RECYCLIZATION REACTIONS OF HETEROCYCLES. XVIII*. SYNTHESIS AND RECYCLIZATION OF THIAZOLIUM AND BENZOTHIAZOLIUM SALTS

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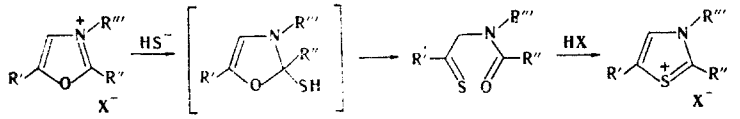
A number of thiazolium salts were obtained, and their reaction with hydrazine was studied. On reaction with hydrazine the aryl-substituted thiazolium salts are recyclized to dihydro-1,2,4-triazines, whereas on reaction with monoalkylhydrazines they are converted to 4H,5H-1,2-4-triazinium salts; thiazolium salts are converted to hydrazidohydrazones on reaction with phenylhydrazine. Recyclization to the dihydro-sym-tetrazine system was observed for 2-phenyl-substituted benzothiazolium tosylate.

N-alkyl-substituted thiazolium salts can be synthesized by reaction of alkylating agents with thiazole derivatives [2]. However, this method is not efficient if the basicity of the thiazole ring is reduced by the presence of electron-acceptor substituents. In addition, there are no gentle methods for the synthesis of N-aryl-substituted thiazolium salts.

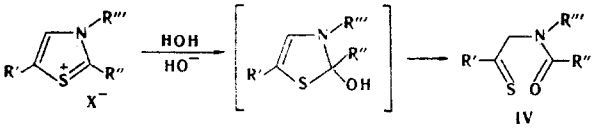
It is known that pyrylium [3] and 1,3,4-oxadiazolium [4] salts are recyclized to the corresponding thia analogs by the action of sulfide ion and subsequent acid treatment of the intermediate. We used this principle for the preparation of thiazolium salts III from oxazolium salts I, which are quite easily obtainable substances [5]:



I II III

The thiolysis of oxazolium perchlorates I proceeds readily under the influence of hydrogen sulfide in a mixture of alcohol and acetone in the presence of an organic base (for example, triethylamine). The conversion of oxazolium tosylates I to thioamido ketones II can also be realized in aqueous solutions of sodium hydrosulfide. Thioamido ketone II is treated with perchloric acid in an acetic acid medium, and thiazolium salt III is obtained in almost quantitative yield. Thiazolium salts containing alkyl or aryl substituents attached to the nitrogen atom of the heteroring can be obtained by this method.

The structure of thiolysis products II makes it possible to assume that nucleophilic attack for the diaryloxazolium salts takes place in the 2 position of the heteryl cation. Alkaline hydrolysis of the thiazolium salts leads to isomeric thioamido ketones IV:



IV

*See [1] for communication XVII.

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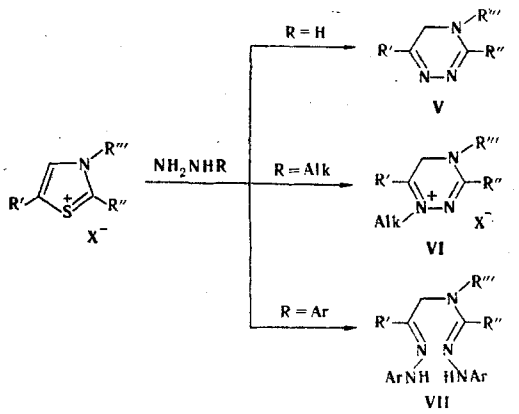
Thus nucleophilic reactions take place in the 2 position of the heteroring in the case of both oxazolium and thiazolium salts.

Recyclization reactions of the thiazole ring under the influence of hydrazines have not been described. It is known [6] that 2-methylmercapto-substituted thiazolium salts in excess hydrazine undergo only substitution of the mercapto group by a hydrazine residue without disruption of the ring. According to our observations, the starting thiazole is recovered when diarylthiazoles are refluxed (for ∿ 2 h) with hydrazine in alcohol. Reactions involving recyclization to triazole [7] and triazine [8,9] systems are known for the hydrogenated thiazole ring containing heteroatomic substituents. In one case we have shown [10] that the thiazole ring, like the oxazole ring, in the cationic state is capable of undergoing recyclization to dihydrotriazine system V under the influence of hydrazine. This reaction is actually a more general reaction, at least for arylthiazolium salts (see Table 1). Dihydro-1,2,4-triazinium salts VI are formed under the influence of monoalkylhydrazines:



The reaction proceeds rapidly (in a few minutes) in alcohol in the presence of a molar excess of hydrazine or in a hydrazine medium and is accompanied by hydrogen sulfide evolution and the formation of colorless (in the case of monoalkylhydrazines) or yellow-orange (in the case of unsubstituted hydrazine) triazine derivatives.

