THE REACTION OF DIETHYL OXALATE WITH SOME AZOLIDONES

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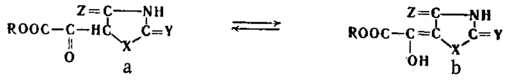
The condensation of thiazolidine-2,4-dione, rhodanine, isorhodanine, 2-thiohydantoin, and pseudothiohydantoin with diethyl oxalate has given products which are azolidone-5-glyoxalic acids or their esters. In these compounds, the glyoxalic acid residue is readily replaced under the action of diazonium salts, aromatic nitroso compounds, and aromatic aldehydes with the formation of 5-arylazo-, 5-arylimino-, and 5-arylideneazolidones. 5-Arylidenerhodanines are also formed from 5-isopropylidene- and 5-(β-acetyl-α-methylethylidene)rhodanines by their reaction with aromatic aldehydes and ketones.

Free 2-phenylimino-4-thiazolidone-5-glyoxalic acid has been obtained from the reaction of diethyl oxalate (I) with 2-phenylimino-4-thiazolidone [1].

In the present work the reactions of rhodanine, isorhodanine [2], pseudothiohydantoin, thiazolidine-2,4-dione, 2-thiohydantoin, and 1-acetyl-2-thiohydantoin with I have been studied. In alcoholic solutions in the presence of sodium alkoxides, one ethoxy group reacts with the formation of azolidone derivatives containing a glyoxalic acid or glyoxalic ester residue in position 5. When the reaction is carried out in methanol in the presence of sodium methoxide, the transesterification of I takes place with the formation of the methyl azolidone-5-glyoxalate. In the reaction of I with 1-acetyl-2-thiohydantoin, the acetyl residue is saponified, and the product is identical with that of the reaction of 2-thiohydantoin with I.

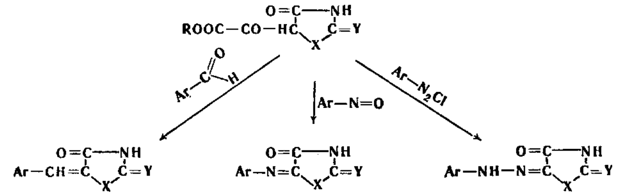
The compounds obtained apparently must be assumed to exhibit keto-enol tautomerism.



II X=S; Y=Z=O; R=CH_3
III X=S; Y=Z=O; R=C_2H_5
IV X=S; Y=Z=O; R=H
V X=Y=S; Z=O; R=CH_3
VI X=Y=S; Z=O; R=C_2H_5
VII X=NH; Y=S; Z=O; R=CH_3
VIII X=NH; Y=S; Z=O; R=C_2H_5
IX X=S; Y=NH; Z=O; R=H
X X=Z=S; Y=O; R=CH_3

All the compounds given possess acidic properties. 0.01 M solutions of the methyl esters have pH values from 2.5 to 4.4 and two dissociation constants; for example, compound V has $pK_{a_1} = 3.2$ and $pK_{a_2} = 7.6$. The products give a black-green coloration with ferric chloride solution, which is characteristic for compounds of type b.

When compounds II, V, and VII are treated with aromatic aldehydes, nitroso compounds, and diazonium salts (Scheme), the glyoxalic acid residue is displaced with the formation of 5-arylidene, 5-arylimino, and 5-arylazo derivatives of the corresponding 4-azolidone. The structure of the reaction products was shown by comparing their physical and chemical properties with the properties of substances described in the literature and also by their chemical reactions and the results of elementary analysis.



The formation of 5-arylidenerhodanines and 5-arylazorhodanines can be carried out both in an alkaline medium and in acetic acid in the presence of sodium acetate, while the corresponding 5-substituted derivatives of thiazolidine-2,4-dione and 2-thiohydantoin can be obtained only in an alkaline medium.

The action of phenylhydrazine on V gave the diphenylhydrazide of oxalic acid and the 2-phenylhydrazone of thiazolidine-2,4-dione.

The ease of replacement of the glyoxalic acid residue in the compounds obtained can be explained by the weakness of the carbon-carbon bond between the glyoxalic acid residue and the azolidone ring because of the accumulation of electronegative groups in position 5. However, this phenomenon is apparently considerably more complex, since we have established that the formation of 5-arylidenerhodanines also takes place in the reaction of 5-isopropylidene- or 5-(β-acetyl-α-methylethylidene)rhodanine with aromatic aldehydes or acetophenone. The yield and rate of formation of the 5-arylidenerhodanines rise if an aromatic aldehyde containing an electronegative substituent is used in the reaction.

