4-THIAZOLIDINONES

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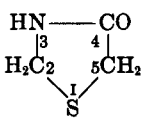
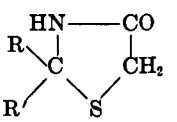
I. INTRODUCTION

4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group in the 4-position (I). Substituents in the 2-, 3-, and 5-positions may be varied, but



I



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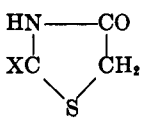
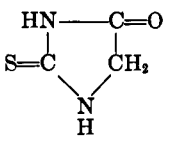


III

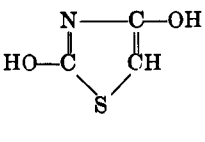
A: X = O
B: X = S
C: X = NR
D: X = NN=CRR′

the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position (X in formula III or R and R′ in formula II). Such groups include alkyl or aryl (formula II), oxygen (formula IIIA: 2,4-thiazolidinedione, which is frequently called "Senfölessigsäure" in the early German literature), sulfur (formula IIIB: rhodanine), imino (formula IIIC: pseudothiohydantoin, although compounds in which alkyl or aryl groups replace the hydrogen atoms are named as derivatives of 2-imino-4-thiazolidinone), and hydrazino (formula IIID: named as the 4-oxo-2-thiazolin-2-ylhydrazones of the aldehyde or ketone). Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by formulas II and III.

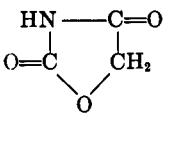
Considerable confusion concerning the structure of 4-thiazolidinones exists in the early literature, and noncyclic formulas were at first proposed for pseudothiohydantoin and for rhodanine (414, 415, 461). An alternative cyclic formula, that of thiohydantoin (IV), was proposed for IIIC (R = H) (15), but recognition of mercaptoacetic acid as a primary product of the hydrolysis of 3-phenyl-2-phenylimino-4-thiazolidinone led to the choice of formula IIIC instead of formula IV as the correct structure for the 2-imino derivatives and, by analogy, to formula IIIB for rhodanine (396, 397), although the analogous formula for 2,4-thiazolidinedione was rejected (398, 399). The presence of a thiazole ring in a tautomeric form of



IV



V



VI

2,4-thiazolidinedione (V), in rhodanine (described as a "geschwefeltes Dioxythiazol"), and in pseudothiohydantoin indicated the close relationship in structure among the three substances (298). Further details of structural determination of individual substances or classes are found in later sections of this review.

Reviews of the hydantoins (657) and of the 2,4-oxazolidinediones (VI) (134), compounds isosteric with each other and closely related to 2,4-thiazolidinedione, have been published.

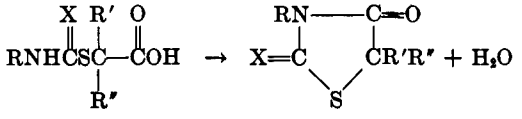
The synthesis of cyanine and merocyanine dyes is an important use of 4-thiazolidinone derivatives, especially the rhodanines. As reviews of this aspect of 4-thiazolidinone chemistry have been published (14, 86, 292), these derivatives will be included only to the extent of indicating their place in the chemistry of 4-thiazolidinones.

II. Synthesis of 4-Thiazolidinones

4-Thiazolidinones are synthesized by the cyclization of acyclic compounds or by interconversions among appropriately substituted thiazolidine derivatives.

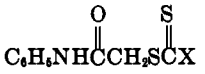
A. Cyclization of Acyclic Compounds

In the cyclization reactions, the acyclic intermediate can be formed by reaction between the atoms which will subsequently be 1 and 5, 1 and 2, or 2 and 3 of the 4-thiazolidinone ring. In most syntheses the intermediate, which is usually not isolated, is an appropriately substituted alkanoic acid, its salt, or its ester, and ring closure occurs between the acid group and the hydrogen attached to the nitrogen, i.e., between atoms 3 and 4 of the thiazolidine ring. In solution, *S*-carboxymethyl dithiocarbamate (VII: R = R′ = R″ = H; X = S) cyclizes to rhodanine. The reaction is monomolecular and has a velocity constant $C = 0.19 \times 10^{-3}$ (time measured in minutes) (309). The ester of this acid, which can be isolated if its synthesis is performed in the cold, cyclizes on being refluxed in alcoholic or aqueous solution (170).



VII

In syntheses of the rhodanine series, fruitless efforts have been made to bring about ring closure between the nitrogen atom and the carbon atom in the 2-position. Neither the 2-xanthate (VIIIA) nor the 2-trithiocarbonate (VIIIB) of acetanilide could be cyclized by the loss of ethanol or ethanethiol, and the cyclization of amides of *S*-carboxymethyl dithiocarbamates (VIIIC) by heating with dilute sulfuric acid yields rhodanine and aniline rather than 3-phenylrhodanine and ammonia (316).



VIII

A: X = OC_2H_5
B: X = SC_2H_5
C: X = NH_2

In the formation of 2-aryl- and 2-alkyl-4-thiazolidinones, ring closure occurs between atoms 1 and 2 or atoms 2 and 3 of the thiazolidine ring.

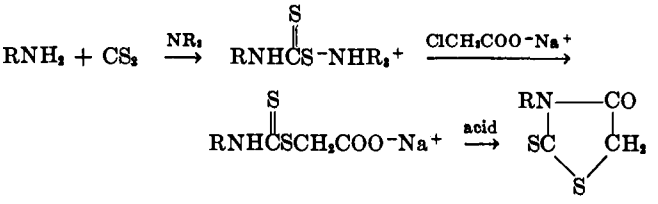
If the α-haloalkanoic acid is higher in the series than chloroacetic acid, R′ and R″ will be alkyl or aryl groups or their substituted derivatives. A tabulation of 5-alkylrhodanines, 5-alkyl-2,4-thiazolidinediones, and 5-alkyl-2-imino-4-thiazolidinones has been made (469).

1. Reaction of α-halo- or α-hydroxyalkanoic acids, α,β-unsaturated acids, or their derivatives

One general method of forming the intermediate acyclic compound uses the reaction of a sulfur- and nitrogen-containing moiety with acids or their derivatives to whose α-carbon atom is attached a halogen atom, a hydroxy group, or a double bond.

(a) Reaction with dithiocarbamates

In the synthesis of rhodanines a dithiocarbamate, formed by the reaction of ammonia or a primary amine with carbon disulfide in the presence of a base, is the source of the hetero atoms of the 4-thiazolidinone ring (437, 503). In the preparation of ammonium dithiocarbamate, an excess of ammonia favors the formation of ammonium trithiocarbonate (123). In the alcoholic solution it is possible for the latter to lose hydrogen sulfide and form ammonium dithiocarbamate. This reaction is partly responsible for the odor of hydrogen sulfide which usually accompanies the preparation of dithiocarbamates.

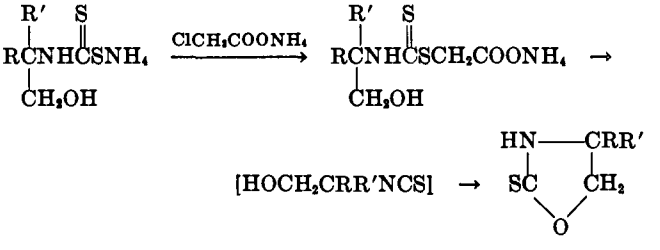


$$NH_2CSSNH_4 + 2NH_3 \rightarrow NH_4SCN + (NH_4)_2S$$
$$CS_2 + (NH_4)_2S \rightarrow S{=}C(SNH_4)_2$$
$$S{=}C(SNH_4)_2 \rightarrow H_2S + NH_2CSSNH_4$$

Another interfering reaction is the formation of the thiourea, which can take place between the amine and the dithiocarbamate. The latter may be present either as the salt or as the *S*-carboxymethyl ester (310).

$$RNH_2 + RNHCSS^- \rightarrow (RNH)_2CS + HS^-$$
$$RNH_2 + RNHCSSCH_2COO^- \rightarrow (RNH)_2CS + HSCH_2COO^-$$

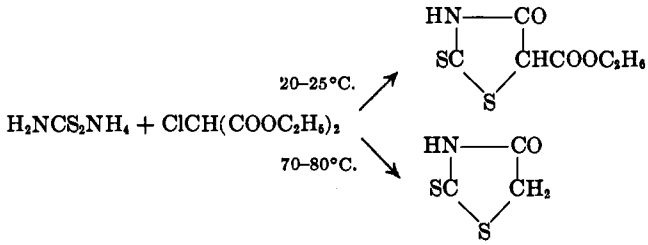
Certain substituents present in the R group can lead to the formation of a different type of product. If the dithiocarbamate contains an alcohol group in the β-position, its carboxymethyl salt is unstable in the ammoniacal solution and the intermediate isothiocyanate cyclizes to a homolog of 2-thioöxazolidine (561).



Most frequently the salt of the *S*-carboxymethyl dithiocarbamate is acidified with hydrochloric acid or sulfuric acid, although the use of acetic acid followed by keeping the solution for 12 to 24 hr. at room temperature has been recommended (310).

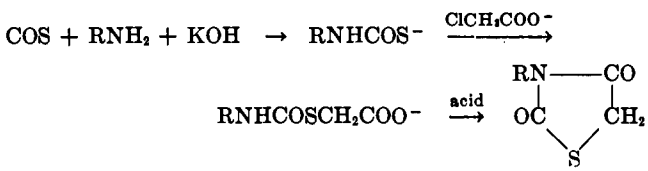
With diethyl chloromalonate as the α-haloalkanoic

ester, the final product depends on the temperature of the reaction. At room temperature or below, 5-carbethoxyrhodanine is obtained, while refluxing the reaction mixture causes saponification and decarboxylation, yielding rhodanine (155, 156).

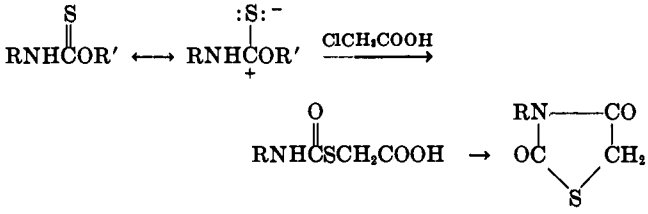


(b) Reaction with thiocarbamates

In an analogous series of reactions, the substitution of carbon oxysulfide for carbon disulfide yields 2,4-thiazolidinedione (309). With the use of primary amines instead of ammonia, the procedure can be adapted to the synthesis of 3-substituted 2,4-thiazolidinediones (348).



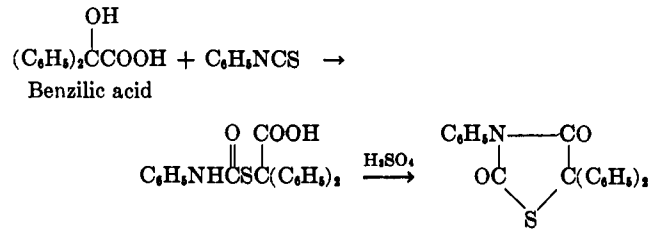
Alkyl thioncarbamates (xanthogenamides) react with α-haloalkanoic acids, forming 2,4-thiazolidinediones (317, 399, 435, 665). Alkyl thioncarbamates are converted into the corresponding thiolcarbamates by reaction with alkyl halides, of which the α-haloalkanoic acid is a specific example. In the reaction, the sulfur of the thione group displaces the halogen of the α-haloalkanoic acid and the R′ alkyl group is lost as a carbonium ion. Cyclization of the *S*-carboxymethyl thiolcarbamate produces 2,4-thiazolidinedione. Isothiocyanates in alcoholic solution can be substituted for the alkyl thioncarbamate (399).



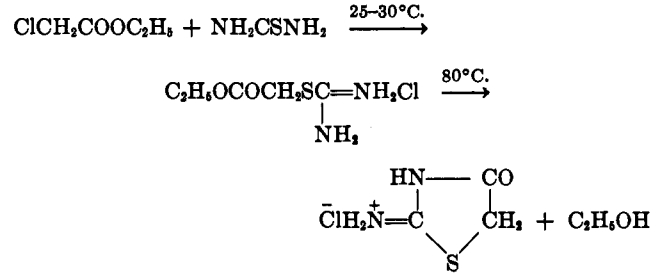
With benzilic acid, in which the electrophilic character of the α-carbon atom is pronounced, reaction with phenyl isothiocyanate takes place by addition to the thione group, followed by ketonization, and yields after cyclization by acid 3,5,5-triphenyl-2,4-thiazolidinedione (53).

(c) Reaction with thioureas

The reaction of α-chloroacetic acid, its esters, or its



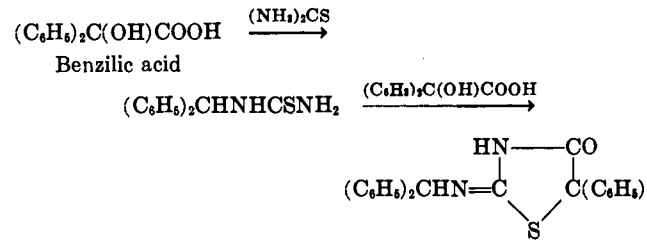
amides with thiourea or *N*-substituted thioureas produces 2-imino-4-thiazolidinones (12, 414, 449, 653). The reaction proceeds through the formation of the isothiouronium salt, which is the chief product if the temperature is kept at 25–30°C., regardless of whether the solvent is acetone, ethanol, or dimethylformamide. Cyclization occurs when the reaction takes place in refluxing ethanol or, with poor yields, in refluxing benzene (562, 626).



Acid bromides of α-alkyl(or α,α-dialkyl)-α-bromoalkanoic acids react with thiourea, forming 5-alkyl(or 5,5-dialkyl)-2-imino-4-thiazolidinones (556, 557).

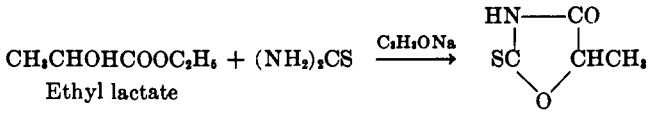
Instead of the α-haloalkanoic acid, other compounds capable of supplying the same moiety can be used. With ethyl diazoacetate, thiourea forms pseudothiohydantoin in 34 per cent yield as contrasted with an 80 per cent yield from chloroacetic acid (365).

Thiourea reacts with α-hydroxy acids. If the latter is a tertiary alcohol, the carbonium ion is attacked by the sulfur of thiourea and a substituted 2-imino-4-thiazolidinone results. With 2-ethyl-2-hydroxybutanoic acid, the product is 5,5-diethyl-2-imino-4-thiazolidinone, whose structure is determined by the isolation of 2-ethyl-2-mercaptobutanoic acid on hydrolysis with barium hydroxide (136). With benzilic acid, one of the reaction products is 2-benzhydrylimino-5,5-diphenyl-4-thiazolidinone,

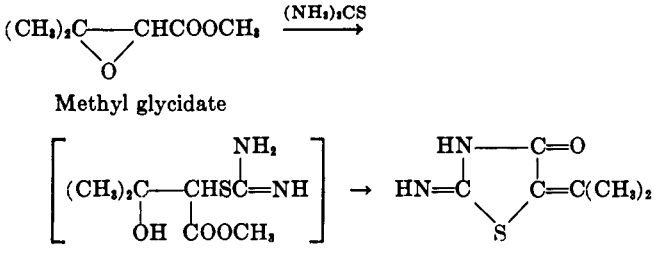


whose structure is indicated by acid hydrolysis to 5,5-diphenyl-2,4-thiazolidinedione, and which arises through the intermediate alkylation of the thiourea and con-

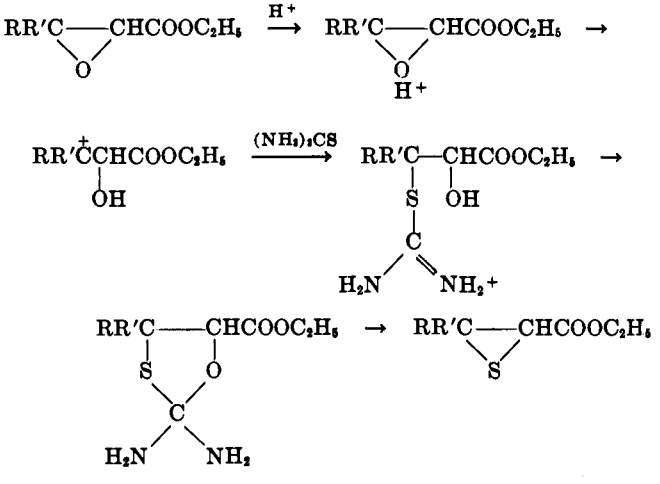
densation with benzilic acid (158). However, it should be pointed out that the reaction between thiourea and ethyl lactate, in which the electrophilic nature of the α-carbon atom is less pronounced, yields 5-methyl-2-thiono-4-oxazolidinone (663).



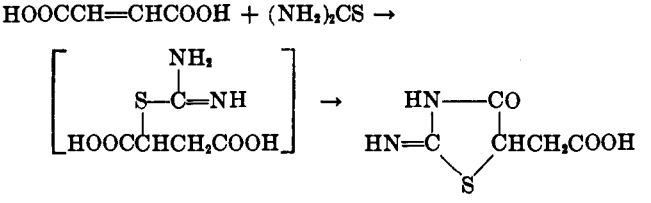
Esters of glycidic acids react slowly with thiourea at room temperature; the unisolated intermediate cyclizes with loss of methanol and water (144). When the reaction takes place in dilute sulfuric acid, the protonated glycidic ester is subjected to an S_N2 attack by thiourea, yielding 2-imino-5-isopropylidene-4-thiazolidinone as described above, or the protonated glycidic ester can, by an S_N1 mechanism, form the carbonium ion



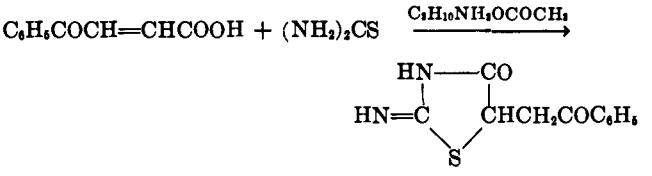
which can react with thiourea. In the latter case the intermediate 1,3-oxathiolane forms an episulfide by loss of urea (196). The nature of R and R′ is the predominant factor in determining which mechanism the reaction will follow.



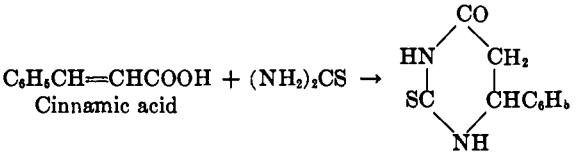
Thiourea adds to the unsaturated carbon–carbon linkage of maleic, fumaric, or citraconic acid, probably by a Michael-type reaction, and cyclization gives a 5-substituted derivative of pseudothiohydantoin (25, 26, 43, 166).



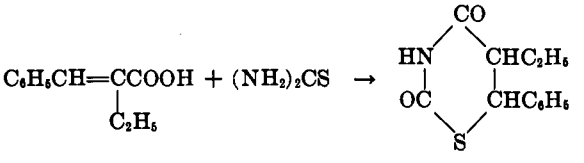
Esters (682) and imides (43, 420) of the unsaturated acids have been used, and benzoyl peroxide has been added to the reaction mixture (455). In the presence of sodium bicarbonate (80) or in refluxing dry toluene (129) 3-benzoylacrylic acid reacts similarly and forms 2-imino-5-phenacyl-4-thiazolidinone.



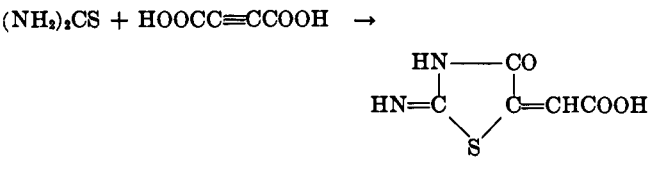
The structure of the product was confirmed by synthesis from β-benzoyl-α-chloropropionic acid and thiourea (80). However, cinnamic acid (210) yields a derivative of dihydropyrimidine



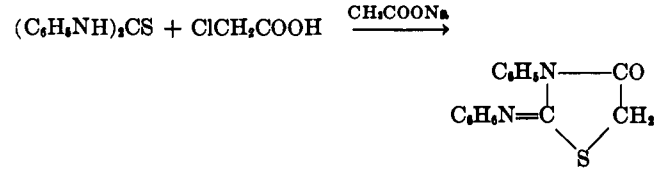
and *trans*-α-ethylcinnamic acid (592) gives a derivative of *m*-thiazane-2,4-dione.



Acetylenecarboxylic acids and their dimethyl esters react with thioureas (451). With dimethyl acetylenedicarboxylate the product is 5-carbomethoxy-2-imino-4-thiazolidinone. Probably this compound is the ester of one prepared earlier from α-bromomaleic acid, whose structure was indicated by the formation of *S*-benzylthiomalic acid after reduction, hydrolysis with base, and reaction with benzyl chloride (26).



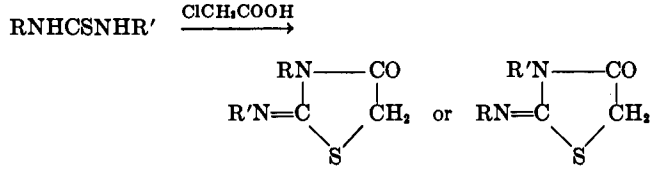
1,3-Disubstituted thioureas with the same substituent attached to both nitrogen atoms unite with α-haloalkanoic acids or their esters to form 3-aryl(alkyl)-2-aryl(alkyl)imino-4-thiazolidinones (397). Since the imino group is sensitive to acid hydrolysis, pyridine (151) or anhydrous sodium acetate (418, 441, 500) is



added to the reaction mixture; good yields of the 3-aryl-2-arylimino-4-thiazolidinone are obtained.

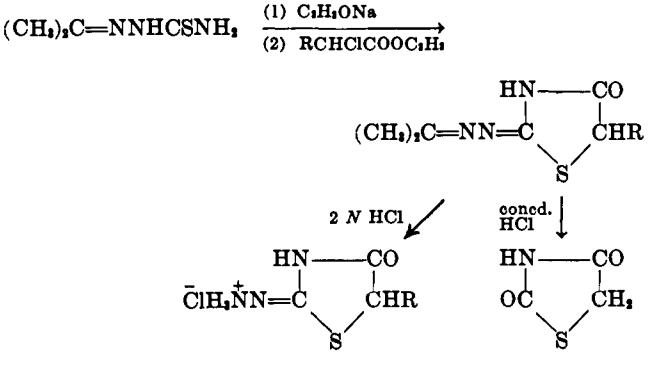
With condensation products derived from 1,1-disubstituted thioureas, both substituents must be attached to the exocyclic nitrogen atom and the ring structure is that of a 2-thiazolin-4-one (158, 668). This reaction has been used to determine the identity of alkylation products of 2-substituted-imino-4-thiazolidinones (Section VI,D,2).

With different substituents attached to the nitrogen atoms of the thiourea two isomers can be formed; the possibility of their existence was recognized in 1877 (434). The reactions by which the locations of the substituents are determined will be considered in connection with syntheses from α-thiocyanoalkanoic acids.



