -halocarbonyl compound. To realize this path it is necessary that the thioamide compound be in the mercapto form and that the activity of the C=O group of the carbonyl compound be reduced, for example, by acetylation. The process is realized in alkaline media.

The second path involves primary reaction at the C-NH₂ group of the thioamide and at the C=O group of the carbonyl compound and is realized in acidic media, in which the thioamide exists in the keto form, and the C=O group of the carbonyl compound is active.

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