The substances obtained are characterized in Tables 1–3.

EXPERIMENTAL

Methyl thiazolidine-2,4-dione-5-glyoxalate (II). With stirring, 11.7 g (0.1 mole) of thiazolidine-2,4-dione and 15 ml of I were added to a solution obtained by dissolving 4.6 g of Na in 75 ml of methanol. After 24 hr, the yellow mass was filtered off, washed with ether, and decomposed with 10% hydrochloric acid. The substance isolated was filtered off and dried. Yield 33 g (87%). Colorless plates with mp 181° C (from dichloroethane or ethanol).

Compounds V, VII, IX, and X were obtained similarly to II from I and, respectively, rhodanine, 2-thiohydantoin or 1-acetyl-2-thiohydantoin, pseudothiohydantoin, and isorhodanine, and compounds III, VI, and VIII were obtained in ethanol in the presence of sodium ethoxide from I and, respectively, thiazolidine-2,4-dione, rhodanine, and 2-thiohydantoin.

Thiazolidine-2,4-dione-5-glyoxalic acid (IV). The yellow mass formed from I and thiazolidinedione was dissolved in water, and the solution was acidified with hydrochloric acid (as in the preparation of II) and extracted with ether, after which the ether was distilled off under reduced pressure at room temperature. The II was extracted from the residue twice with boiling dichloroethane and the undissolved

Table 1

Characteristics of the Esters of Azolidone-5-glyoxalic Acids

Compound	Name	Mp, °C	Empirical formula	Found, %		Calculated, %		pH*	Yield, %
				N	S	N	S		
II	Methyl thiazolidine-2,4-dione-5-glyoxalate	181 (from dichloroethane)	$C_6H_5NO_5S$**	6.81	15.97	6.90	15.78	3.4	87
III	Ethyl thiazolidine-2,4-dione-5-glyoxalate	131 (from ethanol)	$C_7H_7NO_5S$	6.44	14.79	6.55	14.76	—	66
IV	Thiazolidine-2,4-dione-5-glyoxoalic acid	249 (from water)	$C_5H_3NO_5S$	7.54	17.16	7.41	16.95	3.0	—
V	Methyl rhodanine-5-glyoxalate	182 (from methanol)	$C_6H_5NO_4S_2$	6.39	29.25	6.55	29.24	2.5	80
VI	Ethyl rhodanine-5-glyoxalate	170 (from ethanol)	$C_7H_7NO_4S_2$	6.28	27.36	6.00	27.49	—	62
VII	Methyl 2-thiohydantoin-5-glyoxalate	188 (decomp., (from ethanol)	$C_6H_6N_2O_4S$***	13.43	15.90	13.92	15.93	3.8	89
VIII	Ethyl 2-thiohydantoin-5-glyoxalate	198 (from ethanol)	$C_7H_8N_2O_4S$	13.31	14.79	12.96	14.83	—	65
IX	Pseudothiohydantoin-5-glyoxalic acid	270	$C_5H_4N_2O_4S$	14.74	17.00	14.90	17.05	3.0	55
X	Methyl isorhodanine-5-glyoxalate	171 (from methanol)	$C_6H_5NO_4S$	6.49	28.84	6.55	29.24	4.4	78

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*For 0.01 M aqueous solutions.

**Found, %: C 35.36; H 2.60%. Calculated, %: C 35.47; H 2.48%.

***Found, %: C 36.04; H 3.12%. Calculated, %: C 35.80; H 3.01%.

Table 2

Characteristics of the Products of the Reaction of Esters of Azolidone-5-glyoxalic acids with Diazonium Salts, p-Nitrosodiethylaniline, Methyl Iodide, and Phenylhydrazine