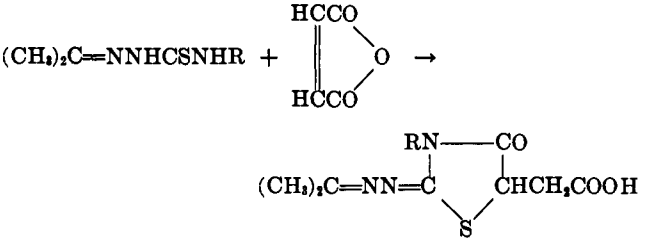
(d) Reaction with thiosemicarbazones

When the thiosemicarbazone of acetone is converted to its sodium salt by sodium ethoxide and allowed to react with an ester of chloroacetic acid (670) or a higher homolog (671), the product is the ketone derivative of 2-hydrazino-4-thiazolidinone. Other conditions for the condensation are heating an alcoholic solution of the thiosemicarbazone with chloroacetic acid and sodium acetate (127), with ethyl chloroacetate and *N*-ethylpiperidine (607), or with chloroacetanilide in ethanol or butanol (618). Refluxing the 4-oxo-2-thiazolin-2-ylhydrazone of acetone for 15 min. with dilute hydrochloric acid gives the salt of 2-hydrazino-4-thiazolidinone, while longer refluxing with concentrated acid produces 2,4-thiazolidinedione (670).



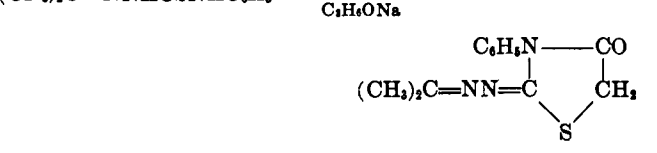
Instead of the α-haloacetic acid or its functional derivatives, 1,2-dichlorovinyl alkyl ethers dissolved in the corresponding alcohol can be used, but the yields are smaller than with the ester and sodium acetate in ethanol (605, 614).

As with the thioureas, the thiosemicarbazones of aldehydes or ketones react with maleic anhydride in refluxing benzene or toluene and form the 5-carboxymethyl-4-oxo-2-thiazolin-2-ylhydrazone of the carbonyl compound (431, 629).



R = H, CH_3, or C_6H_5.

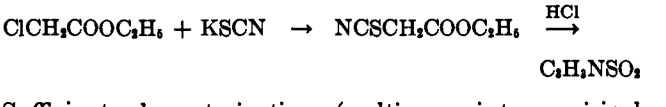
If the acetone derivative of 4-phenylthiosemicarbazide is used, the corresponding derivative of 2-hydrazino-3-phenyl-4-thiazolidinone is obtained (569).



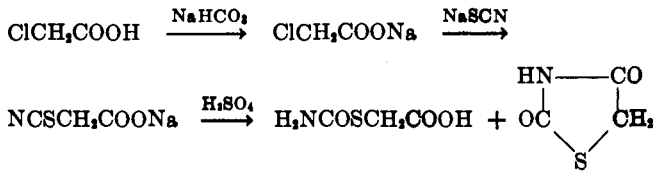
Thiosemicarbazones of a large number of aldehydes and ketones have been converted into the corresponding 2-hydrazino-4-thiazolidinones, which can also contain alkyl or aryl substituents in the 3-position or alkyl substituents in the 5-position (79, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 126, 127, 128, 172, 256, 264, 431, 450, 457, 569, 585, 602, 603, 604, 605, 606, 607, 608, 609, 610, 612, 613, 614, 616, 618, 648, 649, 652, 670, 671, 676, 677).

(e) Reaction with alkali thiocyanates

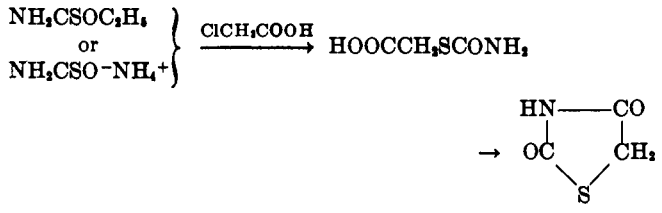
The first 4-thiazolidinone to be reported was 2,4-thiazolidinedione, which was synthesized by treating the product of the reaction of ethyl chloroacetate and potassium thiocyanate with dilute hydrochloric acid (303).



Sufficient characterization (melting point, empirical formula, and formation of salts with barium, silver, and mercury(II) ions) was given to afford convincing evidence of its identity as 2,4-thiazolidinedione to subsequent investigators. With the use of the acid instead of the ester, the intermediate carbamoylmercaptoacetic acid can be isolated (251, 304, 368).

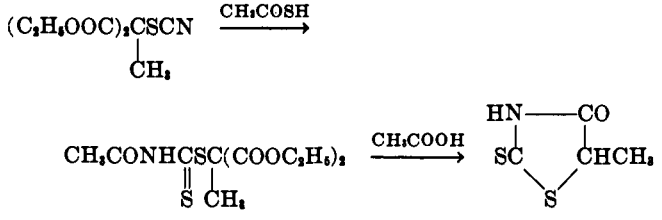


This intermediate is identical with the compound prepared from chloroacetic acid and ethyl thioncarbamate or ammonium thioncarbamate (309, 665).

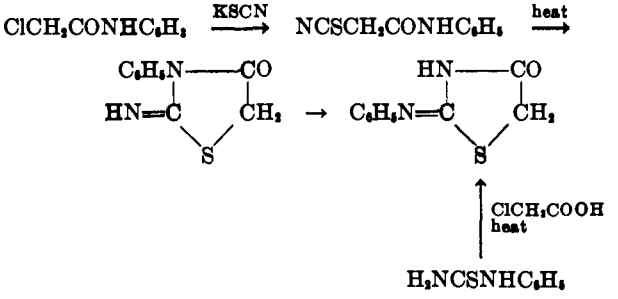


If an aqueous solution of chloroacetic acid and thiocyanic acid (or its ammonium or alkali metal salt) is heated at 70°C., a different compound, rhodanine, is obtained in 25–30 per cent yield (49, 461). By-products of the reaction include hydrogen cyanide, thiocyanic acid, carbon oxysulfide, carbon dioxide, and hydrogen sulfide. Hydrogen sulfide was isolated in smaller proportions than the other gases and its addition to the N≡C— linkage of ethyl thiocyanoacetate is a reasonable explanation for the formation of rhodanine (437). The 5-methyl derivative was prepared similarly from α-chloropropionic acid (60).

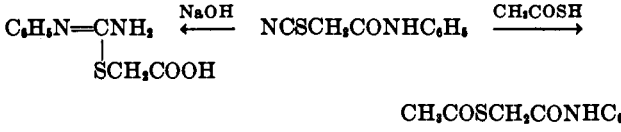
Thiolacetic (668) or thiolbenzoic (153) acid adds to α-thiocyanomalonic esters, and on acidification rhodanine or a 5-substituted derivative is obtained.



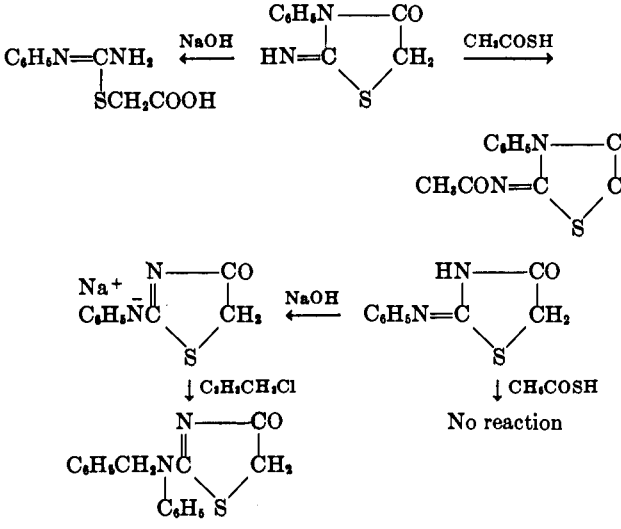
The reaction of chloroacetanilide with thiocyanates leads to a variety of products. Different products, the open-chain compound and a cyclic compound, were obtained, dependent upon the length of time the components were heated (54, 252, 286, 506). The early experimental evidence and confusion in assignments of structure were reviewed by Wheeler and Johnson (667), who isolated and characterized the three compounds obtained from derivatives of aniline and other amines. If chloroacetanilide and potassium thiocyanate are warmed in alcoholic solution for 30 min., the uncyclized thiocyanoacetanilide is obtained, which on being melted for 15 min. gives the labile 2-imino-3-phenyl-4-thiazolidinone. If the heating is continued for a longer time or the temperature is raised to 150–155°C. or the reaction is carried out in dilute alcoholic solution, the labile isomer is converted to the stable one, 2-phenylimino-4-thiazolidinone, which is identical with the compound derived from heating phenylthiourea and chloroacetic acid.



Evidence for the three forms consists in their different reactions with thiolacetic acid and with cold sodium hydroxide solution. With the uncyclized amide the thiolacetate group displaces the thiocyano group;

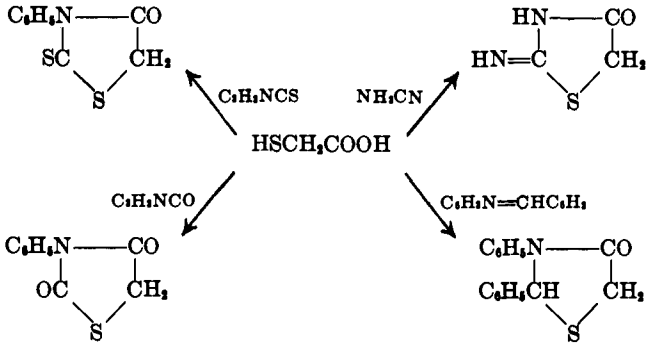


with the labile isomer the 2-imino group is acetylated, and with the stable isomer, no reaction takes place. Cold sodium hydroxide hydrolyzes the α-thiocyanoacetanilide and the labile isomer to the *S*-carboxymethyl derivative of phenylisothiourea, but converts the stable isomer to a sodium salt, in which the heterocyclic structure is maintained and which can be alkylated with benzyl chloride to the compound identical with that obtained from 1-benzyl-1-phenylthiourea and ethyl chloroacetate (Section VI,D,2).



2. Reaction of α-mercaptoalkanoic acids

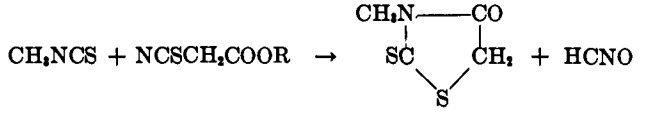
The reaction of α-mercaptoalkanoic acids with compounds of the structure RN=C=X is another general method of synthesis of 4-thiazolidinones.



(a) Reaction with isothiocyanates

The reaction of an isothiocyanate with mercaptoacetic acid forms a derivative of rhodanine (35, 36, 37, 59, 254). With aroyl isothiocyanates the product is 3-aroylrhodanine (330).

In a variation of this method, the isothiocyanate is heated with an acetic acid solution of methyl thiocyanoacetate in the presence of a catalytic amount of lead acetate until the evolution of carbon dioxide, from the decomposition of cyanic acid, has stopped (258, 259, 685).



(b) Reaction with isocyanates

Isocyanates react with mercaptoacetic acid, forming derivatives of 2,4-thiazolidinedione (32, 254).

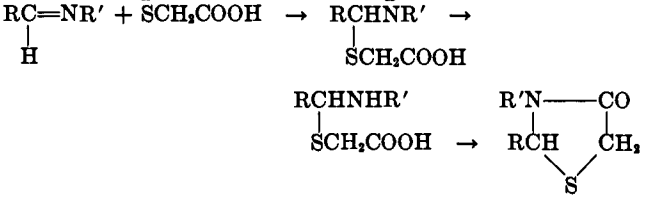
(c) Reaction with cyanamide

The identification of mercaptoacetic acid and cyanamide as products of the basic hydrolysis of pseudothiohydantoin led to the synthesis of the latter from its hydrolysis products (17, 19, 21). This method of synthesis was used as an argument for the structure of the compound as a derivative of 4-thiazolidinone rather than of thiohydantoin.

(d) Reaction with Schiff bases

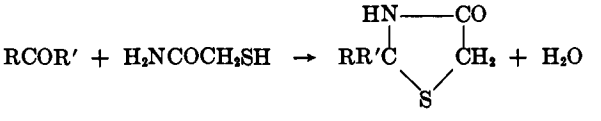
The only extensive use of α-mercaptoalkanoic acids in the synthesis of 4-thiazolidinones has been in the preparation of 2-aryl-4-thiazolidinones. The other component is a Schiff base, usually formed from an aromatic or heterocyclic aldehyde. The reaction takes place in an inert solvent such as dry ether (216), dry benzene (319, 577), or Skellysolve E for anils derived from aliphatic amines (579). With the above solvents, yields are of the order of 60–70 per cent, while in ethanolic solution the yield drops to below 10 per cent (216). The use of a water separator has been found advantageous, and the course of the reaction can be followed by the volume of water collected. With an aromatic or heterocyclic aldehyde or ketone, and ammonium carbonate as a source of ammonia, an α-mercaptoalkanoic acid gives 4-thiazolidinones with a hydrogen attached to nitrogen (584). The reaction is believed to take place by the intermediate formation of an aldimine or ketimine.

The reaction proceeds by the attack of the mercaptoacetic acid upon the $\rangle C{=}N-$ group, with the $\bar{S}CH_2COOH$ adding to the carbon atom, followed by the capture of a proton by nitrogen, and subsequent



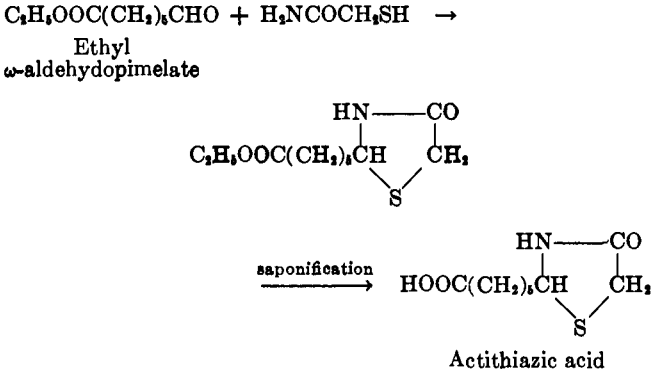
cyclization. In several cases the uncyclized addition product has been isolated (216, 577); subsequent cyclization of certain compounds was effected by heating the open-chain compound with phosphorus pentoxide in dioxane solution for 30 min. (216). Likewise, the effects of electrophilic and nucleophilic substituents on the positive character of the carbon atom or the negative character of the nitrogen atom of the azomethine linkage and therefore on the susceptibility of the carbon to nucleophilic attack by the anion of mercaptoacetic acid are evident in the yields of the 4-thiazolidinones (237, 582).

In a variation of this method, which has been found useful in the synthesis of 4-oxazolidinones, α-mercaptoacetamide is used instead of the acid and reacts with the carbonyl component. The reaction takes place in an inert solvent, in the presence of a catalytic amount of *p*-toluenesulfonic acid, with the water being removed by a water separator (484).

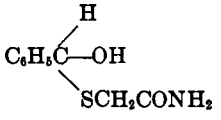


Most of the 4-thiazolidinones prepared by this method are derived from aliphatic aldehydes or ketones, with the aldehydes giving better yields than the ketones. If an α-mercaptobutyramide or the corresponding derivative of diethylacetic acid is substituted for mercaptoacetamide, the corresponding 4-thiazolidinones with alkyl groups attached to the carbon atom in the 5-position are obtained. The best known example of the use of this method is the synthesis of actithiazic acid from ethyl ω-aldehydopimelate and mercaptoacetamide, followed by saponification of the ester, and resolution of the racemic acid (48, 133, 429, 430).

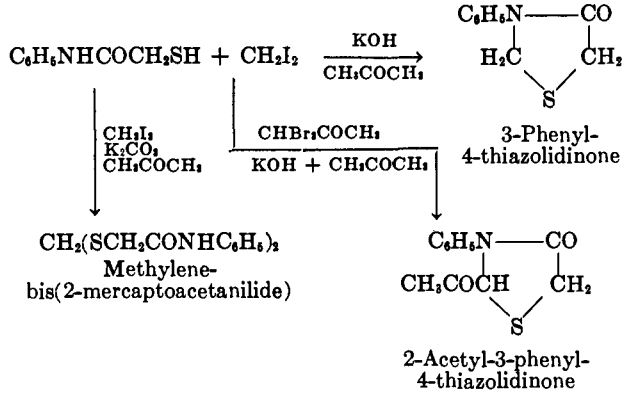
If benzaldehyde is heated with mercaptoacetamide and water is not removed as it is formed, a compound, originally believed to be 2-phenyl-4-thiazolidinone (163) but later shown to be the unstable hemimercaptal



of benzaldehyde and mercaptoacetamide, results (484, 584).

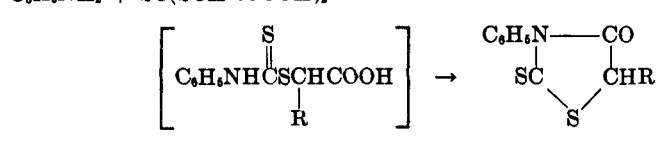


Instead of the carbonyl compound, diiodomethane may be used to prepare 4-thiazolidinones (473). Satisfactory experimental conditions for *S*- and *N*-alkylation are found by using potassium hydroxide in dry acetone (474). The concentration of base is important; with higher concentrations of base, the chief product is the result of *S*-alkylation, methylenebis-(2-mercaptoacetanilide). Under similar experimental conditions, 1,1-dibromoacetone gives 2-acetyl-3-phenyl-4-thiazolidinone.

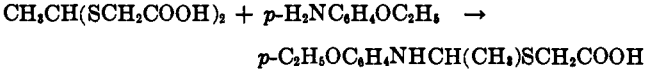


3. *Reaction of di(α-carboxyalkyl) trithiocarbonates with primary amines*

A useful method of preparing certain 3-substituted rhodanines involves the attack of a primary amine on the carbon atom of the thiono group of dicarboxymethyl trithiocarbonate, with elimination of the anion of mercaptoacetic acid, followed by cyclization of the *S*-carboxymethyl dithiocarbamate (310, 573).



Excess of amine can displace the second mercaptoacetic acid group, forming the symmetrical thiourea, while smaller concentrations of amines which are stronger bases, such as ethylamine, can produce the same result. This method is therefore not as general in its applicability as the dithiocarbamate procedure, but if it can be used, the simplicity of the experimental procedure recommends it. The use of the trithiocarbonate from thiolactic acid (R = CH_3) gives 5-methyl-3-phenylrhodanine (312). An effort to prepare 3-(*p*-ethoxyphenyl)-2-methyl-4-thiazolidinone by a variation of this method gave the uncyclized product (216).



B. INTERCONVERSIONS AMONG 4-THIAZOLIDINONES

Several methods are available for the conversion of 2-substituted 4-thiazolidinones into compounds with other substituent groups at the 2-position. Such reactions will be considered in Section VI, but are listed at this point to indicate their synthetic value.

The most useful general method of synthesis of 2,4-thiazolidinediones is the hydrolysis with dilute acids of the corresponding 2-imino-4-thiazolidinones (Section VI,C,2). Other syntheses of the same compounds are the oxidation of the 2-thiono derivatives (Section VI,F) or their reaction with chloroacetic acid or the hydrolysis of the quaternary salt of the 2-thiono derivative (Section VI,D,4). 2-Substituted imino derivatives have been prepared from the reaction of organic bases with other 4-thiazolidinones (Section VI,C,4). Carbon disulfide, if heated for 6 hr. at 180°C. with a 2-imino-4-thiazolidinone, yields the corresponding rhodanine (179, 437).

Table 1 lists references to compounds of the three series IIIA, IIIB, and IIIC (see page 464), while table 2 lists references to derivatives of the compounds with the structure shown in formula II (see page 464).

III. Physical Properties of 4-Thiazolidinones

The 3-unsubstituted 4-thiazolidinones are usually solids, often melting with decomposition, but the attachment of an alkyl group to the nitrogen lowers the melting point, sometimes enough to make the compound an oil (165, 567). Polymorphism occurs with 3-phenyl-2,4-thiazolidinedione (266, 438) and with 3-aminorhodanine (526). Crystallographic data, density, and indices of refraction have been reported for rhodanine (432) and for pseudothiohydantoin (477).