The yields of triazines in the recyclization of thiazolium salts with hydrazine hydrate are lower than in the case of methylhydrazine and in the case of hydrazination of oxazolium salts.

As in the case of the related oxazolium salts [5], only dihydrazinated product VII was obtained by the action of phenylhydrazine on thiazolium salt I.

It may be assumed that the mechanisms of the cyclotransformations in the hydrazination of thiazolium and oxazolium salts are extremely similar (we previously examined the mechanism for the latter in [5]).

The structures of the products of hydrazination of the thiazolium salts were proved by identification with the corresponding compounds obtained by the method in [5].

Annelation of the thiazolium ring has a substantial effect on the direction of recyclization during hydrazination.

According to [6], only replacement of the mercapto group by a hydrazine residue occurs in the hydrazination of 2-mercaptobenzothiazolium salts. However, we have observed that when there is a phenyl substituent in the 2 position of benzothiazolium salt VIII, reaction with hydrazine leads to recyclization to sym-dihydrotetrazine IX with splitting out of o-(methylamino)thiophenol (X) [isolated in the form of the bis-(o-methylaminophenyl)disulfide].

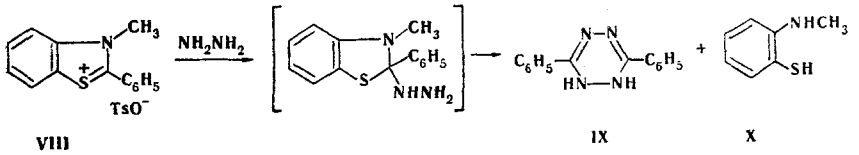
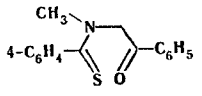
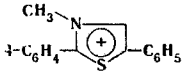


TABLE 1. Thioamido Ketones IIa-e and Thiazolium Perchlorates IIIa-e

Compound	R′	R″	R‴	mp, °C (crystallization solvent)	Found, %				Calc., %				Empirical formula	Yield, %
					C	H	S	Hal	C	H	S	Hal		
II a	C_6H_5	C_6H_5	CH_3	96—97 (ethanol)	71,6	5,8	11,9		71,4	5,5	11,8		$C_6H_{15}NOS$	100
II b	C_6H_5	4-$C_6H_4C_6H_5$	CH_3	186—187 (dec., ethanol)	76,8	5,2	9,3		76,6	5,5	9,2		$C_{22}H_{19}NOS$	100
II c	C_6H_5		CH_3	199—200 (dec., ethanol)	67,5	5,5	13,5		67,8	5,2	13,9		$C_{26}H_{24}N_2O_2S_2$	100
II d	4-C_6H_4Br	C_6H_5	4-$C_6H_4CH_3$	176—178 (methanol)	62,7	4,5	7,4	Br 18,4	62,2	4,5	7,5	Br 18,8	$C_{22}H_{18}BrNOS$	58
II e	C_6H_5	C_6H_5	C_6H_5	128—129 (ethanol)	75,7	5,7	9,8		76,1	5,1	9,7		$C_{21}H_{17}NOS$	51
III a	C_6H_5	C_6H_5	CH_3	172—174 (ethanol	54,2	3,8	8,8	Cl 10,5	54,5	4,0	9,1	Cl 10,2	$C_{16}H_{14}ClNO_4S$	100
III b	C_6H_5	4-$C_6H_4C_6H_5$	CH_3	243—245 (dec., acetic acid)	61,9	4,3	7,5	Cl 8,2	61,7	4,2	7,7	Cl 8,3	$C_{22}H_{18}ClNO_4S$	100
III c	C_6H_5		CH_3	354—357 (dec., nitromethane)	49,9	3,7	10,5	Cl 11,6	49,9	3,5	10,2	Cl 11,4	$C_{26}H_{22}Cl_2N_2O_8S_2$	100
III d	4-C_6H_4Br	C_6H_5	4-$C_6H_4CH_3$	206—207 (methanol)	51,8	3,8	6,2	Br 15,3	52,0	3,4	6,3	Br 15,7	$C_{22}H_{17}BrClNO_4S$	40
III e	C_6H_5	C_6H_5	C_6H_5	225—227 (ethanol)	61,2	3,6	7,9	Cl 8,7	60,9	3,9	7,7	Cl 8,7	$C_{21}H_{16}ClNO_4S$	80