Compound	Name	Mp, °C		Empirical formula	Found, %		Calculated, %		Yield, %
		found	lit. data		N	S	N	S	
XI	5-o-Carboxyphenylazothiazolidine-2,4-dione	259 (from dioxane)	—	$C_{10}H_7N_3O_4S$	15.78	11.81	15.84	12.09	90
XII	5-Phenylazothiazolidine-2,4-dione	244 (from acetic acid)	184[3]	$C_9H_7N_3O_2S$	18.65	14.48	19.00	14.49	90
XIII	5-o-Methoxyphenylazothiazolidine-2,4-dione	174 (from dichloroethane)	—	$C_{10}H_9N_3O_3S$	16.46	12.99	16.73	12.76	70
XIV	5-p-Nitrophenylazothiazolidine-2,4-dione	247 (from acetic acid)	—	$C_9H_6N_4O_4S$	21.32	—	21.05	—	60
XV	5-Phenylazorhodanine	234 (from ethanol)	234—236[4]	$C_9H_7N_3OS_2$	17.90	27.33	17.71	27.02	78
XVI	Sodium salt of 5-p-sulfophenylazorhodanine	300 (from water)	—	$C_9H_6N_3O_4NaS_3$*	12.03	—	12.38	—	90
XVII	5-Phenylazo-2-thiohydantoin	257 (from methanol)	258[5]	$C_9H_8N_4OS$	24.90	14.36	25.44	14.56	82
XVIII	5-o-Carboxyphenylazo-2-thiohydantoin	241 (from 2-propanol)	243—244[5]	$C_{10}H_8N_4O_3S$	21.24	12.04	21.20	12.13	53
XIX	5-p-Diethylaminophenylimino-2-thiohydantoin	195 (from methanol)	—	$C_{13}H_{16}N_4OS$	19.48	11.76	19.40	11.52	43
XX	5-p-Diethylaminophenyliminorhodanine	210 (from butanol)	—	$C_{13}H_{15}N_3OS_2$	14.03	—	14.23	—	40
XXI	Methyl 2-methylthiothiazolin-4-one-5-glyoxalate	203 (from acetone)	—	$C_7H_7NO_4S_2$	6.18	—	6.01	—	80
XXII	2-Phenylhydrazone of thiazolidine-2,4-dione	176 (from ethanol)	176[6]	$C_9H_9N_3OS$	19.93	15.68	20.29	15.46	40

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*Found, %: Na 6.60. Calculated, %: Na 6.78

Table 3

Preparation of 5-Arylidene Derivatives of 4-Azolidones and their Characteristics

Compound	Name	Starting material	Condensation conditions	Yield, %	Mp, °C	
					found	literature data
XXIII	5-p-Nitrobenzylidenerhodanine	V	ROH, NH_4Cl, NH_4OH	60	250	250—252[7]
XXIII	5-p-Nitrobenzylidenerhodanine	5-Isopropylidenerhodanine	ROH, NH_4Cl, NH_4OH	100	250	250—252[7]
XXIII	5-p-Nitrobenzylidenerhodanine	5-(β-acetyl-α-methylethylidene)rhodanine	ROH, NH_4Cl, NH_4OH	100	250	250—252[7]
XXIII	5-p-Nitrobenzylidenerhodanine	5-(β-acetyl-α-methylethylidene)rhodanine	CH_3COOH, CH_3COONa	100	252	250—252[7]
XXIV	5-p-Chlorobenzylidenerhodanine	V	ROH, NH_4Cl, NH_4OH	58	226	231[8]
XXIV	5-p-Chlorobenzylidenerhodanine	5-(β-acetyl-α-methylethylidene)rhodanine	ROH, NH_4Cl, NH_4OH	70	225	231[8]
XXIV	5-p-Chlorobenzylidenerhodanine	5-(β-acetyl-α-methylethylidene)rhodanine	ROH, RONa	40	225.5	231[8]
XXV	5-Benzylidenethiazolidine-2,4-dione	II	ROH, NH_4Cl, NH_4OH	50	242	240—242[9]
XXVI	5-p-Chlorobenzylidenethiazolidine-2,4-dione	II	ROH, NH_4Cl, NH_4OH	60	229	223—225[10]
XXVII	5-p-Nitrobenzylidene-2-thiohydantoin	VII	ROH, NH_4Cl, NH_4OH	33	265	266[11]
XXVIII	5-p-Chlorobenzylidene-2-thiohydantoin	VII	ROH, NH_4Cl, NH_4OH	40	269	265—268[11]
XXIX	5-Benzylidenerhodanine	5-(β-acetyl-α-methylethylidene)rhodanine	ROH, RONa	50	204	200[12]
XXX	5-Cinnamylidenerhodanine	5-(β-acetyl-α-methylethylidene)rhodanine	ROH, RONa	30	219	220—221[13]
XXXI	5-α-Phenylethylidenerhodanine	5-(β-acetyl-α-methylethylidene)rhodanine	ROH, NH_4Cl, NH_4OH	80	167	165—166[14]

matter was recrystallized from water. Flat light yellow crystals associated into clusters with mp 249° C.

5-o-Carboxyphenylazothiazolidine-2, 4-dione (XI). A solution of diazotized anthranilic acid was added to a solution of 2.03 g (0.01 mole) of II in 5% ammonia. After 20 min, the solution was acidified with hydrochloric acid and the yellow substance was filtered off. Yield 2.4 g (90%), mp 259° C with decomposition (from aqueous dioxane).