The 4-thiazolidinones that do not contain aryl or higher alkyl substituents are somewhat soluble in water. Rhodanine has a solubility of 2.25 g. per liter at 25°C. (309), and some of the low-molecular-weight 4-thiazolidinones can be recrystallized from water

TABLE 1

*4-Thiazolidinones with a functional group attached to the 2-position**

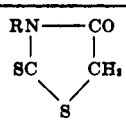
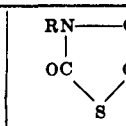
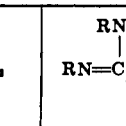
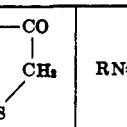
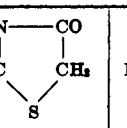
R	 (IIIB)	 (IIIA)	 (IIIC)	 (IIIC)	 (IIIC)
H	(123, 437, 461, 503)	(303, 304, 368, 665)	(12, 414, 562, 653)	(12, 414, 562, 653)	(12, 414, 562, 653)
CH_3	(37, 59, 258)	(44, 317, 369, 659)	(23)	(22)	
C_2H_5	(37, 310)	(152)	(27)	(27, 224)	
$(CH_3)_2CH$	(669)				
$(CH_3)_2CHCH_2$	(456)	(403)			
$CH_3CH_2CH(CH_3)$				(224)	
$(CH_3)_2CH(CH_2)_2$	(567)		(224)	(224)	
n-C_6H_{13}	(190)				
$(CH_3)_2CH(CH_2)_3$	(349)			(224)	
n-C_8H_{17}		(403)			
n-$C_{12}H_{25}$	(472)				
CH_2=$CHCH_2$	(36, 105)	(198)	(198, 224)	(224)	(21, 198)
CH_2=$CClCH_2$				(180)	
$(CH_3)_2CCH_2C(CH_3)_2$ | CH_2CH=$CHCH_2$		(403)			
$HO(CH_2)_2$	(362, 519)				
$HO(CH_2)_3$	(519)				
$HO(CH_2)_4$	(519)				
$CH_3O(CH_2)_2$	(124)				
$C_6H_{10}NCH_2$		(75)			
$O(C_2H_4)_2NCH_2$		(75)			
$(CH_2)_2NCH_2$		(75)			
C_2H_5OOC	(330)			(181)	
$HOOCCH_2$	(92, 383)				
$C_2H_5OOCCH_2$	(310, 383)	(403)			
$HOOC(CH_2)_2$	(92)				
$HOOCCH(CH_3)$	(30, 92)				
$HOOC(CH_2)_2CHCOOH$	(92)				
$HO_3S(CH_2)_3$	(92)				
C_6H_5	(36, 59, 85, 310, 685)	(154, 181, 192, 218, 335, 396, 398, 399, 418, 435, 665)	(4, 182, 390, 397, 418, 492, 501, 617)	(21, 54, 174, 252, 435, 481, 496, 506, 617, 667, 668)	(335, 667)
o-$CH_3C_6H_4$	(38, 296, 310)	(67, 68, 218, 655)	(63, 67, 68, 492, 501, 666)	(174, 179, 667)	(667)
m-$CH_3C_6H_4$	(29, 296, 310)	(55)	(66, 151, 501)	(55, 146, 174)	
p-$CH_3C_6H_4$	(38, 296, 310, 493)	(73, 151, 218, 655)	(63, 65, 151, 492 501)	(159, 174, 335, 481, 667)	(667)
3,4-$(CH_3)_2C_6H_3$				(667)	(667)
2,4-$(CH_3)_2C_6H_3$	(38, 295)			(339)	
2,5-$(CH_3)_2C_6H_3$	(99, 295)				(667)
2,6-$(CH_3)_2C_6H_3$	(99)				
2-CH_3-5-$(CH_3)_2CHC_6H_3$				(165)	
2,4,5-$(CH_3)_3C_6H_3$	(295, 349)			(55, 165)	
m-$CF_3C_6H_4$	(99)				
p-FC_6H_4	(99)				
o-ClC_6H_4	(99)		(500, 501)		
m-ClC_6H_4	(99)	(55)	(500, 501)	(55, 481)	
p-ClC_6H_4	(95, 459)	(55, 151)	(131, 151, 500, 501)	(55, 481, 495)	
2,5-$Cl_2C_6H_3$	(99)				
o-BrC_6H_4	(99)				
m-BrC_6H_4	(99)				
p-BrC_6H_4	(310)	(151, 198)	(131, 151)	(148)	
p-IC_6H_4	(99)			(165)	
2,4-$I_2C_6H_3$				(165)	
o-$O_2NC_6H_4$				(55, 406)	
m-$O_2NC_6H_4$				(55, 406, 481)	(339)
p-$O_2NC_6H_4$	(59, 459)		(131)	(55, 406, 481, 510)	
p-$H_2NC_6H_4$				(510)	
p-$(CH_3)_2NC_6H_4$	(343)		(441)	(666)	
p-$CH_3CONHC_6H_4$	(573)				
o-HOC_6H_4	(38)				
m-HOC_6H_4	(615)				
p-HOC_6H_4			(567)		
o-$CH_3OC_6H_4$	(295, 310)	(55)	(248, 501)	(55, 165)	
m-$CH_3OC_6H_4$				(165)	
p-$CH_3OC_6H_4$	(42, 295, 310)	(55, 441)	(62, 501)	(55, 165)	
o-$C_2H_5OC_6H_4$			(500)	(165)	
p-$C_2H_5OC_6H_4$	(259, 656)	(55)	(62, 441, 501)	(55, 165, 227, 667)	(667)
p-$C_3H_7OC_6H_4$		(441)	(441, 442)	(227)	
p-$C_4H_9OC_6H_4$			(441, 442)	(227)	
p-$(CH_3)_2CHCH_2OC_6H_4$			(441, 442)		

TABLE 1 (*Continued*)

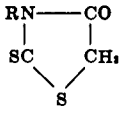
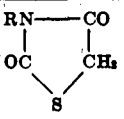
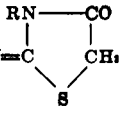
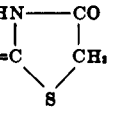
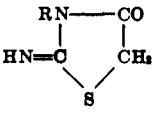
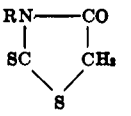
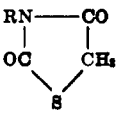
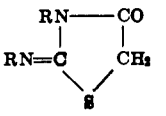
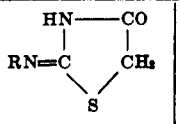
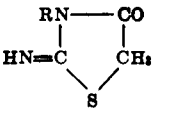
R	 (IIIB)	 (IIIA)	 (IIIC)	 (IIIC)	 (IIIC)
p-$(CH_3)_2CH(CH_2)_2OC_6H_4$		(441)	(441, 442)		
p-$C_6H_{13}OC_6H_4$			(441)		
p-$CH_3CH_2CH(CH_3)(CH_2)_2OC_6H_4$			(441, 442)		
p-$(C_2H_5)_2CHCH_2OC_6H_4$			(441)		
p-$C_7H_{15}OC_6H_4$			(441, 442)		
p-$CH_2{=}CHCH_2OC_6H_4$		(441)	(441, 442)		
o-$C_3H_7OC_6H_4$				(507)	(507)
p-$C_3H_7OC_6H_4$			(507)	(507)	(507)
p-$CH_3COC_6H_4$	(99)				
o-$HOOCC_6H_4$	(494)				
m-$HOOCC_6H_4$	(99)				
p-$HOOCC_6H_4$	(88, 92)			(481)	
p-$C_2H_5OOCC_6H_4$	(686)				
p-$HO_3SC_6H_4$	(92)				
p-$H_2NSO_2C_6H_4$	(99, 600)				
2,5-$(HO_3S)_2C_6H_3$	(92)				
2-CH_3-3-ClC_6H_3	(99)				
2-CH_3-4-ClC_6H_3	(99)				
2-CH_3-4-BrC_6H_3	(99)				
2-Br-4-$CH_3C_6H_3$	(99)				
2-CH_3-4-$O_2NC_6H_3$				(55, 150)	
2-CH_3-5-$O_2NC_6H_3$				(149)	
2-NO_2-4-$CH_3C_6H_3$				(55, 406)	
3-NO_2-4-$CH_3C_6H_3$				(55, 406)	
2,6-Br_2-4-$CH_3C_6H_3$				(148)	
2-CH_3-4-NO_2-6-BrC_6H_3				(150)	
2-HO-4-$HOOCC_6H_3$	(494)				
3-HO-4-$HOOCC_6H_3$	(509, 686)				
4-HO-3-$HOOCC_6H_3$	(92)				
2-HO-5-$O_2NC_6H_3$	(99)				
1-$C_{10}H_7$	(656)	(64)	(62, 64, 218, 492, 501)	(160, 174, 481)	
2-$C_{10}H_7$	(656)	(69)	(62, 64, 218, 492, 501)	(174, 339, 481, 512)	(339)
C_6H_5CO	(330)				
p-$CH_3OC_6H_4CO$	(330)				
$C_6H_5CH_2$	(29, 310)	(83, 403)	(165)	(224, 646)	
o-$CH_3C_6H_4CH_2$	(99)	(83)			
m-$CH_3C_6H_4CH_2$	(99)	(83)		(549)	
p-$CH_3C_6H_4CH_2$	(99)	(83)		(549)	
p-$(CH_3)_2CHC_6H_4CH_2$				(269)	
2,4-$(CH_3)_2C_6H_3CH_2$				(549)	
2,5-$(CH_3)_2C_6H_3CH_2$				(549)	
p-$FC_6H_4CH_2$	(99)				
o-$ClC_6H_4CH_2$	(99)	(83, 403)		(646)	
p-$ClC_6H_4CH_2$	(99)	(83, 403)		(646)	
o-$BrC_6H_4CH_2$				(549)	
m-$BrC_6H_4CH_2$				(549)	
p-$BrC_6H_4CH_2$	(99)			(646)	
m-$IC_6H_4CH_2$				(646)	
p-$IC_6H_4CH_2$	(99)				
2,4-$Cl_2C_6H_3CH_2$	(99)	(403)			
3,4-$Cl_2C_6H_3CH_2$	(99)	(403)			
m-$O_2NC_6H_4CH_2$		(83)			
p-$O_2NC_6H_4CH_2$	(99)	(83, 403)			
p-$CH_3OC_6H_4CH_2$	(99)			(549)	
o-$CH_3SC_6H_4CH_2$	(99)				
p-$H_2NO_2SC_6H_4CH_2$	(615)				
$C_6H_5CH(CH_3)$	(311, 347)		(393)		
p-$HOC_6H_4CH(COOC_2H_5)$	(686)				
$C_6H_5CH_2CH(COOH)$	(686)				
$C_6H_5(CH_3)_2$				(464)	
p-$ClC_6H_4(CH_3)_2$	(99)				
3,4-$(CH_3O)_2C_6H_3(CH_3)_2$	(103)				
3,4-$CH_3O_2C_6H_3(CH_3)_2$	(103)				
2,4-$Cl_2C_6H_3O(CH_3)_2$		(403)			
2,4-$Cl_2C_6H_3O(CH_3)_2O(CH_3)_2$		(403)			
Cyclohexyl				(224)	
Camphyl	(261)				
2-(2,2,3,4-Tetramethyl-3-cyclopenteno)ethyl	(261)				
2-Pyridyl	(378, 380)				
3-Pyridyl	(380)				

TABLE 1 (*Continued*)

R	 (IIIB)	 (IIIA)	 (IIIC)	 (IIIC)	 (IIIC)
4-Pyridyl	(378, 380)				
2-(6-Methyl)pyridyl	(378, 380)				
3-Quinolyl	(378, 380)				
2-Furfuryl	(99)				
2-Thenyl	(99)				
2-(5-Chloro)thenyl	(99)				
2-Thiazolyl	(378, 380)				
4-Amino-2-methyl-5-pyrimidylmethyl	(308)				
6-(2-Methyl)benzothiazolyl	(684)				
5-(2-Methyl)benzothiazolyl	(684)				
2-Benzothiazolylmethyl	(684)				

* See formula I on page 464.

(23, 303, 437). With the exception of phenylsulfonic acid groups (7), the introduction of substituents decreases the water solubility to such an extent that the usefulness of the compounds in aqueous solution is restricted (103, 341, 394, 548).

The heats of combustion of pseudothiohydantoin and of its open-chain precursor have been measured (424). The conversion of the latter to the former is endothermic but sufficient heat of neutralization is present to make the overall process exothermic.

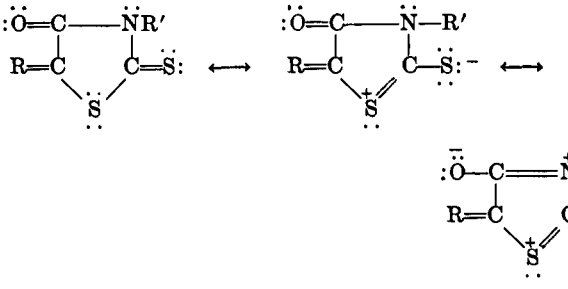
Dipole moments for the following compounds have been reported: 2,4-thiazolidinedione, 2.03 D (338); rhodanine, 2.20 D (338); 3-ethylrhodanine, 1.75 D (553).

IV. Molecular Spectra of 4-Thiazolidinones

A. Ultraviolet Spectra

The ultraviolet spectra of several 4-thiazolidinones are listed in table 3. These data, in conjunction with other published data on rhodanine derivatives (101, 632), show that rhodanine, its 3-substituted derivatives, and its 5-alkyl derivatives have characteristic peaks in the region near 250 mμ and 290 mμ. These peaks have been assigned as follows: (*a*) to the C—N bond in conjugation with the thione group and to the dithio ester group (491), and (*b*) to the thione and amide groups (632). Decrease of the strain present in the five-membered ring, brought about either by increasing the number of atoms in the ring to six (as in 4-keto-2-thiono-1,3-thiazane) or by opening the ring structure (as in ethyl *N*-acetyldithiocarbamate), causes a slight bathochromic shift (491).

Unsaturation at position 5 causes a bathochromic shift of the position of the peaks in rhodanine (408, 491, 632). Introduction of vinyl groups between the rhodanine and aromatic moieties of 5-benzylidenerhodanine causes a further bathochromic shift of 25 mμ per vinyl group in the high-intensity peak of 376 mμ (673). The same effect is present if the aromatic moiety contains a methoxyl substituent (672). The bathochromic shift in 5-benzylidenerhodanine has been ascribed to resonance forms in which the sulfur of the 4-thiazolidinone ring acquires a positive charge (491).



The similarity, both in the positions of maxima and minima and in the intensity of the spectra of 5-(*p*-acetaminobenzylidene)rhodanine and of 5-(*p*-acetaminobenzylidene)-3-phenylrhodanine, originally was used to indicate a thione rather than a 2-mercapto-2-thiazoline structure for rhodanine (638). However, the similarity in ultraviolet spectra of the 4-phenylthiosemicarbazone of *p*-acetaminobenzaldehyde (I), the 4-thiazolidinone (II) prepared from it, the 2-phenylthiosemicarbazone (III) of benzaldehyde, and the 2-thiazolin-4-one (IV) obtained from it casts doubt on the usefulness of ultraviolet spectra in resolving the structure problem involved in tautomerism within the 4-thiazolidinone nucleus (650).

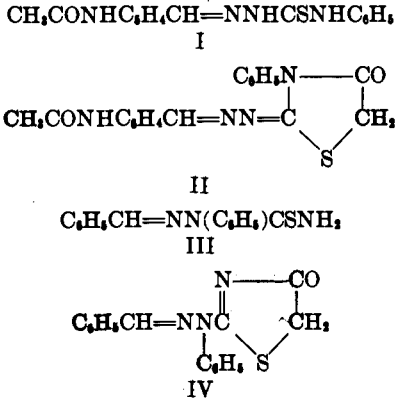
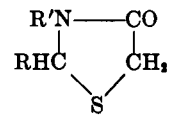


TABLE 2

2-Alkyl(or aryl)-4-thiazolidinones

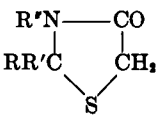


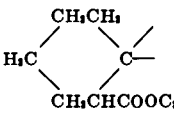
R	R'	References
H	H	(331)
H	CH_3	(331)
H	C_6H_5	(473)
H	C_6H_5CSNH	(315)
CH_3CO	C_6H_5	(473)
n-C_4H_9	H_2NCONH	(582)
n-C_6H_{13}	H	(484)
CH_2=$CH(CH_2)_6$	H	(484)
$CH_3OOC(CH_2)_2$	H	(484)
$CH_3OOC(CH_2)_3$	H	(484)
$CH_3OOC(CH_2)_4$	H	(484)
$CH_3OOC(CH_2)_5$	H	(484, 429, 536)
$CH_3OOC(CH_2)_6$	H	(484)
$CH_3OOC(CH_2)_7$	H	(484)
$CH_3OOC(CH_2)_8$	H	(484)
$HOOC(CH_2)_8$	H	(429, 537)
$C_2H_5OOC(CH_2)_8$	H	(484, 536, 537)
$C_2H_5OOCCH(CH_2)_8$ | CH_3	H	(484)
$C_2H_5OOCCH(CH_2)_4$ | CH_3	H	(484)
$CH_3OOC(CH_2)_8$	C_6H_5	(484)
$H_2NCO(CH_2)_8$	H	(484, 536)
$CH_3NHCO(CH_2)_8$	H	(484, 536)
$H_2NNHCO(CH_2)_8$	H	(484)
$HONHCO(CH_2)_8$	H	(484)
$HOCH_2(CH_2)_8$	H	(484)
L-Arabinose	C_6H_5CSNH	(314)
C_6H_5	H	(331, 484, 584)
C_6H_5	CH_3	(630)
C_6H_5	C_2H_5	(630)
C_6H_5	n-C_3H_7	(630)
C_6H_5	$(CH_3)_2CH$	(578)
C_6H_5	CH_3=$CHCH_2$	(630)
C_6H_5	n-C_4H_9	(544, 630)
C_6H_5	n-C_5H_{11}	(544)
C_6H_5	n-C_6H_{13}	(544)
C_6H_5	n-$C_{10}H_{21}$	(544)
C_6H_5	n-$C_{12}H_{25}$	(544)
C_6H_5	n-$C_{14}H_{29}$	(544)
C_6H_5	n-$C_{16}H_{33}$	(544)
C_6H_5	n-$C_{18}H_{37}$	(544)
C_6H_5	$(CH_3)_2N(CH_2)_2$	(579)
C_6H_5	$(C_2H_5)_2N(CH_2)_2$	(579, 630)
C_6H_5	$(C_2H_5)_2N(CH_2)_3$	(579)
C_6H_5	$(C_2H_5)_2NCH_2CHCH_2$ | OH	(579)
C_6H_5	$C_4H_9NH(CH_2)_2$	(580)
C_6H_5	H_2NCONH	(237, 582)
C_6H_5	HO	(538)
C_6H_5	C_6H_5	(216, 577)
C_6H_5	m-ClC_6H_4	(577)
C_6H_5	p-ClC_6H_4	(577)
C_6H_5	o-HOC_6H_4	(577)
C_6H_5	p-HOC_6H_4	(577)
C_6H_5	m-$HOOCC_6H_4$	(577)
C_6H_5	p-$HOOCC_6H_4$	(577)
C_6H_5	p-$C_2H_5OOCC_6H_4$	(577)
C_6H_5	p-$C_2H_5OC_6H_4$	(216)
C_6H_5	p-$O_2NC_6H_4$	(216)
C_6H_5	C_6H_5NH	(235, 244, 539)
C_6H_5	p-$O_2NC_6H_4NH$	(235, 244)
C_6H_5	p-BrC_6H_4NH	(244)
C_6H_5	$C_6H_5CH_2$	(630)
C_6H_5	C_6H_5CH=N	(244, 539)
p-$(CH_3)_2CHC_6H_4$	p-$C_2H_5OC_6H_4$	(216)
o-ClC_6H_4	H_2NCONH	(237)
o-ClC_6H_4	C_6H_5NH	(235)

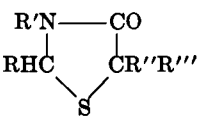
TABLE 2 (*Continued*)

R	R'	References
o-ClC_6H_4	$O_2NC_6H_5NH$	(235)
m-ClC_6H_4	H_2NCONH	(237)
p-ClC_6H_4	H	(584)
p-ClC_6H_4	CH_3	(630)
p-ClC_6H_4	C_2H_5	(630)
p-ClC_6H_4	n-C_3H_7	(630)
p-ClC_6H_4	$(n$-$C_4H_9)_2N(CH_2)_2$	(579)
p-ClC_6H_4	C_6H_5NH	(235)
p-ClC_6H_4	$O_2NC_6H_4NH$	(235)
p-ClC_6H_4	H_2NCONH	(237, 582)
p-ClC_6H_4	HO	(538)
3,4-$Cl_2C_6H_3$	H	(584)
p-BrC_6H_4	H	(584)
o-$O_2NC_6H_4$	C_6H_5	(422)
o-$O_2NC_6H_4$	C_6H_5NH	(235, 244)
o-$O_2NC_6H_4$	H_2NCONH	(237)
m-$O_2NC_6H_4$	C_6H_5	(422)
m-$O_2NC_6H_4$	$C_6H_5CH_2$	(630)
m-$O_2NC_6H_4$	C_6H_5NH	(235, 244)
m-$O_2NC_6H_4$	H_2NCONH	(237)
p-$O_2NC_6H_4$	C_6H_5	(422)
p-$O_2NC_6H_4$	$C_6H_5(CH_2)_2$	(578)
p-$O_2NC_6H_4$	$(C_2H_5)_2N(CH_2)_2$	(579)
p-$O_2NC_6H_4$	n-$C_4H_9NH(CH_2)_2$	(580)
p-$O_2NC_6H_4$	C_6H_5NH	(235, 244)
p-$O_2NC_6H_4$	H_2NCONH	(237, 582)
p-$O_2NC_6H_4$	HO	(538)
p-$CH_3CONHC_6H_4$	H	(484, 584)
p-$H_2NC_6H_4$	$C_6H_5(CH_2)_2$	(578)
p-$(CH_3)_2NC_6H_4$	$(C_2H_5)_2N(CH_2)_2$	(579)
p-$H_2NC_6H_4$	$(C_2H_5)_2N(CH_2)_2$	(579)
m-HOC_6H_4	H_2NCONH	(237)
p-HOC_6H_4	C_6H_5NH	(235)
p-HOC_6H_4	$O_2NC_6H_4NH$	(235)
p-HOC_6H_4	H_2NCONH	(237)
p-HOC_6H_4	HO	(538)
p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	(577)
p-$CH_3OC_6H_4$	$(C_2H_5)_2N(CH_2)_2$	(579)
p-$CH_3OC_6H_4$	$(C_2H_5)_2NCH_2CHOHCH_3$	(579)
p-$CH_3OC_6H_4$	$C_6H_{11}NH(CH_2)_2$	(580)
p-$CH_3OC_6H_4$	H_2NCONH	(582)
p-$C_4H_9OC_6H_4$	n-$C_3H_7NH(CH_2)_2$	(580)
3-CH_3O-4-HOC_6H_3	H_2NCONH	(582)
3-CH_3O-4-HOC_6H_3	HO	(538)
3-CH_3O-4-HOC_6H_3	3-CH_3O-4-HOC_6H_3CH=N	(539)
3,4-$(CH_3O)_2C_6H_3$	$(C_2H_5)_2N(CH_2)_2$	(579)
3-CH_3O-4-$C_2H_5OC_6H_3$	$C_6H_5(CH_2)_2$	(578)
3-CH_3O-4-$C_2H_5OC_6H_3$	n-$C_4H_9NH(CH_2)_2$	(580)
3,4,5-$(CH_3O)_3C_6H_2$	$(C_2H_5)_2N(CH_2)_2$	(579)
3,4-$CH_2O_2C_6H_3$	$(C_2H_5)_2N(CH_2)_2$	(579)
3,4-$CH_2O_2C_6H_3$	$(n$-$C_4H_9)_2NCH_2$	(579)
3,4-$CH_2O_2C_6H_3$	$(C_2H_5)_2N(CH_2)_3$	(579)
3,4-$CH_2O_2C_6H_3$	$HO(CH_2)_2NH(CH_2)_2$	(580)
3,4-$CH_2O_2C_6H_3$	$C_6H_{11}NH(CH_2)_2$	(580)
3,4-$CH_2O_2C_6H_3$	$HO(CH_2)_2NH(CH_2)_3$	(580)
3,4-$CH_2O_2C_6H_3$	n-$C_3H_7NH(CH_2)_3$	(580)
3,4-$CH_2O_2C_6H_3$	$(CH_3)_2CHNH(CH_2)_2$	(580)
3,4-$CH_2O_2C_6H_3$	n-$C_4H_9NH(CH_2)_3$	(580)
3,4-$CH_2O_2C_6H_3$	$(CH_3)_2CHCH_2NH(CH_2)_3$	(580)
3,4-$CH_2O_2C_6H_3$	n-$C_5H_{11}NH(CH_2)_2$	(580)
3,4-$CH_2O_2C_6H_3$	n-$C_5H_{11}NH(CH_2)_3$	(580)
3,4-$CH_2O_2C_6H_3$	n-$C_6H_{13}NH(CH_2)_3$	(580)
3,4-$CH_2O_2C_6H_3$	$C_6H_5NH(CH_2)_2$	(580)
3,4-$CH_2O_2C_6H_3$	$C_6H_{11}NH(CH_2)_2$	(580)
3,4-$CH_2O_2C_6H_3$	$C_6H_5CH_2NH(CH_2)_2$	(580)
3,4-$CH_2O_2C_6H_3$	$C_6H_{11}NH(CH_2)_3$	(580)
C_4H_3S	CH_3	(630)
C_4H_3O	H	(484, 584)
C_4H_3O	CH_3	(630)
C_4H_3O	C_6H_5	(240)
C_4H_3O	o-$CH_3C_6H_4$	(240)
C_4H_3O	o-HOC_6H_4	(240)
C_4H_3O	p-HOC_6H_4	(240)
C_4H_3O	o-$CH_3OC_6H_4$	(235)
C_4H_3O	p-$CH_3OC_6H_4$	(240)
C_4H_3O	o-$C_2H_5OC_6H_4$	(240)
C_4H_3O	p-$C_2H_5OC_6H_4$	(240)
C_4H_3O	p-$H_2NSO_2C_6H_4$	(240)
5-(2-$C_5H_{10}N$-4-OH)C_4N_2	C_6H_5	(319)

TABLE 2 (*Continued*)



R	R′	R″	Reference
CH_3	CH_3	H_2NCONH	(582)
CH_3	*p*-ClC_6H_4	H	(584)
CH_3	$CH_3OOC(CH_2)_4$	H	(484)
CH_3	$CH_3OOC(CH_2)_3$	H	(484)
$C_2H_5OOC(CH_2)_3$	$C_2H_5OOC(CH_2)_3$	H	(484)
		H	(484)
C_6H_5	C_6H_5	H	(163)



R	R′	R″	R‴	Reference
$CH_3OOC(CH_2)_4$	H	C_6H_5	C_6H_5	(484)
C_6H_5	*n*-$C_4H_9NH(CH_2)_3$	C_6H_5	H	(580)
p-ClC_6H_4	H	C_6H_5	H	(584)

The low intensity of the peaks in 2,4-thiazolidinedione in comparison with the 2-imino-4-thiazolidinone or rhodanine is noteworthy. Actithiazic acid, with a substituted alkyl group and a hydrogen atom attached to the 2-carbon atom, gives only end-group absorption in the ultraviolet (429). Certain similarities are present in the ultraviolet spectral data of 5-benzylidene-2-imino-4-thiazolidinone and the chalcones (574). Peaks in the ultraviolet region of the spectra for derivatives of rhodanine and of the 2-hydrazones of 2,4-thiazolidinedione are assigned to characteristic structures present in the molecules (631).