With respect to its mechanism, this reaction is evidently similar to the conversion of 1,3,4-oxadiazolium salts to dihydro-sym-tetrazines [1], which is realized as a result of the reaction of hydrazine only in the 2 position of the heteroring. In this respect, it differs substantially from the recyclization reactions of the nonannelated oxazolium [5] and thiazolium salts described above, in which the carbon atoms corresponding to the 2 and 5 positions of the heteroring participate in the cyclotransformations.

EXPERIMENTAL

Thiolysis of Oxazolium Salts I. A) Sodium hydrosulfide (25 mmole) was added to a suspension of 10 mmole of oxazolium tosylate I in 50 ml of ethanol, and a precipitate formed from the resulting solution after 2-3 min. Water (15-20 ml) was added until the product had precipitated completely, after which the mixture was filtered, and the solid was washed with water and vacuum dried at 50°. The yields of aroylamino thio ketones II were almost quantitative.

B) Triethylamine (3 ml) was added to a suspension of 10 mmole of oxazolium perchlorate in a mixture of 50 ml of ethanol and 50 ml of acetone, and hydrogen sulfide was passed through the mixture for 1 h. The resulting turbid yellow-brown solution was filtered, and water was added to the filtrate until precipitation of the reaction product was complete. The precipitate was removed by filtration, washed with water, and vacuum dried at 50°.

The thioamido ketones obtained by method A (Ia-c) and by method B (IIId,e) are presented in Table 1. They were obtained as yellow crystals that were soluble in alcohol, benzene, acetone, dioxane, and nitromethane but insoluble in water.

Formation of Thiazolium Salts IIIa-e. A mixture of 0.8 ml of 70% perchloric acid in 10 ml of acetic anhydride was added to a suspension of 10 mmole of aroylamino thio ketone IIa-e in 5 ml of glacial acetic acid. The reaction product began precipitation from the resulting solution after 2-3 min. The mixture was cooled, and ether was added until precipitation of thiazolium salt III was complete. When the precipitated substance was oily (for example, in the case of IIId), it was washed several times with ether and triturated. The resulting white crystalline substance was removed by filtration, washed with ether, dried, and crystallized from a suitable solvent (see Table 1).

Hydrolysis of Thiazolium Tosylate IIa. A 25% solution of sodium hydroxide was added to a solution of 4.2 g (10 mmole) of thiazolium tosylate IIa in 15 ml of ethanol, and the mixture was allowed to stand at room temperature for 1 h. Water was added, and the mixture was neutralized with acetic acid. The solution initially took on a red color, which subsequently changed to red-violet. The mixture was diluted with water to completely precipitate the oily product, and the product was washed several times with water and dissolved in ether. The ether solution was dried over calcium chloride and evaporated. The residue was dried in vacuo, and the oily product was crystallized. The yield of N-methyl-N-benzoyl-ω-aminothioacetophenone (IV), with mp 62°, was almost quantitative. Found: C 71.8; H 5.7; S 11.8%. $C_{16}H_{15}NOS$. Calculated: C 71.4; H 5.5; S 11.8%.

1,4-Bis(4-methyl-6-phenyl-4,5-dihydro-1,2,4-triazin-3-yl)benzene (Vc). A 5-ml (100 mmole) sample of hydrazine hydrate was added to 5.94 g (10 mmole) of bisthiazolium diperchlorate IIIc, and the mixture was refluxed for 30 min. A brown solution, from which the reaction product began to precipitate, was formed. After hydrogen sulfide evolution had ceased, the mixture was cooled, and water was added until precipitation of the product was complete. The mixture was filtered, and the solid was washed with water and vacuum dried at 60° to give 1.7 g (40%) of yellow crystals with mp 248-250° [from ethanol; mp 250° [10] (a melting point of 150° was erroneously included in the table in the cited paper)].

3,6-Diphenyl-4-methyl-4,5-dihydro-1,2,4-triazine (Va). This compound was obtained by mixing 2.4 mmole of thiazolium tosylate with 12 mmole of hydrazine hydrate (an oily product was formed) with subsequent (after 10 min) addition of water. Workup gave yellow crystals with mp 128-130° (from ethanol; mp 130° [5]) in 90% yield.

