

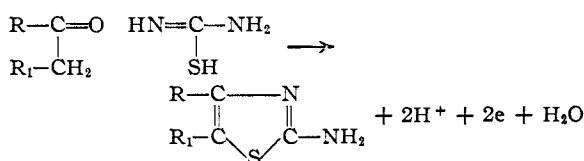
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

## The Reaction of Acetophenone with Thiourea and Oxidizing Agents

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In a recent paper from this Laboratory it was demonstrated that thiourea reacts with a ketone and a halogen to form a substituted 2-aminothiazole.<sup>1</sup> Since 2-aminothiazoles have previously been made by the reaction of thiourea with  $\alpha$ -haloketones,<sup>2</sup> it is of interest to determine whether the formation of the  $\alpha$ -haloketone is a necessary intermediate in the present synthesis, or if the function of the halogen is simply that of an oxidizing agent.

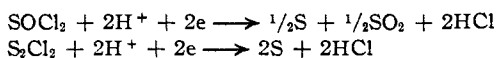
In accordance with the latter possibility, the formation of a 2-aminothiazole from a ketone and thiourea can be written as:



A reagent which would accept two electrons per molecule of 2-aminothiazole formed should be capable of effecting the reaction.

In order to test this possibility, mixtures of thiourea and acetophenone were treated with a variety of oxidizing agents, namely, sulfuryl chloride, chlorosulfonic acid, thionyl chloride, sulfur monochloride, sulfur trioxide, sulfuric acid, nitric acid, and sulfur. In each case a considerable quantity of 2-amino-4-phenylthiazole was obtained (Table I). Since some of the above reagents could not possibly produce an intermediary  $\alpha$ -haloketone, it is evident that the formation of a thiazole from a ketone and thiourea can be accomplished by an oxidative process.

In each of the reactions carried out a quantity of sulfur was observed among the by-products. With the exception of reaction 7<sup>3</sup> in which nitric acid was used as an oxidizing agent, this sulfur could have been formed either from the reduction of the oxidizing agent or from oxidation of thiourea. When sulfuryl chloride (reaction 1) or when chlorosulfonic acid (reaction 2) was used as the oxidizing agent, very little sulfur was formed and the yield of thiazole was good. When thionyl chloride (reactions 3a and 3b) or when sulfur monochloride (reaction 4) was used as the oxidizing agent, a large quantity of sulfur was obtained and a good yield of thiazole was also observed. In these cases, most of the sulfur was probably produced by reduction of the oxidizing agent as follows



- (1) R. M. Dodson and L. C. King, *THIS JOURNAL*, **67**, 2242 (1945).  
 (2) V. Traumann, *Ann.*, **249**, 31 (1888).  
 (3) For identification of reactions see Table I.

When sulfur trioxide (reaction 5), sulfuric acid (reaction 6) or nitric acid (reaction 7) was used as the oxidizing agent, an appreciable amount of sulfur was formed in each reaction, and in each case the yield of 2-amino-4-phenylthiazole was lower than that obtained with the first four oxidizing agents. In these cases, it appears that two competing reactions are taking place: (1) The reaction of acetophenone with thiourea and the oxidizing agent to form the thiazole, and (2) the direct oxidation of thiourea to form sulfur. This mutual destruction of thiourea and the oxidizing agent could account for the lower yields of 2-amino-4-phenylthiazole obtained in reactions 5, 6, and 7.

TABLE I  
SUMMARY OF REACTIONS<sup>a</sup>

Reaction number	Oxidizing agent	Oxidizing agent, mole	Products			
			2-Amino-4-phenylthiazole g.	% <sup>b</sup>	Sulfur, g.	Other substances observed
1	SO <sub>2</sub> Cl <sub>2</sub>	0.2	28.5	81	0.5	SO <sub>2</sub> , H <sub>2</sub> O, HCl
2	HSO <sub>3</sub> Cl	.2	22	63	0.5	SO <sub>2</sub> , H <sub>2</sub> O, HCl
3(a)	SOCl <sub>2</sub>	.2	23	63	3.7	SO <sub>2</sub> , H <sub>2</sub> O, HCl
3(b)	SOCl <sub>2</sub>	.1	15.5	88 <sup>c</sup>	2.2	SO <sub>2</sub> , H <sub>2</sub> O, HCl
4	S <sub>2</sub> Cl <sub>2</sub>	.2	27	76	12	H <sub>2</sub> O, HCl
5	SO <sub>3</sub>	.2	11.5	32	5	SO <sub>2</sub> , H <sub>2</sub> O
6	H <sub>2</sub> SO <sub>4</sub>	.2	15	43	7	SO <sub>2</sub> , H <sub>2</sub> O
7	HNO <sub>3</sub> (60%)	(excess)	4	11	2	Oxides of nitrogen
8	S	.2	0.25	0.7	..	....

<sup>a</sup> In each reaction 0.2 mole of acetophenone and 0.4 mole of thiourea were used. <sup>b</sup> Yield based on ketone or oxidizing agent. <sup>c</sup> Yield based on oxidizing agent only.

## Experimental

In each case the reaction was carried out as follows: Two-tenths mole of acetophenone and 0.4 mole of thiourea were treated with the indicated amount of the oxidizing agent, and the reaction mixture heated overnight on the steam-bath. The 2-amino-4-phenylthiazole and sulfur were recovered as previously described.<sup>1</sup> The thiazole obtained was compared directly with the 2-amino-4-phenylthiazole produced previously in this laboratory.<sup>1</sup> When elementary sulfur was used as the oxidizing agent the reaction mixture was refluxed in Dowtherm.<sup>4</sup>

## Summary

It has been demonstrated that acetophenone and thiourea react with a variety of oxidizing agents to form 2-amino-4-phenylthiazole, and that an  $\alpha$ -haloketone is not a necessary intermediate in the reaction.

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(4) A commercial mixture of diphenyl ether and biphenyl, b. p. ca. 240°.