B. INFRARED SPECTRA

The infrared spectra of the 4-thiazolidinones are useful in determining the structure of the compounds. The carbonyl peak (see table 4), usually found between 1760 cm.$^{-1}$ and 1655 cm.$^{-1}$, is strong and characteristic, while twin peaks occur in this region for the 2,4-thiazolidinediones. 2-Thionothiazolidine, which lacks a carbonyl group, has no peak in this region (499). With rhodanine derivatives a saturated alkyl group in the 5-position does not have a significant effect on the position of the peak caused by the 4-carbonyl group, but unsaturation at the 5-carbon atom, being conjugated with the carbonyl group, produces a bathochromic shift.

4-Thiazolidinones with hydrogen attached to the nitrogen show absorption in the region 3100–3400 cm.$^{-1}$, characteristic of the N—H stretching. The thiureide band (58, 499) is usually found between 1580 cm.$^{-1}$ and 1450 cm.$^{-1}$. With the rhodanine derivatives strong bands, which are found in the 1100 cm.$^{-1}$ to 1250 cm.$^{-1}$ region, are present in the general region assigned to the C=S group (101).

TABLE 3

Ultraviolet spectra of selected 4-thiazolidinones and related compounds

Compound	Wavelength	log ε	Wavelength	log ε	Wavelength	log ε	Wavelength	log ε	References
	mμ		mμ		mμ		mμ		
Rhodanine			250.5	4.17	291.2	4.32			(431a)
			252.5	4.15	295	4.24	383	1.5	(491)
			ca. 250	4.1	ca. 300	4.2			(258, 638)
3-Methylrhodanine			259	4.2	293.8	4.21	382	1.7	(491)
			255	4.3	295	4.3			(638)
3-Phenylrhodanine			258	4.0	296.5	4.16	392.5	1.8	(491)
5-Ethylrhodanine			253	4.12	296	4.28	346	2.1	(491)
1,1-Bis(5-rhodanyl)ethane			253.5	4.3	299	4.55	385	2.1*	(491)
5-Ethylidenerhodanine	220	3.64	283	3.9	333	4.43	402	2.04	(491)
5-Isopropylidenerhodanine	224	3.66	279.5	3.84	342	4.59	392	2.26	(491)
5-Benzylidenerhodanine	233	3.93	271.5	3.97			376	4.54	(491)
5-(2-Thenylidene)rhodanine			287–289	3.86			397	4.53	(141)
4-Keto-2-thiono-1,3-thiazane			258.5	4.15	309	4.16			(491)
Ethyl *N*-acetyldithiocarbamate			258.5	4.16	309.5	4.11			(491)
2,4-Thiazolidinedione					295	0.5	371	0.2	(491)
					ca. 275–300*	2.5			(638)
5-Ethylidene-2,4-thiazolidinedione			277	3.68					(196)
5-Carboxymethylidene-2,4-thiazolidinedione	236	3.6			302	3.8			(166)
Potassium 5-carboxymethylidene-2,4-thiazolidinedione	235	3.1			298	3.4			(166)
5-Carbethoxymethylidene-2,4-thiazolidinedione	240	3.6			305	3.8			(166)
Pseudothiohydantoin	220	4.17	250	3.81					(196)
	ca. 225	4.4	ca. 250	4.0					(638)
5-Ethylidene-2-imino-4-thiazolidinone			255	4.33	295	3.88			(196)
2-Imino-5-isopropylidene-4-thiazolidinone			257	4.36	295	4.07			(196)
5-Benzylidene-2-imino-4-thiazolidinone			287	4.15	335	4.38			(574)

* Shoulder.

TABLE 4

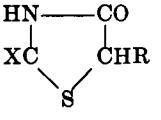
Carbonyl peaks found in 4-thiazolidinones

Compound	Frequency	Reference
	cm.$^{-1}$	
Rhodanine	1700	(499)
3-Anilinorhodanines	1745–1760	(101)
p-Dimethylaminobenzylidenerhodanine	1680	(499)
Pseudothiohydantoin	1655	(196)
2,4-Thiazolidinedione	1732 and 1660	(499)
2-Alkyl-4-thiazolidinone	1680	(484)
5-Carboxymethyl-2,4-thiazolidinedione	1760 and 1740	
	1700 (acid C=O)	(166)
5-Carbethoxymethylidene-2,4-thiazolidinedione	1770 and 1720	
	1690 and 1630 (α,β-unsaturated C=O)	(166)

V. Stereochemistry of the 4-Thiazolidinones

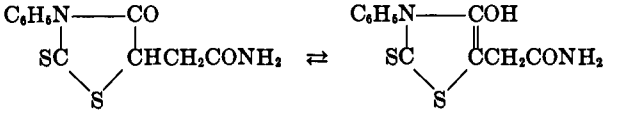
A. Optical Isomerism

The existence of optical isomers was predicted for derivatives of pseudothiohydantoin with an asymmetric methylene carbon atom (25),



but efforts to resolve inactive 2-imino-4-thiazolidinone-5-acetic acid by means of its brucine salt were unsuccessful (340). Inactive 2-imino-5-methyl-4-thiazolidinone is obtained from active thiolactic acid and cyanamide (393).

In the rhodanine series, the reaction of active di-(α-carboxyethyl) trithiocarbonate with ammonia (312) produces inactive 5-methylrhodanine; with aniline (346) it yields inactive 5-methyl-3-phenylrhodanine, while *l*-bromosuccinamidic acid and ammonium phenyldithiocarbamate form inactive 5-carboxamidomethyl-3-phenylrhodanine. Lack of optical activity in the cyclized product was attributed to the rapid establishment of equilibrium between the tautomeric forms.



Likewise, an optically inactive 3-amino-5-carboxymethylrhodanine is obtained from ammonium dithiocarbazinate and sodium *l*-bromosuccinate (526). When both hydrogen atoms on the methylene carbon are replaced by alkyl or substituted alkyl groups, and such tautomerism is not possible, optically active rhodanine derivatives are formed from the corresponding optically active α-haloalkanoic acids, while inactive rhodanine derivatives are obtained from the racemic acids (347).

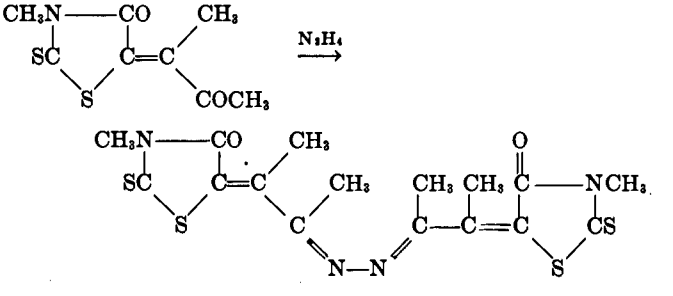
In the synthesis of 5-carboxymethyl-3-methyl-2,4-thiazolidinedione, the use of an optically active α-bromosuccinic acid permits the isolation of an optically active cyclic compound, provided the product is isolated shortly after its precipitation from the acid solution (348). Long contact with hydrochloric acid racemizes the compound. Cyclization of active carbamoylthiolactic acid in the presence of hydrochloric acid forms racemic 5-methyl-2,4-thiazolidinedione (251).

If the asymmetric carbon atom is not involved in the keto–enol tautomerism, optically active cyclized products can be obtained. The use of active amines in the synthesis of rhodanine derivatives (313, 347) and of thioureas derived from active amines in the synthesis of 2-imino-4-thiazolidinones (393) gives active cyclized products. Racemic 2-(5-carboxypentyl)-4-thiazolidinone is resolved by means of its brucine salts (429).

B. Geometric Isomerism

Geometric isomers of the 5-substituted methylidene derivatives of 4-thiazolidinones are theoretically possible, but in only a few instances have two isomers, believed to be cis and trans, been isolated. The reaction of 3-cyclohexyl-5-(1-ethoxyethylidene)rhodanine with mercaptans in the presence of zinc chloride and anhydrous hydrogen chloride gives two isomers, differing widely in melting point and solubility (372). Similar treatment of the 3-benzyl- and 3-carbethoxymethyl derivatives also yields two isomers. Two isomers result from the reaction of 3-(2-thiazolyl)rhodanine with ethyl orthoacetate and acetic anhydride (380).

With a few compounds, specific evidence for the trans configuration is available. The carbonyl frequency of 3,3′-diallyl-4,4′-dioxo-2,2′-dithio-5,5′-dithiazolylidene indicates that the α,β-unsaturated carbonyl groups are conjugated and trans (409). The formation of a ketazine rather than a cyclic structure from the reaction of 3-methyl-5-(3-oxobut-2-ylidene)rhodanine and hydrazine is explained on the basis of the trans configuration of the rhodanine derivative (476).



VI. Reactions of 4-Thiazolidinones

A. Reactions Dependent upon the Nucleophilic Activity of the Methylene Carbon Atom

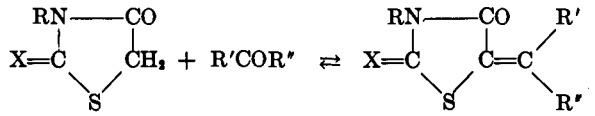
The methylene carbon atom at the 5-position of a 4-thiazolidinone possesses nucleophilic activity and attacks an electrophilic center. If it is structurally

possible, the reaction product loses water, forming a 5-unsaturated derivative of the 4-thiazolidinone. Most frequently, the reaction occurs in the presence of a base and the anion of the 4-thiazolidinone is the attacking species.

The ease of formation of the anion and hence the degree of the nucleophilic activity is dependent not only on the electron-withdrawing effect of the adjacent carbonyl group, but also on the presence of other electron-withdrawing groups such as those attached to the 2-carbon atom (372). The electron attraction of the sulfur of a 2-thione group is greater than that of the oxygen of a 2-carbonyl group. For example, the carbonyl group of a ketone, which has a less electrophilic carbon atom than that of an aldehyde, reacts less readily with 2,4-thiazolidinedione than with rhodanine. The nucleophilic activity of the 5-methylene carbon atom of a 2-aryl-4-thiazolidinone or a 2-arylimino-4-thiazolidinone should be influenced by the nature of the substituents attached to the aryl group.

1. Aldol condensations with aldehydes and ketones

The first reaction of this type to be investigated and one that has received much attention is the aldol condensation of the methylene group with the carbonyl group of an aldehyde or ketone, followed, if possible, by loss of water. The product of the reaction contains



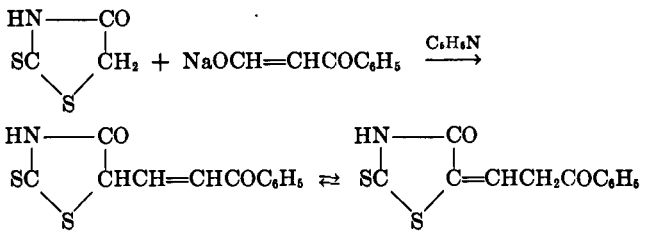
an α,β-unsaturated carbonyl group. There is evidence that the aldol reaction of rhodanine derivatives is reversible, since 5-arylmethylenerhodanines, if treated with alkali, give the odor of the aldehyde (121, 462). The reverse aldol reaction is complicated by the decomposition of the rhodanine nucleus with alkali.

The reaction was first performed with rhodanine and benzaldehyde or acetaldehyde, using sulfuric acid as the condensing agent (462), and the isolation of a product was believed to support an open-chain formula for rhodanine, $HSCH_2COSCN$. Later, sodium hydroxide in ethanolic solution (683), sodium ethoxide in ethanolic solution (666), anhydrous sodium acetate in acetic acid (36, 345), anhydrous sodium acetate, acetic anhydride, and acetic acid (386), ammonia and ammonium chloride in ethanolic solution (11, 96, 268), ammonium hydroxide in ethanolic solution (143), diethanolamine (332), and piperidine (490, 571) were used as condensing agents. Sometimes the reaction proceeds so rapidly that the refluxing solution without an additional condensing agent is sufficient (37, 486). With sulfuric acid as the condensing agent, the aldehyde diacetate can be used instead of the aldehyde (96).

With most aromatic and heterocyclic aldehydes, the yields in reaction with rhodanine are above 75 per cent and the reaction is used to prepare derivatives of the aldehyde (122, 141, 305). Rhodanine derivatives of aldehydes and ketones can be detected by paper chromatography (249). Both formamide and dimethylformamide can serve as the stationary phase, and R_f values have been tabulated for various eluting solvents. Variations in the possibilities of hydrogen bonding are used to explain the differences in R_f values with different solvents.

Although acetaldehyde was one of the first aldehydes to be condensed with rhodanine, attempts to condense other aliphatic aldehydes in the presence of sulfuric acid have been reported to be unsuccessful (36, 50). Representative aliphatic aldehydes condense with rhodanine on refluxing for several hours in acetic acid solution (33, 35, 275). Equimolar quantities of the aliphatic aldehydes and rhodanine can be condensed to the 5-alkylidene derivatives, using either sodium acetate in acetic acid or ammonium chloride and ammonia in ethanolic solution (81). With 3-substituted rhodanines, anhydrous sodium acetate and acetic anhydride give the desired product, but it is sometimes necessary to heat the reagents in an autoclave (373).

If the aldehyde exists predominantly in the enol form, its sodium derivative reacts with rhodanine in pyridine solution and produces the tautomer of the aldol condensation product (679).



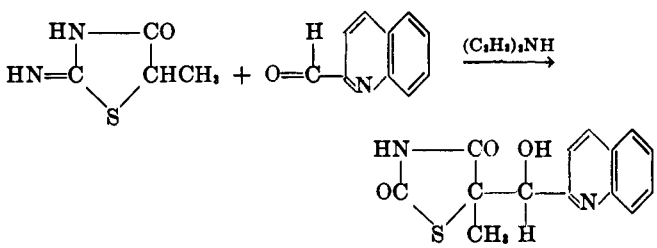
Sulfuric acid does not bring about the condensation of rhodanine with acetone, methyl nonyl ketone, ethyl acetoacetate, acetophenone, or benzil (36, 50), but in the presence of ammonia and ammonium chloride, many ketones whose carbonyl group is not markedly affected by steric hindrance yield the desired 5-disubstituted methylene derivatives (100). Ketones, including α-diketones such as biacetyl, condense with 3-substituted rhodanines if zinc chloride is added to the dioxane or methanol solution (373).

Aromatic aldehydes react with 2,4-thiazolidinedione and form the 5-arylidene derivatives of the latter. The reaction takes place in the presence of mineral acid (24), a few drops of piperidine (513), or anhydrous sodium acetate in glacial acetic acid (69, 386, 400, 404, 419). When the sodium acetate–acetic acid method is used with aliphatic aldehydes, small yields of 5-alkylidene-2,4-thiazolidinediones are obtained, but no

product was isolated on reaction with ketones (143). A small yield of 5-isopropylidene-2,4-thiazolidinedione is obtained when the reaction is performed in ethanol using ammonia and ammonium chloride as the condensing agent, but much more favorable conditions utilize piperidinium acetate as the catalyst and the continuous removal of water by a Stark–Dean water separator from a benzene solution of the reactants (97).

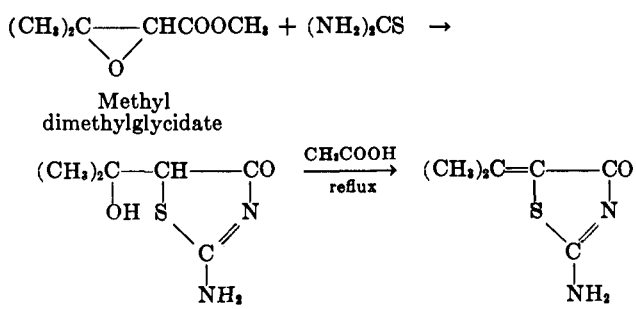
In the synthesis of 5-arylidene derivatives of pseudothiohydantoin acid was the first condensing agent used (24), but small amounts of sodium hydroxide (165, 683) or sodium ethoxide (666) in ethanolic solution are preferable. Other condensing agents include diethylamine (486), sodium acetate in acetic acid solution (159), and pyridine (65, 67, 68).

With 2-imino-5-methyl-4-thiazolidinone, an aldol condensation takes place with cinchoninaldehyde or quinaldehyde but the product, which cannot be dehydrated to an α,β-unsaturated carbonyl compound, is a carbinol (486). Similar products have been obtained from 2-arylimino-5-methyl-4-thiazolidinones and aldehydes (439).



Several methyl ketones have been condensed with pseudothiohydantoin in approximately 30 per cent yields by heating equimolar quantities with ammonia and ammonium chloride in methanolic solution at 50–60°C. for several hours (599). Alicyclic ketones, such as cyclopentanone and cyclohexanone, react with pseudothiohydantoin when they are refluxed with sodium acetate in acetic acid solution for 12 hr., but some hydrolysis of the 2-imino group to the 2-oxo group also occurs (226).

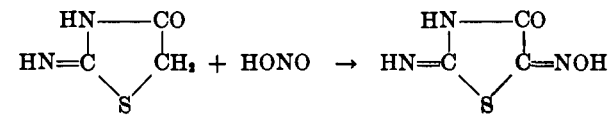
2-Imino-5-isopropylidene-4-thiazolidinone is also obtained if the condensation product of thiourea with methyl dimethylglycidate is refluxed with glacial acetic acid for 1 hr. (144).



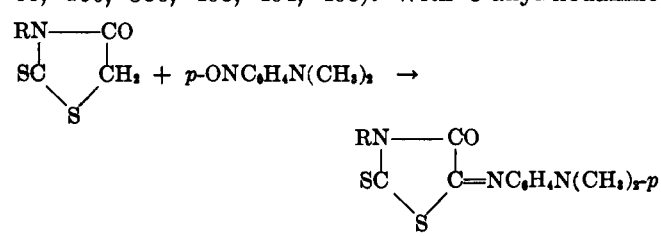
Aldehydes and ketones that undergo the aldol condensation with rhodanines, 2,4-thiazolidinediones, and 2-imino-4-thiazolidinones are listed in table 5. No examples of this reaction with 2-alkyl- or 2-aryl-4-thiazolidinones were found.

2. Reaction with nitrous acid and nitroso compounds

Pseudothiohydantoin on treatment with nitric acid gives a low yield of 5-oximinopseudothiohydantoin. The same product is obtained in better yield by the action of nitrous acid, which is prepared by the reduction of nitric acid (416) or by the addition of sodium nitrite to a hydrochloric acid solution of the pseudothiohydantoin (297). Similar derivatives of rhodanine and its 3-substituted derivatives are obtained with amyl nitrite (281) or isopropyl nitrite (485) and hydrochloric acid. The reactions of 5-oximino-4-thiazolidinones with acids and bases are described in Section VI,C.



Aromatic nitroso compounds, such as *p*-nitrosodimethylaniline and the nitrosonaphthols, react with 3-substituted rhodanines and with 2-substituted-imino-4-thiazolidinones forming 5-arylimino derivatives (4, 66, 160, 386, 493, 494, 495). With 3-allylrhodanine and *p*-nitrosodimethylaniline, the reaction does not stop with the formation of the anil (409). In acetic acid solution, a second molecule of 3-allylrhodanine displaces the arylimino group, forming the same type of compound that would be produced if 3-allylrhodanine were oxidized with selenium dioxide or brominated and subsequently treated with triethylamine (Section VI,F,3). In ethanolic solution the 4-



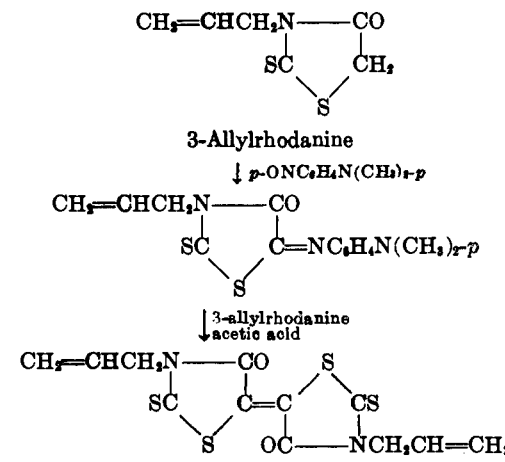
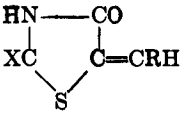


TABLE 5

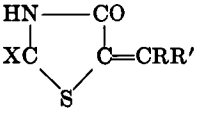
5-Alkylidene(or arylidene)-4-thiazolidinones



R	X = S	X = O	X = NH
CH_3	(275, 462)		
$(CH_3)_2CH$	(35)	(143)	
$(CH_3)_2CHCH_2$	(35, 275)		
$(C_2H_5)_2CH$	(96)		
n-$C_5H_{11}CHC_2H_5$	(96)		
n-C_9H_{19}	(96)		
$(CH_3)_2CCH_2CH(CH_3)(CH_3)_2$		(143)	
$CH_2CH=CH$	(275)		
$CH_3(CH_2)_2CH=C(C_2H_5)$	(96)		
$(CH_3)_2C=CH(CH_2)_2C(CH_3)=CH$	(96)		
$C_6H_5CH_2$	(275)		
HOOC	(275)	(166)	
$C_6H_5COCH_2$	(679)		
$C_6H_5CH=CH$	(50, 490, 683)	(683)	(683)
o-$O_2NC_6H_4CH=CH$	(96)		
$C_6H_5CH=C(CH_3)_4CH_3$	(96)		
o-$C_2H_5CH=CHC_6H_4$	(458)		
C_6H_5	(50, 462)	(24, 400)	(386, 400, 567)
o-$CH_3C_6H_4$	(96)		
m-$CH_3C_6H_4$	(96)		
p-$CH_3C_6H_4$	(96)		
p-$(CH_3)_2CHC_6H_4$	(50, 261, 490)		
o-FC_6H_4	(96)		
m-FC_6H_4	(96)		
p-FC_6H_4	(96)		
o-ClC_6H_4	(35, 123)		
m-ClC_6H_4	(123)		
p-ClC_6H_4	(123)	(404)	(261)
o-BrC_6H_4	(123)		
m-BrC_6H_4	(123)		
p-BrC_6H_4	(123)		
2,4-$Cl_2C_6H_3$	(96)		
3,4-$Cl_2C_6H_3$	(96)		
o-$HOOCC_6H_4$	(9, 177)		
o-$CH_3OOCC_6H_4$	(177)		
p-$HOOCC_6H_4$	(9)		
o-$HO_3SC_6H_4$	(7)		
o-$H_2NC_6H_4$	(76)		
p-$H_2NC_6H_4$	(33)	(33)	
p-$CH_3CONHC_6H_4$	(680)	(680)	(680)
p-$(CH_3)_2NC_6H_4$	(38, 50)		
p-$(C_2H_5)_2NC_6H_4$	(518)		
2,4-$[(CH_3)_2N]_2C_6H_3$	(516)		
o-$O_2NC_6H_4$	(9, 50, 76, 279, 620)	(620)	(620)
m-$O_2NC_6H_4$	(9, 50, 620)	(567, 620)	(567, 620)
p-$O_2NC_6H_4$	(9, 50, 467, 620)	(620)	(620)
3-NO_2-4-$(CH_3)_2CHC_6H_3$	(488)		
o-HOC_6H_4	(50, 620, 683)	(620, 683)	(620, 683)
m-HOC_6H_4	(50, 620)	(620)	(620)
p-HOC_6H_4	(33, 50, 620)	(620)	(620)
1-(2-HO)$C_{10}H_6$	(50)		
5-Cl-2-HOC_6H_3	(96)		
5-Br-2-HOC_6H_3	(620)	(620)	(620)
5-CH_3-2-HOC_6H_3	(50)		
2-CH_3-4-HO-5-$C_3H_7C_6H_2$	(50)		
3-HO_3S-4-HOC_6H_3	(7)		
p-$CH_3OC_6H_4$	(28, 50, 268)	(404)	
3,4-$(HO)_2C_6H_3$	(261, 263, 508)	(263)	(263)
3,4-$(CH_3O)_2C_6H_3$	(345)		(400)
3-CH_3O-2-HOC_6H_3	(96)		
3-CH_3O-4-HOC_6H_3	(50, 332)		
3,4-$CH_2O_2C_6H_3$	(50)	(386)	(567)
3-C_2H_5O-4-HOC_6H_3	(96)		
3-HO_3S-4-$CH_3OC_6H_3$	(7)		
3,4-$(C_2H_5O)_2C_6H_3$	(96)		
3,4,5-$(HO)_3C_6H_2$	(508)		
2-CH_3OOC-3,4-$(CH_3O)_2C_6H_2$	(177)		
2,4,5-$(CH_3O)_3C_6H_2$	(299)		
1-$C_{10}H_7$	(5)		
2-$C_{10}H_7$	(5)		