3-(p-Diphenylyl)-6-phenyl-4-methyl-4,5-dihydro-1,2,4-triazine (Vb). A 0.22-ml (4.4 mmole) sample of hydrazine hydrate was added to a suspension of 0.93 g (2.2 mmole) of thiazolium perchlorate IIIb in 25 ml of ethanol. A brown solution was formed, and hydrogen sulfide was evolved. The mixture was cooled, water was added, and the resulting precipitate

was removed by filtration, washed with water, and vacuum dried at 60° to give 0.6 g (65%) of orange crystals with mp 189-193° (from benzene; mp 193° [5]).

Similarly, thiazolium salts IIId,e were converted to the corresponding dihydrotriazines Vd (R' = 4-C_6H_4Br, R'' = C_6H_5, and R''' = 4-$C_6H_4CH_3$), with mp 166-169° (from ethanol), and Ve (R' = R'' = R''' = C_6H_5), with mp 176-178° (from isopropyl alcohol); no melting-point depression was observed for mixtures of these products with authentic samples obtained by the method in [5].

1,4-Dimethyl-3,6-diphenyl-4H,5H-1,2,4-triazinium Perchlorate (VIa). A 0.25-ml (5 mmole) sample of methylhydrazine was added to a suspension of 0.9 g (2.5 mmole) of thiazolium perchlorate IIIa in 20 ml of ethanol, and the mixture was refluxed for 15-20 min. A brown solution was formed, and hydrogen sulfide was evolved. The mixture was cooled, and the resulting precipitate was removed by filtration, washed with ether, and dried to give 0.7 g (75%) of white crystals with mp 221-222° (from ethanol; mp 222° [5]).

1-Ethyl-4-methyl-3,6-diphenyl-4H,5H-1,2,4-triazinium Perchlorate (VIb). The procedure used to obtain VIa was used to prepare this compound from thiazolium perchlorate IIIa and ethylhydrazine. The product was obtained as white crystals with mp 169-170° (from ethanol) in 60% yield. Found: C 57.0; H 5.1; Cl 9.2; N 10.9%. $C_{18}H_{20}ClN_3O_4$. Calculated: C 57.1; H 5.3; Cl 9.5; N 11.1%.

1,3,6,8-Tetraphenyl-4-methyl-1,2,4,7,8-pentaaza-3,6-octadiene (VII). A 1-g (10 mmole) sample of thiazolium tosylate IIIa was heated in excess phenylhydrazine for 10 min, during which hydrogen sulfide was evolved. The mixture was cooled and treated with water, and the precipitated oily product was washed several times with water. A small amount of ethanol was added, and the resulting precipitate was removed by filtration and dried to give 0.4 g (40%) of a product with mp 143-144° (from ethanol; mp 144° [5]).

Hydrazination of 2-Phenyl-3-methylbenzothiazolium Tosylate (VIII). A 10-ml (200 mmole) sample of hydrazine hydrate was added to 3.9 g (10 mmole) of tosylate VIII, obtained by the method in [11], and the mixture was refluxed for 5-6 min. The salt dissolved, after which a crystalline precipitate began to form. The mixture was cooled, and 15-20 ml of water was added. The mixture was filtered (the filtrate was saved for subsequent workup), and the solid material was washed with water and vacuum dried at 70° to give 1.2 g (55%) of yellow-orange crystals of 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine (IX) with mp 191-102° (from ethanol; mp 192° [12]). UV spectrum (in ethanol): λ_{max} 248 nm (ε $2.81 \cdot 10^4$). No melting-point depression was observed for a mixture of this product with a sample obtained by the method in [12]. Oxidation of the product with a 10% ethanol solution of ferric chloride gave dark-green crystals of 3,6-diphenyl-1,2,4,5-tetrazine XI with mp 191-192° (from ethanol; mp 192° [12]) in almost quantitative yield. UV spectrum (in ethanol): λ_{max} 294 nm (ε $3.04 \cdot 10^4$). No melting-point depression was observed for a mixture of this compound with tetrazine XI obtained by the method in [12], but a depression was observed for a mixture with dihydrotetrazine IX. The filtrate was extracted with chloroform, and the chloroform extract was dried over anhydrous magnesium sulfate and evaporated to give 0.42 g (30%) of bis(o-methylaminophenyl) disulfide with mp 67-68° (from ethanol; mp 68° [13]).

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