Under similar conditions, compounds XII-XVI were obtained from II, XV and XVI from V, and XVII and XVIII from VII and the appropriate diazonium salts.

5-p-Diethylaminophenylimino-2-thiohydantoin (XIX). A solution of 2.2 g (0.01 mole) of VII and 1.78 g of p-nitrosodiethylaniline in 30 ml of methanol was boiled for 20 min, cooled, and treated with 40 ml of water, and the dark violet precipitate was filtered off. Yield 1.2 g (43%), mp 195° C (from methanol). Compound XX was obtained similarly from VI and p-nitrosodiethylaniline.

Methyl 2-methylthio-4-thiazolin-one-5-glyoxalate (XXI). Three milliliters of CH_3I was added to a solution of 0.46 g of Na and 2.19 g of V in 30 ml of methanol. The precipitate that deposited was filtered off and dissolved in water, and the solution was acidified with hydrochloric acid. Yield 1.86 g (80%), mp 203° C (from acetone), with decomposition and the formation of a mercaptan. With ferric chloride the substance gave a dark green coloration.

2-Phenylhydrazone of thiazolidine-2, 4-dione (XXII). A solution of 2.19 g (0.01 mole) of V and 3.3 g (0.03 mole) of phenylhydrazine in 30 ml of methanol was boiled until the evolution of hydrogen sulfide ceased, and the crystals of oxalic acid diphenylhydrazide that had deposited were filtered off. The solution was evaporated and diluted with water, and the precipitate of XXII was filtered off. Yield 0.83 g (40%), mp 176° C (from ethanol).

5-p-Nitrobenzylidenerhodanine (XXIII).

a) A mixture consisting of 0.55 g (0.0025 mole) of V, 0.38 g of p-nitrobenzaldehyde, 1 g of NH_4Cl, 1 ml of NH_4OH, and 10 ml of methanol was boiled for 1 hr, after which it was diluted with an equal volume of water and the product was filtered off. Yield 0.4 g (60%). Yellow needles with mp 250° C (from CH_3COOH).

Similarly, V and p-chlorobenzaldehyde gave XXIV, II and benzaldehyde and p-chlorobenzaldehyde gave XXV and XXVI, and VII and p-nitrobenzaldehyde and p-chlorobenzaldehyde gave, respectively, XXVII and XXVIII.

b) A mixture consisting of 0.87 g (0.005 mole) of 5-isopropylidenerhodanine, 0.76 g of p-nitrobenzaldehyde, 1 g of NH_4Cl, 1 ml of NH_4OH, and 10 ml of methanol was boiled for 10 min and was then diluted with water and the precipitate was filtered off. Yield 1.33 g (100%). Yellow needles with mp 250° C (from CH_3COOH).

c) Under the same conditions, 5-(β-acetyl-α-methylethylidene)-rhodanine was boiled with p-nitrobenzaldehyde for 30 min. The yield of XXIII was about 100%, mp 250° C (from CH_3COOH). Similarly, 5-(β-acetyl-α-methylethylidene)rhodanine and p-chlorobenzaldehyde gave XXIV.

d) A mixture of 1.07 g of 5-(β-acetyl-α-methylethylidene)rhodanine and 0.76 g of p-nitrobenzaldehyde in 10 ml of glacial CH_3COOH and 2 g of CH_3COONa was boiled for 1 hr. The yield was about 100%, mp 250° C.

5-Benzylidenerhodanine (XXIX). This was obtained from 5-(β-acetyl-α-methylethylidene)rhodanine and benzaldehyde by boiling them in methanol in the presence of sodium methoxide for 1 hr. The solvent was evaporated off, the residue was acidified with hydrochloric acid, and the precipitate was filtered off and recrystallized from ethanol. Mp 204° C, yield about 50%.

Compounds XXIV and XXX were obtained similarly from p-chlorobenzaldehyde and cinnamaldehyde, respectively.

5-α-Phenylethylidenerhodanine (XXXI). A mixture consisting of 1.07 g (0.005 mole) of 5-(β-acetyl-α-methylethylidene)rhodanine, 0.6 g of acetophenone, 1 g of NH_4Cl, 1 ml of NH_4OH, and 10 ml of methanol was boiled for 5 hr and was then diluted with water, and the substance that deposited was recrystallized from ethanol. Yield 0.94 g (80%), mp 167° C.

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