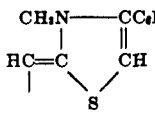
TABLE 5 (*Continued*)

R	X = S	X = O	X = NH
9-$C_{14}H_9$ (anthraldehyde)	(5)		
9-$C_{14}H_9$ (phenanthraldehyde)	(5)		
2-C_4H_3N	(306, 490)		
2-(1-CH_3)C_4H_3N	(305)		
2-[1-($O_2NC_6H_4$)]C_4H_3N	(490)		
2-[4,5-$(CH_3)_2$-3-C_2H_5OOC]C_4HN	(245)		
3-[4-CH_3-5-C_6H_5-2-C_2H_5OOC]C_4HN	(246)		
3-C_5H_5N	(463)		
2-C_5H_4N	(10, 241, 463)		
3-C_5H_4N	(10, 241, 463)		
4-C_5H_4N	(10, 241, 463)		
2-C_5H_3N	(10, 467, 486)		(486)
4-C_5H_4N	(10, 486)		(486)
5-[2-NH_2-4-HO-6-CH_3]C_4N_2	(319)		
5-[2-$C_5H_{10}N$-4-$OCOCH_3$-6-CH_3]C_4N_2	(319)		
2,4,6-(2-HOC_6H_4)C_3N_3	(6)		
2,4,6-[3-HOC_6H_4]C_3N_3	(6)		
2,4,6-[4-HOC_6H_4]C_3N_3	(6)		
2-C_4H_3O	(38, 50)	(400)	(400)
2-(5-O_2N)C_4H_2O	(96, 521)	(521)	(529)
2-(5-Cl)C_4H_2O	(96)		
2-$C_4H_3O(CH{=}CH)_n$	n = 1 (96) n = 1–2 (490)		
2-(4-C_2H_5OOC-3-CH_3)C_4HO	(521)	(521)	
2-C_4H_3S	(140, 207)	(400)	
3-C_4H_3S	(122)		
2-(3-CH_3)C_4H_2S	(140)		
2-(5-CH_3)C_4H_2S	(140)		
2-(5-C_6H_5)C_4H_2S	(140)		
2-(5-C_6H_5)C_4H_2S	(140)		
2-(5-Cl)C_4H_2S	(140)		
2-(5-Br)C_4H_2S	(140)		
2-[3,4-$(CH_3)_2$]C_4HS	(141)		
2-[3,4,5-$(CH_3)_3$]C_4S	(141)		
3-C_5H_5S	(141)		
2-C_4H_3Se	(676)		
2-(5-CH_3)C_4H_2Se	(677)		
2-(5-O_2N)C_4H_2Se	(678)		
2-Dicyclopentadienyl iron	(272)		

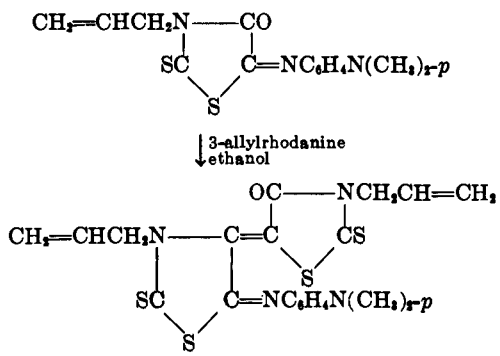


R	R′	X = S	X = O	X = NH
CH_3	CH_3	(100, 144, 413, 599)	(97, 143, 144, 599)	(599)
C_2H_5	CH_3	(100, 599)	(97, 143, 599)	(599)
n-C_3H_7	CH_3	(100)	(97)	
$(CH_3)_2CH$	CH_3	(100)		
n-C_4H_9	CH_3	(100)	(97)	
$(CH_3)_2CHCH_2$	CH_3	(100, 599)	(97, 599)	(599)
n-C_5H_{11}	CH_3	(100)	(97)	
n-C_6H_{13}	CH_3	(100, 599)	(97, 599)	(599)
n-C_7H_{15}	CH_3	(100)		
$CH_2{=}CH(CH_2)_3$	CH_3		(97)	
HOOC	CH_3	(599)	(599)	
$HOOCCH_2$	CH_3			(223)
$C_2H_5OOCCH_2$	CH_3	(599)		
$HOOC(CH_2)_3$	CH_3	(11, 599)	(599)	
$CH_3(CH_2)_nSCH_2$	CH_3	n = 0–5 (82)		
$(CH_3)_2CH(CH_2)_nSCH_2$	CH_3	n = 0–1 (82)		
$(CH_3)_2CSCH_2$	CH_3	(82)		
$C_6H_5CH_2$	CH_3	(100)		
$C_6H_5CH{=}CH$	CH_3	(100)		
C_6H_5	CH_3	(100, 177)		
p-$CH_3C_6H_4$	CH_3	(100)		
p-ClC_6H_4	CH_3	(100)		
p-BrC_6H_4	CH_3	(100)		
o-$HOOCC_6H_4$	CH_3	(177)		
2-$C_{10}H_7OCH_2$	CH_3	(100)		
2-C_4H_3O	CH_3	(100)		
2-(5-CH_3)C_4H_2O	CH_3	(100)		
2-$C_4H_3OCH{=}CH$	CH_3	(100)		
2-C_4H_3S	CH_3	(100)		

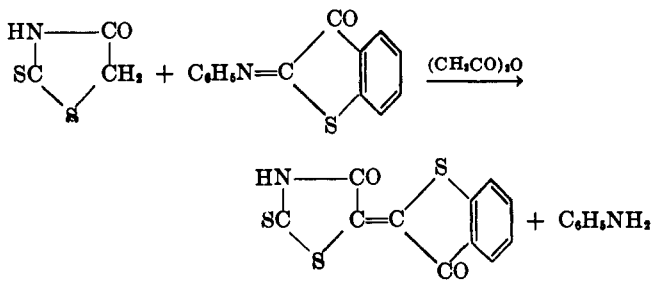
TABLE 5 (*Continued*)

R	R′	X = S	X = O	X = NH
2-(5-Cl)C_4H_3S	CH_3	(100)		
2-(5-Br)C_4H_3S	CH_3	(100)		
2-[5-$(CH_3)_3C$]C_4H_3S	CH_3	(100)		
	CH_3	(482)		
C_2H_3	C_2H_4	(100)		
C_3H_5	C_2H_5	(100)		
2-C_4H_3O	C_2H_5	(100)		
2-C_4H_3O	n-C_3H_7	(100)		
C_3H_5		(100, 490)	(226)	(226)
C_5H_{10}		(100, 599)	(143, 400, 599)	(222, 226, 599)
2-$CH_3C_6H_4$		(100)		
3-$CH_3C_6H_4$		(100)		
4-$CH_3C_6H_4$		(100)		
4-$(CH_3)_3CC_6H_4$		(100)		
$HOOC(CH_2)_n$	C_6H_5	n = 2–3 (11)		

carbonyl group of the anil condenses with the methylene group of a second molecule of 3-allylrhodanine.

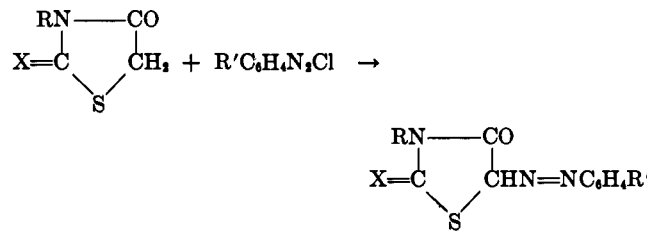


A similar reaction to the one taking place in acetic acid occurs if rhodanine reacts with the anil from isatin or thianaphthenone in the presence of acetic anhydride. The product is a vat dye (234).

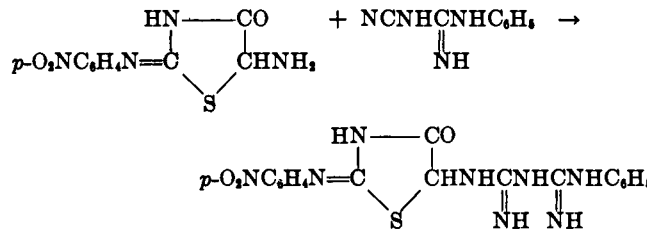


3. Reaction with diazonium salts

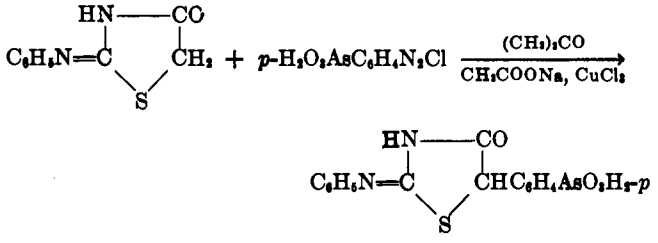
Diazonium salts undergo a coupling reaction with the 5-methylene group of rhodanines (283, 284, 485), 2,4-thiazolidinediones (69, 72, 73), and 2-substituted-imino-3-substituted(or hydrogen)-4-thiazolidinones (64, 65, 70, 445, 481).



Reduction of the phenylazo group of the 2-arylimino-5-phenylazo-4-thiazolidinones with sodium hydrosulfite is reported to yield the corresponding 5-amino-2-arylimino-4-thiazolidinones (479, 481). The amino group adds to the cyano group of *N′*-cyano-*N*-phenylguanidine (511).

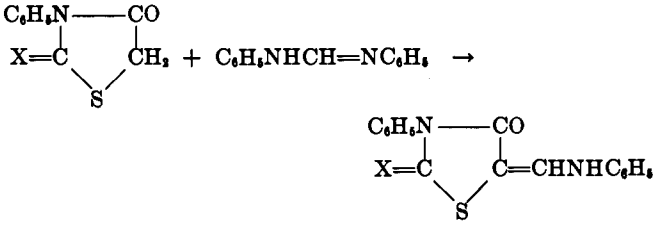


Performance of the coupling reaction between 2-arylimino-4-thiazolidinones and the diazonium salt under the conditions of the Meerwein reaction (in acetone solution in the presence of sodium acetate and cupric chloride) is reported to give 2-arylimino-5-phenyl-4-thiazolidinone in 50–68 per cent yield (480). This reaction has been used to introduce the *p*-arsenophenyl group into the 5-position of 2-phenylimino-4-thiazolidinone (498).



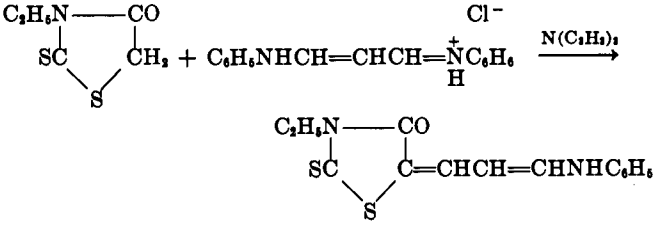
4. Reaction with diphenylformamidine

The electrophilic carbon atom of diphenylformamidine is attacked by the nucleophilic methylene carbon atom of rhodanines (147), 2,4-thiazolidinediones (154), and 2-substituted-imino-4-thiazolidinones (151, 154). The product is a 5-anilinomethylene derivative or, if the reaction is run in acetic anhydride, the 5-*N*-acetanilinomethylene derivative (587). The ease of formation of the 5-anilinomethylene derivative depends on the nature of X. If X = S, the reactants are heated in kerosene at 120°C. for 1 hr.; if X = O, heating for 3 hr. at 140–150°C. is required; while if X = NC_6H_5, heating for 5 hr. at the same temperature is necessary.



X = S, O, or NC_6H_5.

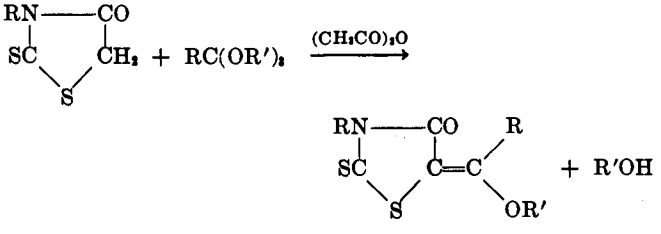
The product is the vinylog of an amide, and higher vinylogs may be prepared by using the appropriate vinylog of diphenylformamidine (167, 293).



Alternate syntheses and characteristic reactions of the 5-aminoalkylidenerhodanines are described in Section VI,B,2.

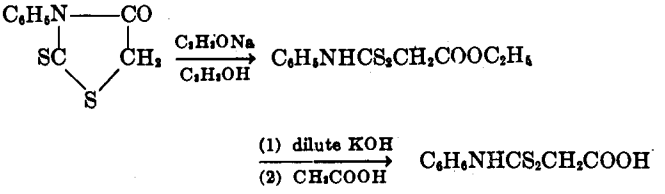
5. Reaction with ortho esters

Compounds containing an active methylene group react with ortho esters, with acetic anhydride being used frequently as a condensing agent. In acetic anhydride solution, rhodanine and its 3-substituted derivatives condense with methyl or ethyl orthoformate, methyl or ethyl orthoacetate, and ethyl orthopropionate and form the 5-(1-alkoxyalkylidene) derivatives (142, 372, 402). The reported yields vary between 22 and 97.5 per cent, depending on the nucleophilic reactivity of the methylene carbon atom of the rhodanine nucleus and the size of the R group of the ortho ester (372). When the ethyl orthobenzoate (R = phenyl) is used, no 3-carbethoxymethyl-5-(1-ethoxybenzylidene)rhodanine is obtained, although yields of 80.5 per cent are obtained from the same rhodanine and the orthoformate (R = H) or the orthoacetate ($R = CH_3$). The ease of the reaction permits the use of the 5-(1-ethoxyethylidene) derivatives for the identification of 3-substituted rhodanines (378).

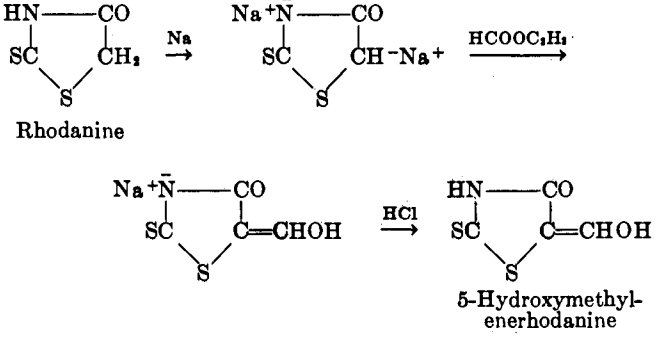


6. Reaction with sodium

Equimolar quantities of sodium in absolute alcohol and 3-phenylrhodanine, if acidified with acetic acid shortly after mixing, yield a product which analyzes for an addition product of one molecule of ethyl alcohol (311). The compound has properties identical with those of the substance produced when ammonium phenyldithiocarbamate reacts in the cold with ethyl bromoacetate (85). On standing more than a few minutes in dilute potassium hydroxide solution the ester is hydrolyzed and acidification gives the acid. Longer contact of 3-phenylrhodanine with sodium ethoxide gives intractable tars.

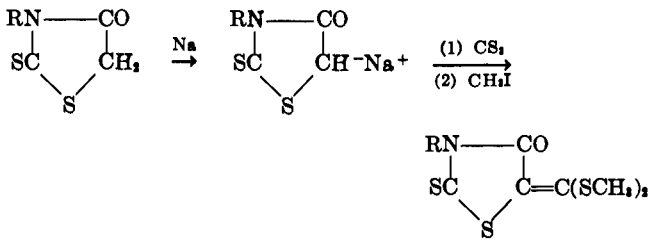


In anhydrous ether solution rhodanine reacts with two moles of sodium. The product, which would be a dianion, on condensation with ethyl formate and subsequent acidification forms 5-hydroxymethylenerhodanine (56). The reaction failed with 3-substituted rhodanine derivatives.

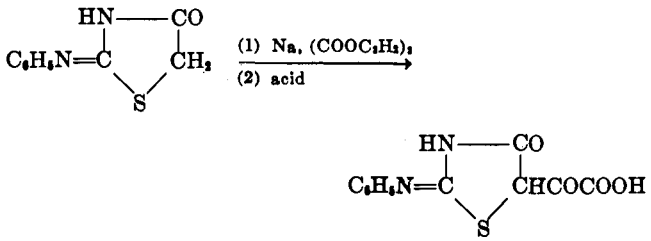


The sodium derivative prepared from a 3-substituted

rhodanine reacts with carbon disulfide, followed by methyl iodide, to form a 5-di(methylthio)methylene-3-substituted rhodanine (200, 202).



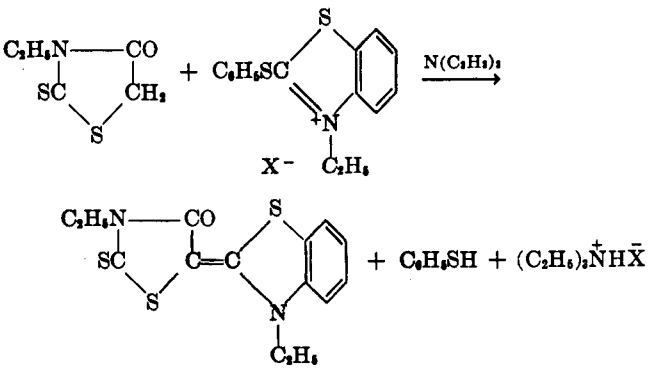
2-Phenylimino-4-thiazolidinone reacts with sodium and diethyl oxalate in ethanol. After acidification, a 5-keto acid is obtained (666).



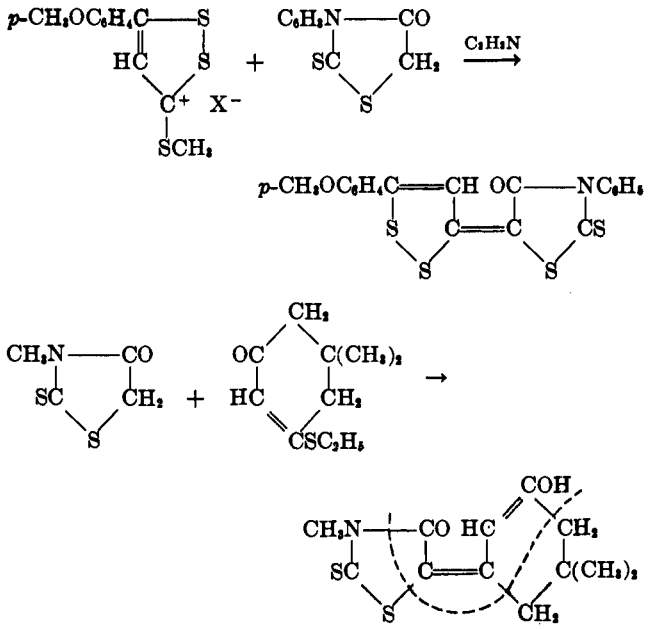
7. Reaction with electrophilic carbon atoms

Certain heterocyclic compounds with carbon atoms having pronounced electrophilic activity condense with the nucleophilic carbon atom of the 4-thiazolidinone nucleus in the presence of a base. The product is a merocyanine dye, a compound in which the carbonyl and nitrogen portions of an amide group are in different heterocyclic nuclei and are separated by one or more vinyl groups. Pyridine (475, 684), triethylamine (88, 336), and acetic anhydride with sodium acetate (483) have been used as condensing agents.

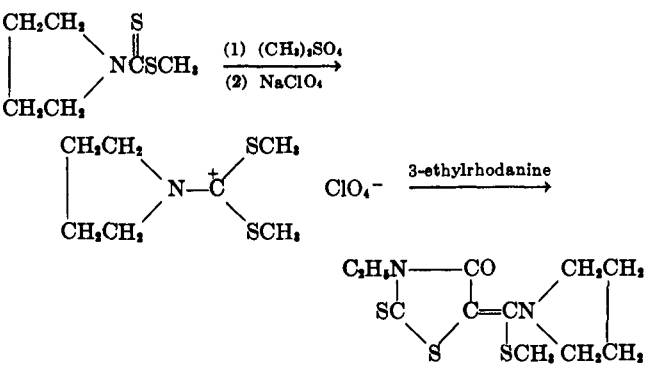
Heterocyclic quaternary ammonium salts with an active alkylthio or arylthio group attached to an electrophilic carbon atom react with the nucleophilic methylene groups of substituted rhodanines, 2,4-thiazolidinediones, and 2-imino-4-thiazolidinones (or the isomeric 2-amino-4(5*H*)-thiazolones). A merocyanine dye is formed and a mercaptan is evolved (1, 57, 88, 243, 336, 354).



Compounds related in method of formation and in structure to merocyanine dyes are ones which are vinylogs of carbamoyl aryl disulfide (542) or of acids (355).

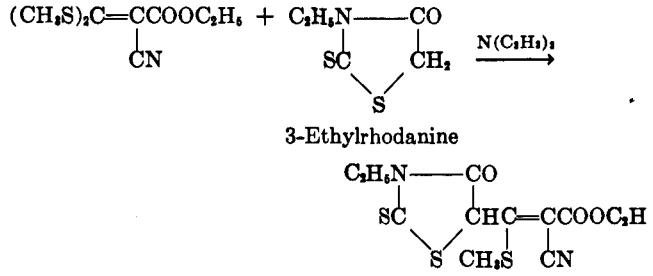


If two thiomethyl groups are attached to the same electrophilic carbon atom, reaction can take place with the nucleophilic carbon atom of a 3-substituted rhodanine. One thiomethyl group is displaced and the product contains two different nucleophilic groups attached to the exocyclic methylene carbon atom. This type of electrophilic carbon atom may also be formed by the methylation of the ester of a dithiocarbamate. The carbonium ion reacts with 3-ethylrhodanine, forming 3-ethyl-5-[(methylthio)(1-pyrrolidyl)methylenerhodanine] (505).



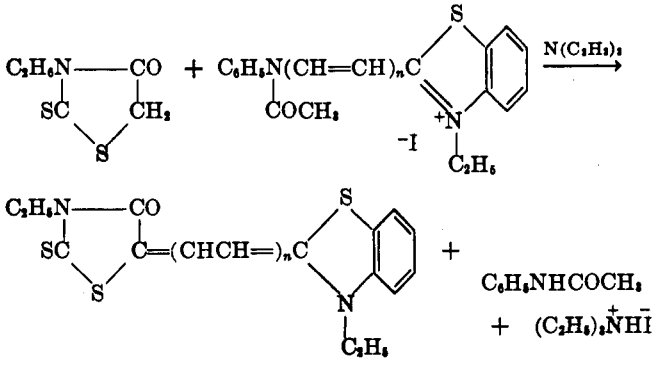
The carbon atom with two methylthio groups attached to it need not be a carbonium ion if other activating groups are present. 3-Ethylrhodanine reacts with ethyl α-cyano-β,β-di(methylthio)acrylate, displacing one methylthio group and forming 5-(2-carbethoxy-2-cyano-1-methylmercaptovinyl)-3-ethylrhodanine (187, 359).

An alkoxy group as well as an alkylthio group can be displaced by the nucleophilic carbon atom of a 3-substituted rhodanine. Such electrophilic carbon atoms



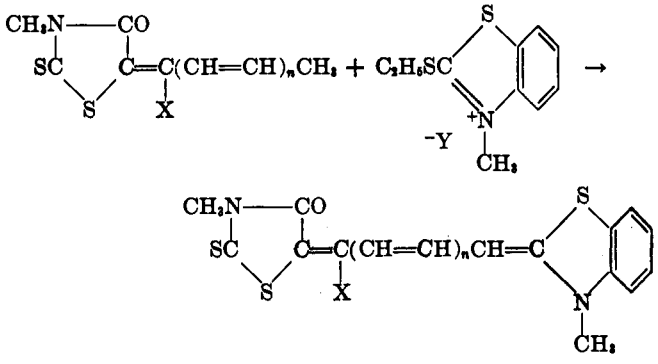
are present in 4-ethoxymethylene-2-thiono-5-thiazolidinone and 4-ethoxymethylene-2-phenyl-5-oxazolidinone (164, 371).

The electrophilic carbon atom can be separated from the quaternary nitrogen atom by one or more vinyl groups and if suitably activated condenses with the nucleophilic methylene carbon of a 3-substituted rhodanine. 2-Acetanilidovinyl-3-ethylbenzothiazolium iodide condenses with 3-ethylrhodanine and a merocarbocyanine dye is formed, while the introduction of additional vinyl groups leads to the formation of merodi(or tri)carbocyanine dyes (88, 90).

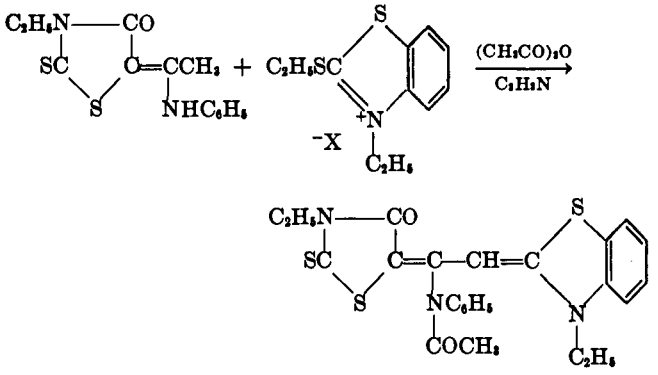


8. Transmission of nucleophilic activity to the vinylog of the methylene carbon

The nucleophilic character of the methylene carbon atom can be transferred by a series of conjugated bonds to the terminal methyl group of 5-ethylidenerhodanine or a higher vinylog (137, 505). The presence of a nucleophilic group on the 1′-carbon atom of the 5-substituent,

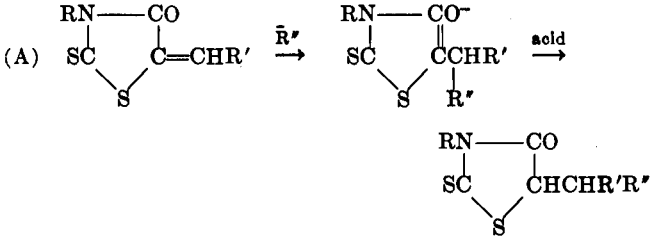


such as the 1′-alkoxy (X = OR) (374), the 1′-alkyl(or aryl)thio (X = SR) (375), the 1′-acetyl (X = $COCH_3$) or the 1′-carbethoxy (X = $COOC_2H_5$) (373), and the 1′-anilino group enhances the nucleophilic activity of the terminal methyl group. With the 1′-anilino substituent the nucleophilic activity of the terminal methyl group, as illustrated by its condensation with quaternary salts, is increased by the acylation of the exocyclic nitrogen (591).

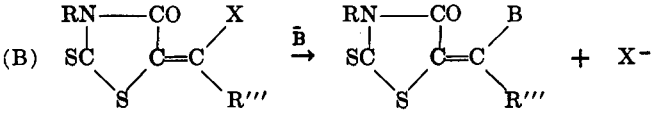


B. REACTIONS DEPENDENT UPON THE ELECTROPHILIC ACTIVITY OF THE EXOCYCLIC METHYLENE CARBON ATOM OF 5-METHYLENE-4-THIAZOLIDINONE

The electrophilic character of the 1′-carbon atom in 5-alkylidene-4-thiazolidinones is the basis for many reactions with nucleophilic reagents. Two general types of reaction have been described: (A) 1,4-addition to the conjugated carbonyl group:



(B) displacement reactions of the S_N2 type.

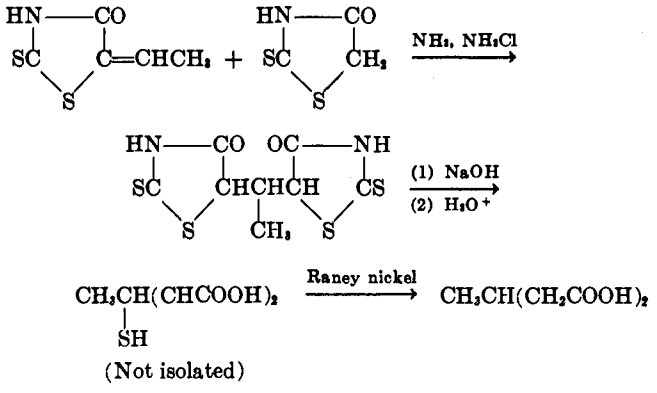


Examples of the addition reaction are found with compounds in which the electrophilic carbon atom is holding hydrogen, alkyl, or aryl, while with the displacement reaction, a potentially nucleophilic group is attached to the electrophilic carbon atom.

1. 1,4-Addition to the conjugated carbonyl group

(a) The Michael reaction

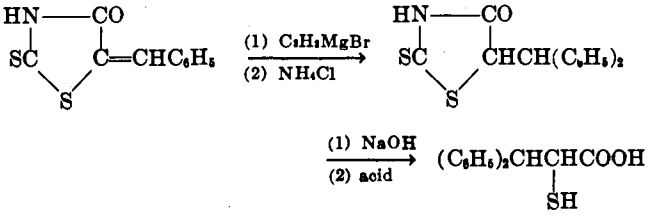
Rhodanine, by virtue of its nucleophilic methylene group, undergoes a Michael reaction with 5-ethylidenerhodanine in the presence of a base (81). The product, 1,1 - bis(4 - ketotetrahydro - 2 - thio - 5 - thiazolyl)-ethane, may also be obtained if two moles of rhodanine react with acetaldehyde under the same conditions. Isolation of the unsaturated compound resulting from the aldol condensation reaction is therefore unneces-



sary. The structure of the Michael condensation product was determined by (*1*) ultraviolet absorption spectra and (*2*) alkaline hydrolysis (see Section VI,C,3), followed by desulfurization with Raney nickel to the known β-methylglutaric acid.

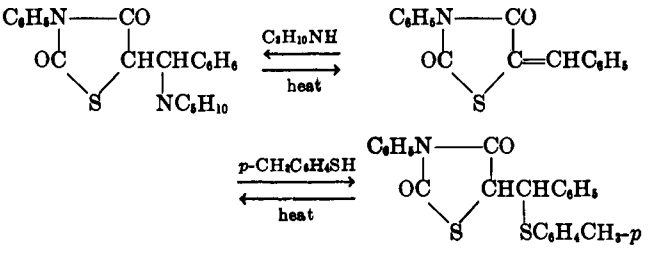
(b) Reaction with the Grignard reagent

The Grignard reagent adds to the conjugated carbonyl linkage of 5-benzylidenerhodanine and of 5-benzylidene-3-phenyl-2,4-thiazolidinedione, forming the 5-aralkyl derivatives (452, 453). A large excess of the Grignard reagent is used. In addition to reaction with the active hydrogen atom of rhodanine, the carbanion of the Grignard reagent attacks the exocyclic electrophilic carbon atom of the 5-benzylidenerhodanine. Acidification of the anion yields the 5-benzhydrylrhodanine, whose structure was assigned on the basis of its hydrolysis by alkali to α-mercapto-β,β-diphenylpropionic acid. The Grignard reagent does not attack the carbonyl or thione groups of the thiazolidine ring; rhodanine and 3-phenyl-2,4-thiazolidinedione are stable to this reagent.

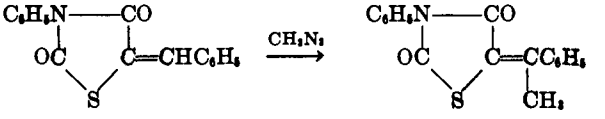


(c) Reaction with other nucleophiles

The above examples of 1,4-addition to the conjugated carbonyl group involve attack by carbanions. Under the proper conditions 5-arylidene-3-phenyl-2,4-thiazolidinediones add thiocresol or piperidine, forming compounds which dissociate into their constituents above the melting point (454). The reaction with piperidine takes place at room temperature; at the reflux temperature, the thiazolidinone ring is ruptured and phenylpiperidylurea is formed (Section VI,C,4). The addition of piperidine is in contrast to earlier work which indicates that amines do not add to the double bond conjugated with the carbonyl group in 3-substituted 5-alkylidenerhodanines (401).

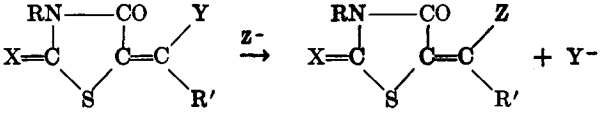


Although the final product is still an α,β-unsaturated carbonyl compound, the addition of diazomethane to 3-aryl-5-arylidene-2,4-thiazolidinedione (454) is a reaction of the α,β-unsaturated carbonyl compound. Diazomethane, either as the carbene or in the resonance form which has an unshared pair of electrons on the carbon atom, attacks the electrophilic carbon of the 3-aryl-5-arylidene-2,4-thiazolidinedione. Migration of the hydrogen atom forms the stable product.



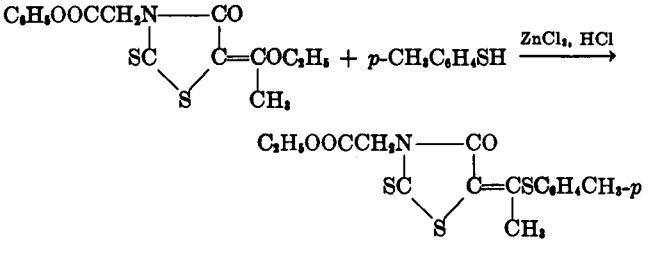
2. Displacement reactions

In the reactions of type B (see page 485) the attachment of a potential anion, such as ethoxy, increases the electrophilic character of the exocyclic methylene carbon atom and displacement by other anions takes place readily.

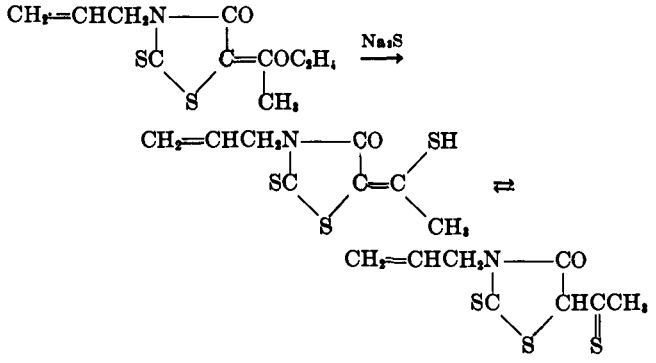


(a) Displacement of alkoxy by alkylthio or arylthio

The alkoxy group of a 5-(1-alkoxyalkylidene)rhodanine can be replaced by an alkylthio or arylthio group and the corresponding alkylthio (or arylthio) derivative is produced (372, 376, 379). Zinc chloride

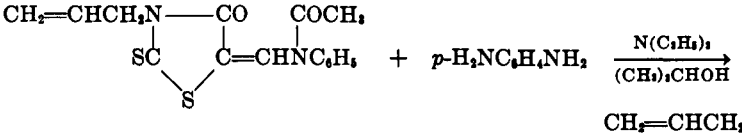


in dioxane solution saturated with hydrogen chloride brings about the reaction, and in several cases two isomers, believed to be cis and trans, are isolated (Section V,B). Sodium sulfide, in aqueous alcoholic solution, converts 3-allyl-5-(1-ethoxyethylidene)rhodanine into the corresponding mercapto derivative, which is tautomeric with the 5-thioacetyl derivative (381). With these derivatives, as with the alkoxy derivative (Section VI,A,8), the carbon atom of the terminal methyl group possesses nucleophilic activity.

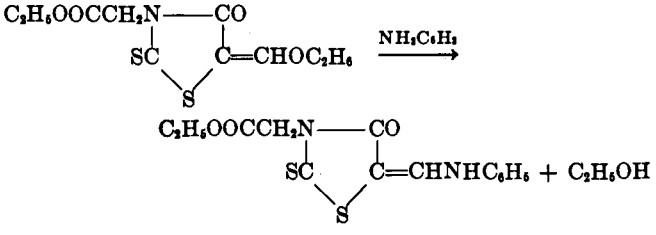


(b) Displacement of alkoxy by amino

Amines, both primary and secondary, react with



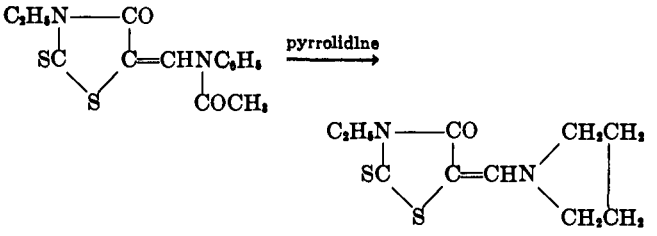
5-(1-ethoxyalkylidene)rhodanines and their 3-substituted derivatives, forming 5-(1-aminoalkylidene)rhodanines (219, 372, 401, 591), identical with the reaction product of rhodanines and substituted formamidines



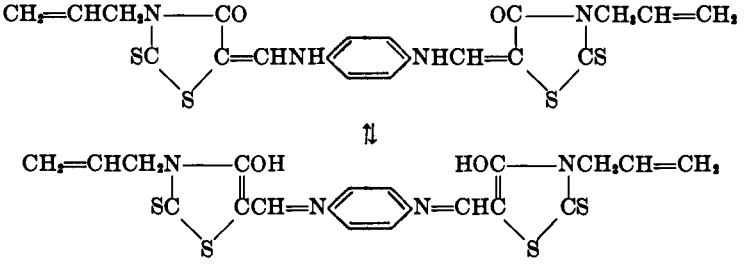
(Section VI,A,4). If a primary amine is used, the nitrogen atom can be acylated with acetic anhydride and triethylamine (89). With 3-unsubstituted rhodanine derivatives, the amine salt of the 5-aminomethylenerhodanine is frequently isolated and acidification gives the 5-aminomethylenerhodanine (401). With a few exceptions, the yields are over 50 per cent and frequently are very high.

(c) Displacement of acetanilino by amino

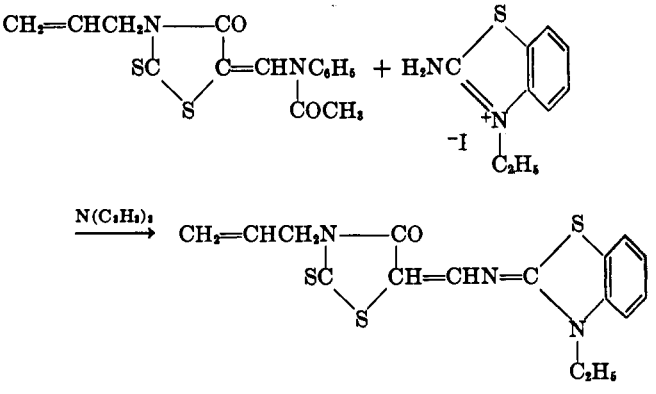
Amines can displace the acetanilino group attached to the electrophilic carbon atom. Refluxing 5-acetanilinomethylene-3-ethylrhodanine with other amines, such as pyrrolidine, yields 3-ethyl-5-pyrrolidylmethylenerhodanine (505).



With diamines, such as *p*-phenylenediamine, two moles of 5-acetanilinomethylene-3-alkylrhodanine form a type of dye known as an azanol (40) from its similarity in structure to an oxonol (Section VI,B,2,(g)). Instead of the rhodanine derivative, the corresponding 2,4-thiazolidinedione or 2-imino-4-thiazolidinone derivatives can be used (41).



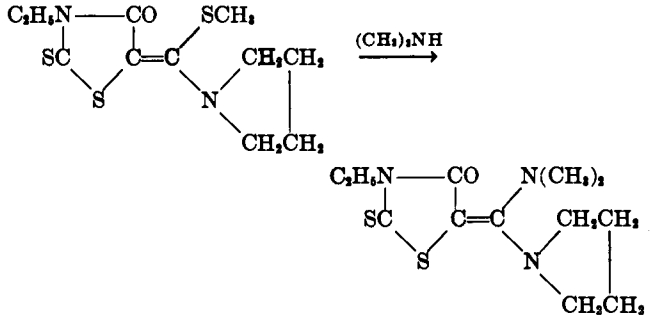
Displacement of the acetanilino group by an amino group also occurs if the amino group is attached to a carbon atom which has a quaternary nitrogen ion attached to it. The product is an azomerocyanine dye in which one methinyl group of the conjugated chain is replaced by nitrogen (262, 628).



(d) Displacement of methylthio by amino

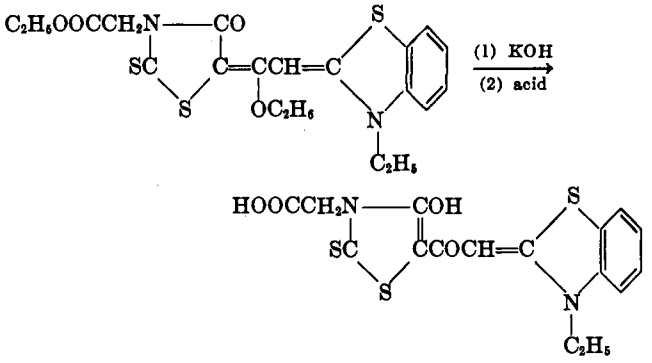
An amino group can also displace a methylthio group. In an example which has both a methylthio and an amino group attached to the electrophilic carbon atom, treatment with an amine results in the displacement of the methylthio group rather than the amino group and the formation of a compound with two amino

groups on the same carbon atom (505). The vinylog of 3-ethyl-5-[(methylthio)(1-pyrrolidyl)methylene]rhodanine undergoes the same type of reaction.



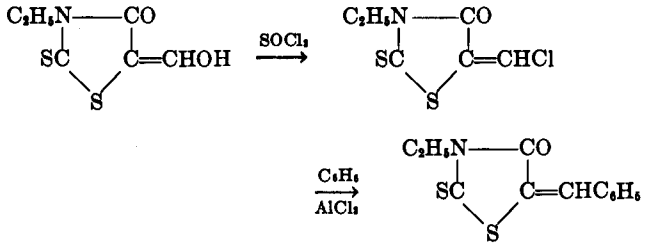
(e) Displacement of ethoxy by hydroxy

3-Substituted 5-ethoxymethylenerhodanines may be hydrolyzed under mild conditions which convert the ethoxy group to hydroxy and do not cleave the thiazolidinone ring. Stirring the compound for 10 hr. or longer at room temperature or below with $N/6$ sodium hydroxide and subsequent acidification gives good yields of the 5-hydroxymethylene derivative (56). If more complex groups replace the hydrogen attached to the electrophilic carbon atom, the ring is sufficiently stable to resist hydrolysis on refluxing with dilute potassium hydroxide and 51–76 per cent yields of the hydroxy derivative (formulated as the tautomer) are obtained (373).



(f) Displacement of hydroxy by chloro

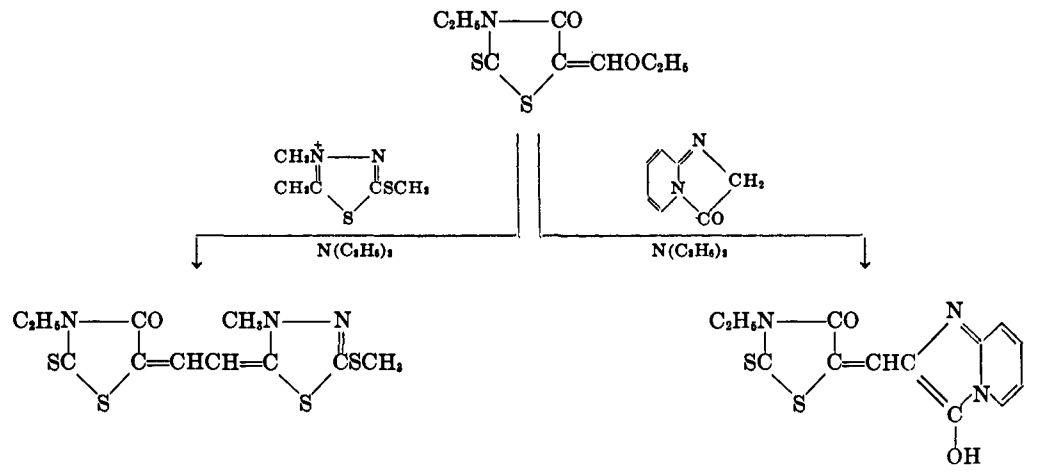
Thionyl chloride converts the 5-hydroxymethylenerhodanines into 5-chloromethylenerhodanines (56) which are vinylogs of acid chlorides. These compounds participate in a Friedel-Crafts reaction with aromatic hydrocarbons. The product is identical with that obtained by the aldol condensation of 3-ethylrhodanine



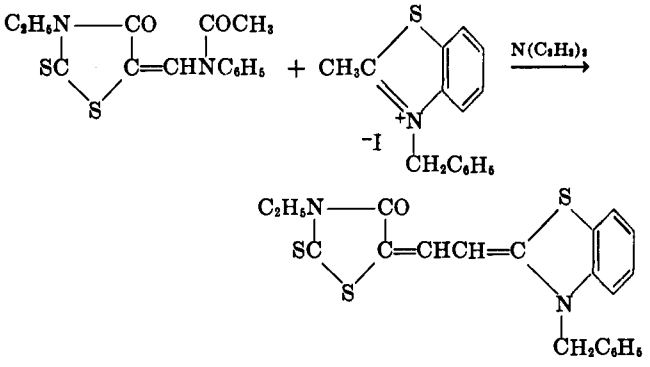
and benzaldehyde. Yields in the individual steps are good, and there is considerable theoretical interest in the participation of rhodanine derivatives in the Friedel–Crafts reaction. Nevertheless, the four-step process from 3-ethylrhodanine is of practical use only when the aldehyde necessary for the aldol condensation is not readily available.

(g) Displacement of nucleophilic groups by carbanions

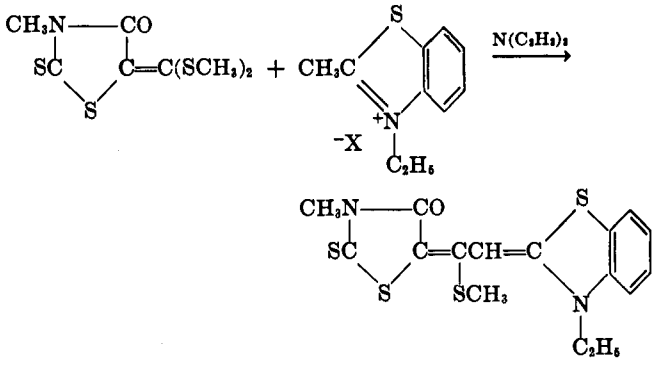
The exocyclic electrophilic carbon atom of 5-(1-alkoxyalkylidene)rhodanines and of 5-(1-acetanilinoalkylidene)rhodanines condenses with nucleophilic centers of heterocyclic compounds and forms merocyanine dyes, similar in structure to and sometimes identical with the ones formed by the reaction of the nucleophilic carbon atom of a rhodanine with an electrophilic carbon atom (Section VI,A,7). Among the reactions of the former type of compound are those of 5-ethoxymethylidene-3-ethylrhodanine with the nucleophilic methyl group attached to the carbon atom adjacent to the quaternary nitrogen atom of a heterocyclic ring (195) or a nucleophilic methylene group (377). It is not necessary to isolate the alkoxyalkylidene derivative;



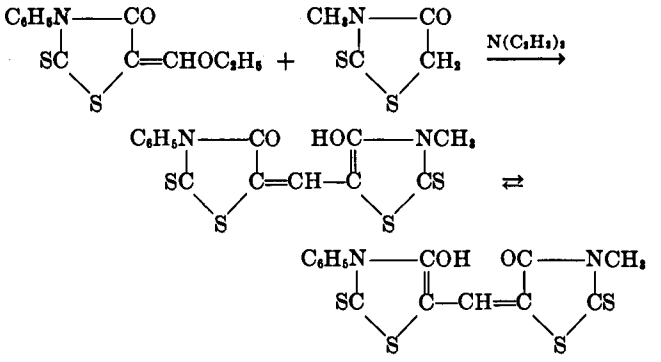
heating 2-diphenylamino-2-thiazolin-4-one and the quaternary salt of 2-methylbenzothiazole with ethyl orthoformate and trialkylamine yields the merocyanine dye (382, 392). Similar reactions are possible where the electrophilic nature of the exocyclic methylene carbon atom is enhanced by an acetanilino group (39, 89, 91, 169, 354, 555, 564, 587, 590). Additional vinyl groups can be present between the carbonyl and acetanilino groups (167).

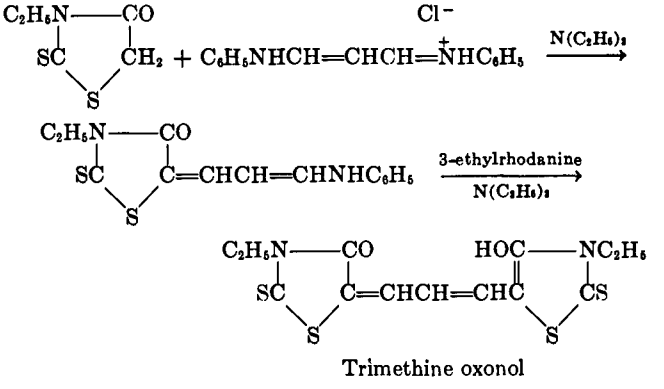


If the electrophilic 5-methylene carbon atom has two thiomethyl groups attached to it (Section VI,A,6), reaction can take place with a nucleophilic methyl group. The carbon atom of the latter displaces one thiomethyl group and forms a merocarbocyanine dye which has a thiomethyl group attached to a carbon atom in the conjugated chain (199, 201).



The nucleophilic methylene group of rhodanines and the suitably activated electrophilic exocyclic carbon atom of 5-substituted methylene derivatives of rhodanine can condense with each other and produce oxonols. The activating group may be ethoxy as in 5-ethoxymethylenerhodanines (402), or acetanilino as in 5-acetanilinorhodanines (169). With different groups attached to the nitrogen atom, an unsymmetrical oxonol is formed. If a symmetrical oxonol is desired, it is unnecessary to isolate the 5-alkoxymethylene intermediate, since excess of the rhodanine and more drastic conditions favor oxonol formation. As reagents for the production of symmetrical oxonols, the ortho esters $RC(OR')_3$ (360), the acetal esters $RC(OR')_2OCOCH_3$ (173), and formamide (321) have been used. If the reaction between 3-phenylrhodanine and diphenylformamide is conducted in acetic anhydride at 160–180°C. instead of in aniline solution at 100°C., the formation of the oxonol rather than the 5-anilinomethylene derivative is favored (468). Equimolar quantities of 3-ethylrhodanine, β-anilinoacraldehyde anil hydrochloride, and triethylamine on being refluxed in ethanol for 2 min. form 3-ethyl-5-(γ-anilinoallylidene)rhodanine, while refluxing for 6 hr. with an excess of the rhodanine yields the trimethine oxonol (293).





Trimethine oxonol

C. REACTIONS WITH ACIDS AND BASES

1. Salt formation

The acidic and basic properties of the 4-thiazolidinones in aqueous solution are dependent on the presence of hydrogen on the nitrogen atom of the 4-thiazolidinone ring and the type of group attached to the carbon atom in the 2-position.

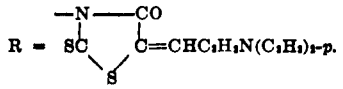
2,4-Thiazolidinedione and rhodanine are weak acids. The ionization constant of the former is 1.46×10^{-7} at 18°C. and 1.81×10^{-7} at 25°C. (351); that of the latter is 1.69×10^{-6} at 20°C. (213). Since 5,5-disubstituted rhodanines and 2,4-thiazolidinediones show little difference in values of ionization constants from the unsubstituted compounds, the acidity is attributed to the hydrogen atom attached to nitrogen (212). Ionization constants of 5,5-disubstituted 2,4-thiazolidinediones increase with increasing size of the alkyl group and with the introduction of unsaturation into the alkyl group (214).

5-(*p*-Diethylaminobenzylidene)rhodanine is an ampholyte. Its protonated form has an ionization constant

of 2×10^{-4} and the compound itself a value of 7×10^{-7} when measured in 20 per cent ethanol and at an ionic strength of 0.05 (524).

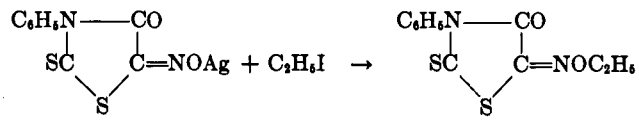
$$\underset{\text{(very pale yellow)}}{HR{-}H^+} \rightleftarrows \underset{\text{(pink)}}{HR} + H^+$$

$$HR \rightleftarrows H^+ + \underset{\text{(yellow)}}{R^-}$$



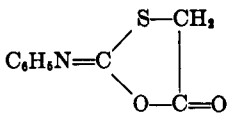
Pseudothiohydantoin is a weak acid and forms a salt on solution in sodium hydroxide. In addition, the 2-imino group confers basic properties on the compound and its hydrochloride is soluble in water. The free base may be recovered on neutralization with ammonia or sodium acetate (12, 414).

Both basic properties and acidic properties are present in 5-oximinopseudothiohydantoin. Its acidic ionization constant is 5.5×10^{-8} (297), and its salts with metals, if water soluble, are hydrolyzed. Salts with heavy metals frequently precipitate as double salts (194). The silver salt of 5-oximino-3-phenylrhodanine reacts with ethyl iodide and forms the *O*-ether (281).

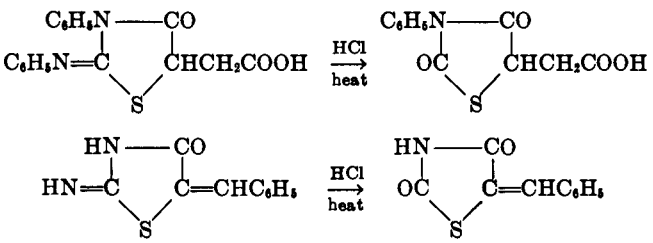


2. Hydrolysis with acid

Heating the aqueous solution of the hydrochloride of pseudothiohydantoin produces a compound with the empirical formula $C_3H_3NSO_2$ (368, 654). Similarly, 3-phenyl-2-phenylimino-4-thiazolidinone yields the phenyl homolog, which was originally formulated as a derivative of 1,3-oxathiole (396). Recognition of its easy synthesis from the 2-imino compound and of

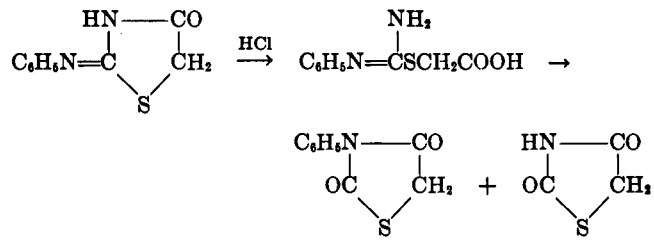


the presence of the thiazole structure indicates that the correct structure is 2,4-thiazolidinedione or its tautomer (298). Acid hydrolysis produces the same type of reaction if saturated or unsaturated substituents are attached to the carbon atom in the 5-position of the 4-thiazolidinone ring (24, 593).



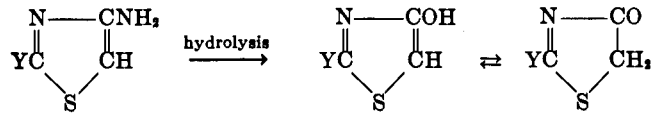
The hydrolysis can be conducted with hydrogen chloride in glacial acetic acid. Neutralization of the hydrogen chloride with sodium acetate (418, 441) or pyridine (151) prevents the hydrolysis. Dilute sulfuric acid will accomplish the hydrolysis in some cases in which hydrogen chloride in glacial acetic acid is not effective, but prolonged hydrolysis with 20 per cent sulfuric acid can hydrolyze the thiazolidinone ring to the urea and mercaptoacetic acid (335).

Since acid hydrolysis of 3-phenyl-2-phenylimino-4-thiazolidinone yields 3-phenyl-2,4-thiazolidinedione (397), it would seem that this reaction might be used to locate the substituent phenyl group as being attached to either the exocyclic nitrogen or the ring nitrogen. However, 2-phenylimino-4-thiazolidinone, whose structure was proven by alkylation with benzyl chloride, gives both 2,4-thiazolidinedione and 3-phenyl-2,4-thiazolidinedione on warming with dilute hydrochloric acid (668). Hydrolysis to an intermediate open-chain acid was believed to be responsible for the isolation of the two cyclic compounds.



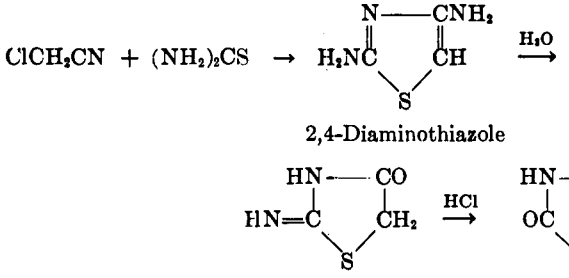
The formation of the 5-benzylidene derivative makes the thiazolidinone ring sufficiently stable to remain intact during mild acid hydrolysis and the reaction can be used to locate the position of substituents in the original compound (148, 165). By means of this reaction and the hydrolysis of the alkylated derivatives, previously assigned erroneous structures (55) were corrected (146, 150, 165, 406).

Thiazoles or 4-thiazolines which contain an amino group attached to the 4-position are extremely sensitive to hydrolysis and are easily converted to the 4-hydroxy derivatives, which are tautomeric with 4-thiazolidinones or 2-thiazolin-4-ones. The hydrochloride of 2,4-diaminothiazole, which is formed when chloroacetonitrile reacts with thiourea, is hydrolyzed by water to pseudothiohydantoin, and by concentrated hydrochloric acid to 2,4-thiazolidinedione (162).

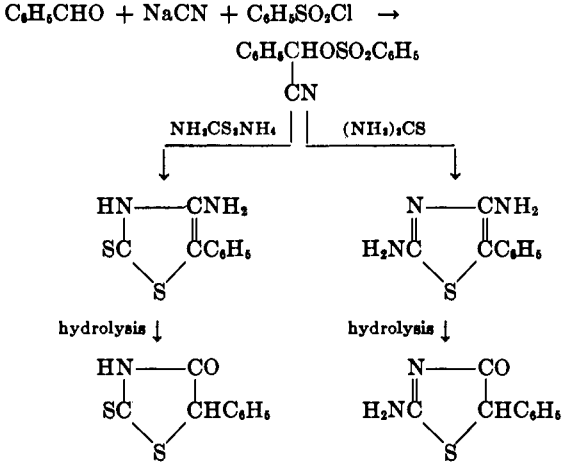


An unidentified sulfur-containing oil has been obtained from the reaction of chloroacetonitrile and ammonium dithiocarbamate.

Instead of chloroacetonitrile, α-cyanobenzyl benzenesulfonate can react with thiourea (184) or with substi-

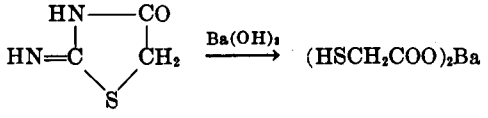


tuted thioureas (624). Either the 5-phenyl-2,4-diaminothiazoles or the corresponding 2-imino-4-thiazolidinones can be isolated if the proper conditions are chosen. The use of ammonium dithiocarbamate instead of thiourea yields the corresponding 4-amino-2-mercaptothiazole, which on acid hydrolysis produces 5-phenylrhodanine (625). Halogen-substituted benzaldehydes form the corresponding α-cyanobenzyl benzenesulfonates (183).



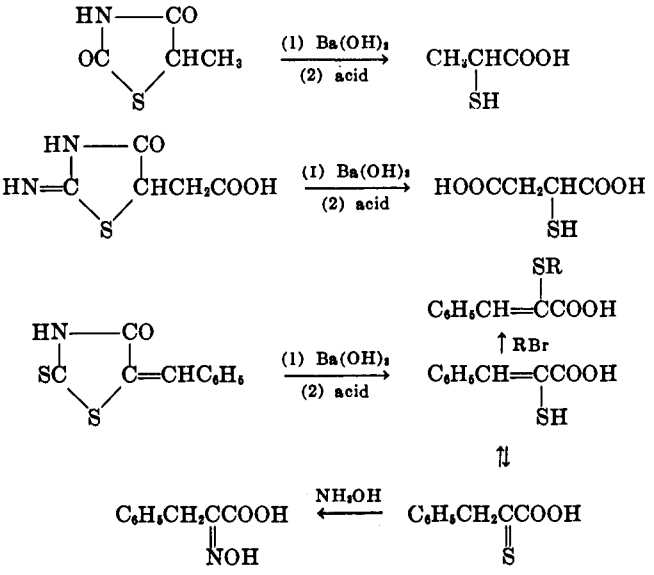
3. Hydrolysis with alkali

Shortly after their discovery, the compounds later recognized as 4-thiazolidinones were subjected to alkaline hydrolysis. An aqueous solution of barium hydroxide, heated in a sealed tube at 100°C. with pseudothiohydantoin, produced an unidentified barium salt (414). After the development of Andreasch's test for mercaptoacetic acid (a positive test is shown by a blue color in the presence of a few drops of 0.1 per cent iron(III) chloride solution, which becomes red on treatment with ammonia (16)), the product of alkaline hydrolysis of pseudothiohydantoin was identified as barium mercaptoacetate.



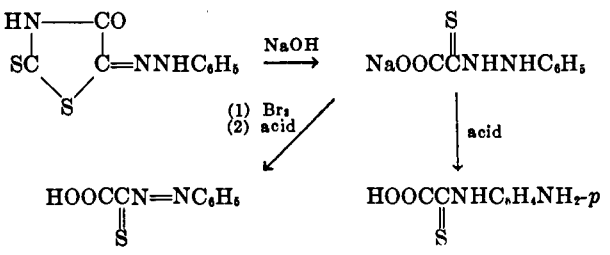
This test has been used as the basis for qualitative tests for 4-thiazolidinones with variations in the colors of the solutions in acid and ammonia being characteristic of individual compounds (635). Mercaptoacetic acid is also formed during the hydrolysis of 3-phenyl-2,4-thiazolidinedione (218), and its disulfide can be isolated from the hydrolysis of rhodanine (267). In addition to mercaptoacetic acid, 1,3-diphenylurea is obtained from the alkaline hydrolysis of 3-phenyl-2-phenylimino-4-thiazolidinone (390), and dicyandiamide from pseudothiohydantoin (15).

Alkaline hydrolysis of 5-alkyl-2,4-thiazolidinediones (178) or of 5-alkylpseudothiohydantoins (465, 470, 540, 593, 660) gives the corresponding α-mercaptoalkanoic acid, while the same reaction, if applied to 5-arylidenerhodanines (76, 261, 683) yields β-substituted α-mercaptoacrylic acids, which can exist in two tautomeric forms.



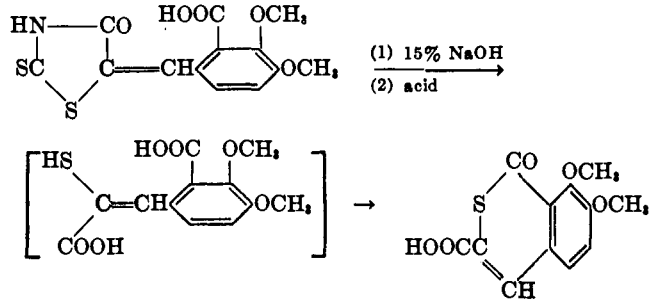
Although some chemical evidence for each form exists, such as the formation of sulfides and oxidation to disulfides from the ene-thiol form (261), and the formation of oximes from the thione form (274), the ultraviolet spectral evidence favors the ene-thiol structure as the predominant form (121). Some 5-arylidenerhodanines which are resistant to cleavage in aqueous or ethanolic solution have been hydrolyzed by sodium in boiling amyl alcohol (33).

5-Phenylazorhodanines are hydrolyzed by heating with 10 per cent sodium hydroxide solution (285). The original hydrolytic product, which is a thioöxalic phenylhydrazide, is oxidized by bromine and is easily isomerized by acids to the *p*-aminophenylthioöxamide.

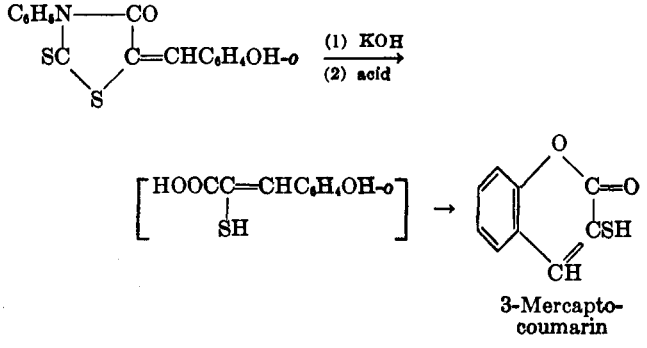


The presence of certain substituents, such as carboxy, hydroxy, or amino, in the ortho position of the

benzene ring of the α-mercapto-β-phenylacrylic acid permits cyclodehydration with the formation of a heterocyclic ring structure. An *o*-carboxyl substituent produces an isothiocoumarin (102, 177, 350).

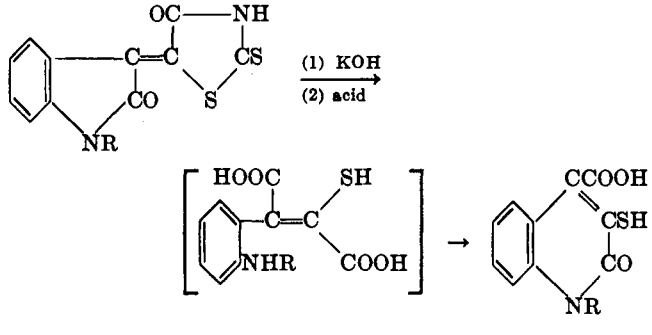


Cyclodehydration of the compound produced by basic hydrolysis of 5-(*o*-hydroxybenzylidene)-3-phenylrhodanine yields 3-mercaptocoumarin, which was analyzed as its *S*-benzyl ether (33).

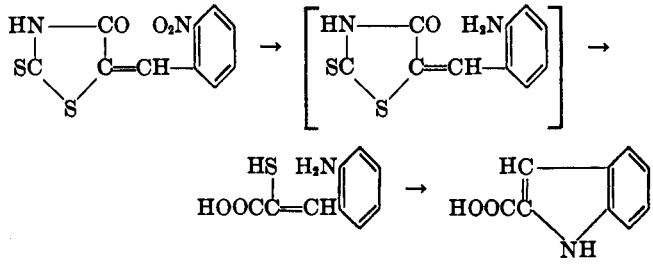


3-Mercaptocoumarin

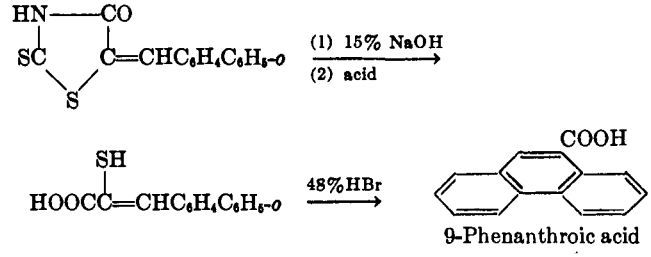
Rhodanine derivatives of isatin or its methyl derivatives on alkaline hydrolysis give mercapto derivatives of ketocinchoninic acids (277, 278, 344).



In certain cases cyclization occurs with loss of hydrogen sulfide. Reduction of 5-(*o*-nitrobenzylidene)rhodanine in an alkaline medium yields 2-indolecarboxylic acid (279).



Similarly, the alkaline hydrolysis of 5-(*o*-phenylbenzylidene)rhodanine gives α-mercapto-β-(*o*-phenylphenyl)-acrylic acid, which is cyclized by refluxing with 48 per cent hydrobromic acid to 9-phenanthroic acid (84).



9-Phenanthroic acid

The α-mercaptoacrylic acids are reduced with sodium amalgam in basic solution to the α-mercaptalkanoic acid (X, table 6) (274). Hydrogenolysis to the desulfurized saturated acid (V) has been accomplished with zinc amalgam in acid solution (274). Heating the α-mercaptoacrylic acid in the presence of ammonia converts it to the corresponding pyruvic acid (IV) (274), and this reaction is considered responsible for the odor of hydrogen sulfide which often accompanies the alkaline hydrolysis of the 5-arylidenerhodanine (121).

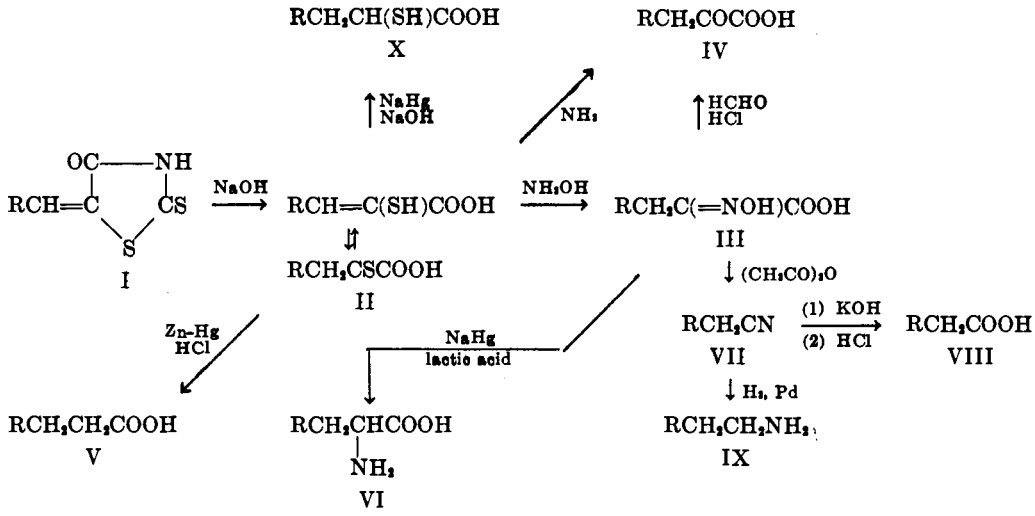
5-Arylidene derivatives of pseudothiohydantoin and of 2,4-thiazolidinedione are also hydrolyzed to the corresponding α-mercaptoacrylic acid (400). With the latter, the hydrolysis reaction requires 8 hr. or longer at 40–50°C. in comparison with 30 min. to 1 hr. at 90–100°C. for the rhodanine derivative. With 5-arylidenepseudothiohydantoin, the product contains disulfides and is not recommended for subsequent reactions (400), but it has been reported that certain 5-arylidene-2-phenylimino-4-thiazolidinones can be converted to α-mercaptoacrylic acids in a form suitable to be used as starting material for subsequent reactions (71, 496).

With the 2-alkyl-4-thiazolidinones, such as the methyl ester of actithiazic acid, an ester group attached to the alkyl group can be saponified without destroying the thiazolidinone ring (429). Optically active salts of this acid are racemized on standing in dilute alkaline solution, and this behavior is assumed to be caused by rupture and reclosure of the thiazolidinons ring.

An important series of reactions has been developed from the α-mercaptoacrylic acids and is frequently called the Gränacher synthesis (274), although its usefulness has been enlarged by its application to the synthesis of types of compounds not included in the original report (345). The α-mercaptoacrylic acid, probably as the thione tautomer, reacts with hydroxylamine and forms the α-oximinoalkanoic acid (III). In general, the crude sulfur-containing acid is used, and its tendency to become oxidized requires that the

TABLE 6

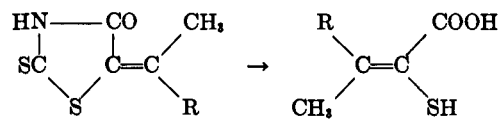
Products obtained from the Grănacher synthesis



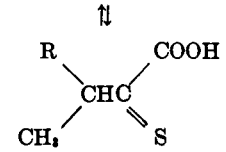
R	Derivatives	Reference
C_6H_5	I, II, III, IV, V, VI, X	(274)
	II*†	(400)
	II*	(71)
	I, II, III, VI	(260)
o-ClC_6H_4	I, II, III, VII, VIII	(123)
	II, III, VII	(71)
m-ClC_6H_4	I, II, III, VII, VIII	(123)
p-ClC_6H_4	I, II, III, VII, VIII	(123)
	II*, VII	(71)
o-BrC_6H_4	I, II, III, VII, VIII	(123)
m-BrC_6H_4	I, II, III, VII, VIII	(123)
p-BrC_6H_4	I, II, III, VII, VIII	(123)
p-$(CH_3)_2CHC_6H_4$	I, II, III, IV, VI	(275)
o-$C_6H_5C_6H_4$	I, II, III	(84)
m-$O_2NC_6H_4$	II*	(71)
p-$(CH_3)_2NC_6H_4$	II*	(71)
m-HOC_6H_4	II*	(71)
o-HOC_6H_4	II*	(71)
p-HOC_6H_4	I, II, III, VI	(260)
	I, II, III, VII, VIII	(385)
	I, II, X	(61)
	II*	(71)
o-$CH_3OC_6H_4$	I, II, III, VII, VIII‡	(575)
m-$CH_3OC_6H_4$	I, II, III, VII	(46)
	I, II, III, VI	(287)
p-$CH_3OC_6H_4$	I, II, III, IV, VI	(275)
	I, II, III, VII, VIII, IX	(345)
	I, II, X	(61)
	II*	(71)
3,4-$(HO)_2C_6H_3$	I, II, X	(61)
3-HO-4-$CH_3OC_6H_3$	I, II, III, VII, VIII	(288)
4-HO-3-$CH_3OC_6H_3$	I, II, III, VII, VIII	(247)
2,3-$(CH_3O)_2C_6H_3$	I, II, III, VII	(51)
2,4-$(CH_3O)_2C_6H_3$	I, II, III, VII	(206)
2,5-$(CH_3O)_2C_6H_3$	I, II, III, VII, VIII	(575)
2,6-$(CH_3O)_2C_6H_3$	I, II, III, VII, VIII	(364)
3,4-$(CH_3O)_2C_6H_3$	I, II, III, VII, VIII, IX	(345)
	II*	(400)
	I, II, X	(61)
3,4-$(CH_2O_2)C_6H_3$	I, II, III, VI	(275)
	I, II, III, VII, VIII, IX	(345)
	II*	(71)
2,6-$(CH_3O)_2$-4-$CH_3C_6H_2$	I, II, III, VII, VIII	(364)
3,4-(CH_2O_2)-5-$CH_3OC_6H_2$	I, II, III, VII, IX	(504)
	II, III	(294)
$(CH_3)_2C{=}CH(CH_2)_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}{=}CH$	I, II, III, VII, VIII	(364)
$C_6H_5CH{=}CH$	I, II, III, IV	(242)
$C_6H_5CH{=}C(CH_3)$	I, II, III	(242)
$C_6H_5CH{=}C(C_6H_5)$	I, II§	(242)
$C_6H_5CH{=}C(C_6H_5)$	I, II§	(242)
1-(2-HOC_6H_3)	I*, II, III, VII	(496)

TABLE 6 (*Continued*)

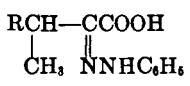
R	Derivatives	Reference
2-C_5H_3O	I, II, III, VI	(274)
	I, II, III, VII, VIII	(489)
	II*†	(400)
	V	(274)
2-C_4H_3S	I, II, III, VII, VIII, IX, VI	(140)
	II†	(400)
2-C_4H_3Se	I, II, III	(675)
2-[3,5-$(CH_3)_2$-4-(C_2H_5OOC)]C_3N	I, II, III, VI	(389)
5-(3-CH_3)C_3HN_2	I, II, III, VII, IX	(329)
4-$C_3H_3N_2$	I, II, III, VII, IX	(550)
4-(1-CH_3)C_3HN_2	I, II, III, VII, IX	(329)
4-(1-C_6H_5)C_3HN_2	I, II, III, VII, IX	(551)
4-(5-C_6H_5)C_3HN_2	I, II, III, VII, IX	(551)
4-[1,5-$(C_6H_5)_2$]C_3N_2	I, II, III, VII, IX	(551)
3-Indoxyl	I, II, V, IV, III	(278)
3-Indole	I, II, IV	(276)
5-(8-HO)C_9H_5N	I*, II, III, VII	(496)
7-(8-HO)C_9H_5N	I*, II, III, VII	(496)



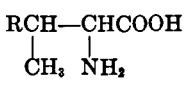
XI



XII



XIII

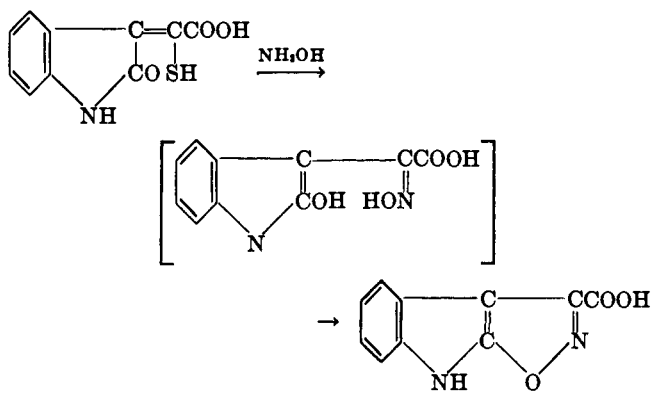


XIV

R	Derivatives	Reference
CH_3	XII, XIII, XIV	(260)
C_6H_5	XII, XIII	(260)

* Prepared from the corresponding pseudothiohydantoin.
† Prepared from the corresponding 2,4-thiazolidinedione.
‡ An ester.
§ Probably disulfides.

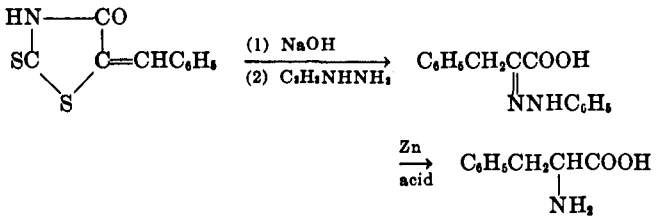
oximation reaction be carried out as rapidly as possible. In one case, ring closure of the intermediate oximino acid yields an isoxazole nucleus fused to indole (278).



General reactions of oximes have been applied to the α-oximino acids. They can be converted to pyruvic acids (IV, table 6) by reaction with formaldehyde and acid (242). Reduction of the α-oximino acid with sodium amalgam and lactic acid in absolute ethanol gives the α-amino acid (VI) (274). Carbon dioxide and water are eliminated from the α-oximino acid by heating with acetic anhydride and the nitrile (VII) is formed (345). The nitrile on hydrolysis yields the acid (VIII); on catalytic reduction with palladium (345) or platinum oxide (329) it yields the amine (IX).

Aromatic aldehydes, especially those containing halogen, hydroxy, or alkoxy substituents attached to the benzene ring, and heterocyclic aldehydes have been most widely investigated in this series of reactions. For the multistep reaction good overall yields can frequently be obtained. Yields of the homo nitriles from the substituted benzaldehydes are 37–65 per cent for the chloro- and bromobenzaldehydes (123) and 62 per cent for 2,4-dimethoxybenzaldehyde (206); of the homo acid or its ester, 73 per cent from furfural (489), 72 per cent from vanillin (247), and 44 per cent from 3-hydroxy-4-methoxybenzaldehyde (288); and of the homo amines, 51 per cent from 3,4-dioxymethylene-5-methoxybenzaldehyde (504) and 53 per cent from 1-phenyl-1,2,3-triazole-4-carboxaldehyde (551). Table 6 lists derivatives which have been prepared by the use of the Gränacher synthesis.

Instead of forming the α-oximino acid, the thiopyruvic acid has been converted to the phenylhydrazone, which can be reduced to the amino acid by zinc and acetic acid (260). It is not necessary to isolate the thiopyruvic acid, and yields of 75–80 per cent of phenylhydrazones have been obtained from 5-arylidenerhodanines. This reaction has been applied, with yields of 20–25 per cent, to rhodanine derivatives of aliphatic ketones.

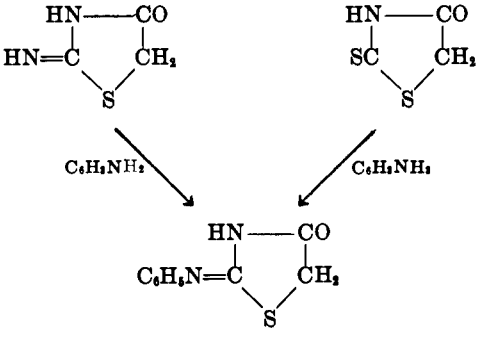


4. Reaction with organic bases

Many organic bases react with 4-thiazolidinones and attack the carbon atom at the 2-position of the heterocyclic ring. In some cases the thiazolidine ring is sufficiently stable to withstand cleavage and the substituent attached to the carbon atom in the 2-position is replaced; in others, the ring is broken and urea, thiourea, or their derivatives are formed.

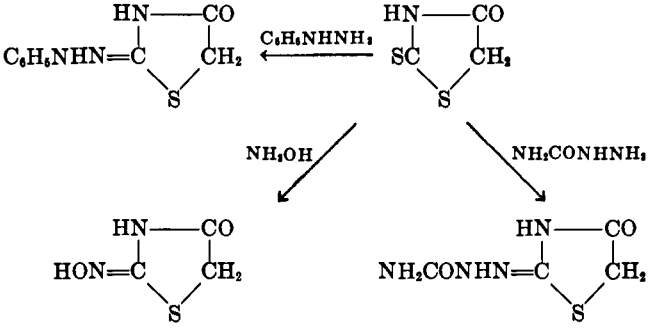
While 3-phenyl-2,4-thiazolidinedione will form 5-arylidene derivatives with aromatic aldehydes in the presence of a few drops of piperidine, larger quantities of piperidine and less reactive carbonyl compounds, such as ethyl acetoacetate, result in the rupture of the heterocyclic ring and the formation of *N*-phenyl-*N'*-piperidylurea and mercaptoacetic acid (513).

2-Phenylimino-4-thiazolidinone is formed on heating aniline with pseudothiohydantoin (222) or with rhodanine (417). The same product is obtained if 2-guanidino-2-thiazolin-4-one hydrochloride is heated with aniline for 6–9 min. (157).



If 3-phenylrhodanine is heated with aniline for 1 hr. at 160–170°C., the attack at the thione group is followed by cleavage of the ring and thiocarbanilide is formed (273). The presence of substituents in the 5-position, as in 5-benzylidenerhodanine, stabilizes the thiazolidine ring, and aniline converts the sulfur of the thione group to the phenylimino derivative (147, 273). This stabilization of the 4-thiazolidinone structure by the attachment of unsaturated substituents in the 5-position is similar to that found in the acid hydrolysis of 5-arylidene-2-arylimino-4-thiazolidinones.

Other organic bases behave analogously (417, 617). Rhodanine and its 5-benzylidene derivatives react with phenylhydrazine. The product is the 2-phenylhydrazone of the corresponding 2,4-thiazolidinedione (273). Refluxing rhodanine with semicarbazide hydrochloride and a base in aqueous or alcoholic solution yields the 2-semicarbazone of 2,4-thiazolidinedione (417, 637), while similar treatment of 2,4-thiazolidinedione with thiosemicarbazide produces the 2-thiosemicarbazone of the same compound (637). Hydroxylamine hydrochloride in the presence of sodium acetate (636) or barium carbonate (417) converts rhodanine, and its 3- or 5-methyl or 5-benzylidene derivatives, into the corresponding 2-oximino-4-thiazolidinones. Substituents in the 5-position of 2-oximino-4-thiazolidinones increase the stability of the thiazolidine ring to alkaline hydrolysis.

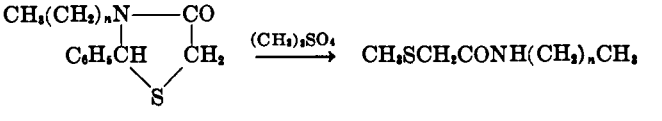


D. ALKYLATION

The substituent attached to the 2-carbon of the 4-thiazolidinone ring and the nature of the alkylating agent influence the kind of product obtained from alkylation reactions.

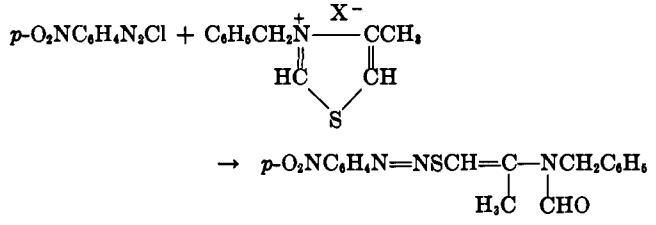
1. Alkylation of 2-phenyl-4-thiazolidinones

With 2-phenyl-4-thiazolidinones, three different alkylating agents produce different results. Diazomethane does not react with 3-(*p*-ethoxyphenyl)-2-phenyl-4-thiazolidinone, while allyl bromide in 4 *N* sodium hydroxide forms the 5,5-diallyl derivative (216). Refluxing a variety of 3-(*n*-alkyl)-2-phenyl-4-thiazolidinones with dimethyl sulfate in benzene solution for 2 to 8 hr. ruptures the heterocyclic ring by an attack on the sulfur atom and yields the *N*-alkylmethylmercaptoacetamide (543).



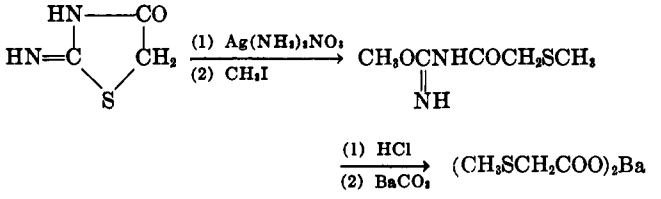
Another example of the reaction of an electrophilic reagent with the sulfur atom of the thiazole ring is

found in the reaction of *p*-nitrobenzenediazonium chloride with quaternary thiazole salts at pH 9.2. The thiazole ring is opened and the diazo group is attached to sulfur (189).



2. *Alkylation of 2-imino-4-thiazolidinones*

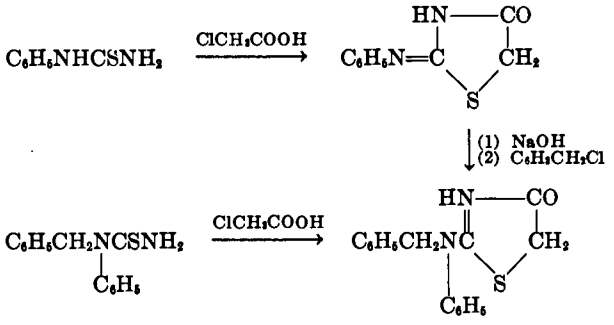
Pseudothiohydantoin reacts with ammoniacal silver nitrate and replaces two hydrogen atoms with silver. On treatment of the silver compound with methyl iodide, the silver is replaced by methyl groups (23). Synthesis of 3-methyl-2-methylimino-4-thiazolidinone from 1,3-dimethylthiourea and chloroacetic acid and of 2-imino-5,5-dimethyl-4-thiazolidinone from α-bromoisobutyric acid and thiourea indicates that the product of methylation of the silver derivative of pseudothiodantoin is not identical with either of these compounds. Repetition of this work (674) shows that the thiazolidinone ring is broken, with the formation of the methyl isoureide of methylmercaptoacetic acid, whose structure is shown by acid hydrolysis to methylmercaptoacetic acid. Similar results are obtained with ethyl iodide or benzyl chloride instead of methyl iodide.



This reaction is similar to that of dimethyl sulfate with 3-(*n*-alkyl)-2-phenyl-4-thiazolidinones (543).

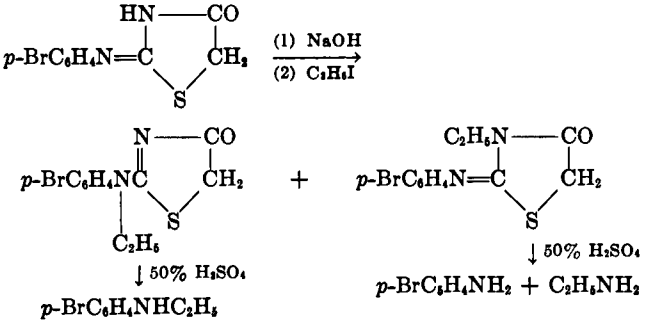
Shaking pseudothiohydantoin with sodium hydroxide and allyl bromide produces an oil which, after refluxing with 30 per cent sulfuric acid, yields 5,5-diallyl-2,4-thiazolidinedione (215). Copper powder has been recommended in this type of alkylation (559).

Considerable confusion is present in the early literature concerning the structure of the 2-imino-4-thiazolidinone derivatives prepared from unsymmetrical thiourea. If one nitrogen atom of the thiourea has only hydrogen atoms attached to it, the structure of the 2-imino-4-thiazolidinone can be determined by alkylation. The compound prepared from phenylthiourea and chloroacetic acid forms a sodium salt which on alkylation with benzyl chloride gives a compound identical with that obtained from 1-benzyl-1-phenylthiourea and chloroacetic acid. It is therefore 2-phenylimino-4-thiazolidinone (667, 668).



On alkylation of 2-(*p*-bromophenylimino)-4-thiazolidinone, two isomers are isolated: 2-(*p*-bromophenylimino-3-ethyl-4-thiazolidinone, which forms about one-sixth of the total product, and 2-(*N*-*p*-bromophenyl-*N*-ethylamino)-2-thiazolin-4-one (148). The isomers may be separated by the solubility of the latter and the insolubility of the former in dilute acid. The structure of each isomer is assigned on the basis of hydrolysis with 50 per cent sulfuric acid; *p*-bromaniline and ethylamine are obtained from the former, ethyl-*p*-bromoaniline from the latter. Acid hydrolysis of the 5-benzylidene derivatives of the alkylated products gives 5-benzylidene-3-ethyl-2,4-thiazolidinedione and 5-benzylidene-2,4-thiazolidinedione, respectively.

Further investigations to determine the effect of the nature of the substituent attached to the exocyclic nitrogen atom on the relative amounts of the 2- and 3-alkylated products confirmed, in general, the higher percentage of the 2-alkyl derivative. Exceptions to this generalization are those compounds in which the 2-phenylimino group has bulky ortho substituents such as iodine, bromine, or methyl (146, 149, 150, 165).

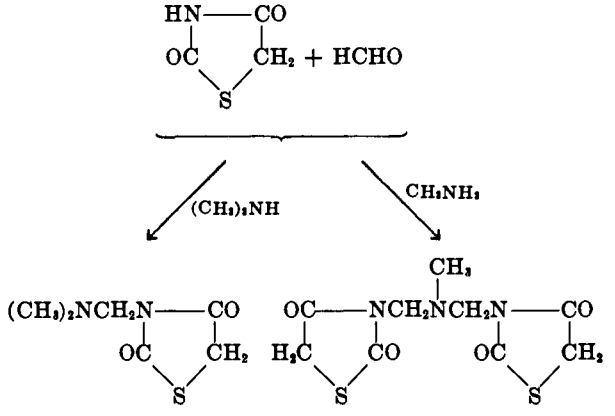


3. *Alkylation of 2,4-thiazolidinediones*

N-Methylation occurs if 2,4-thiazolidinedione or its 5-substituted derivatives are converted into salts and allowed to react with alkyl or aralkyl halides. Sodium metal in methanol (44, 83), potassium hydroxide in ethanol (403, 404), sodium hydroxide in aqueous solution (143), potassium carbonate in dry acetone (627), or silver nitrate in an alkaline solution (665) have been used to form the salt. The alkyl halide may be added directly to the alcoholic solution but better yields are obtained if the salt is isolated, suspended in dimethylformamide, and treated with the alkyl halide

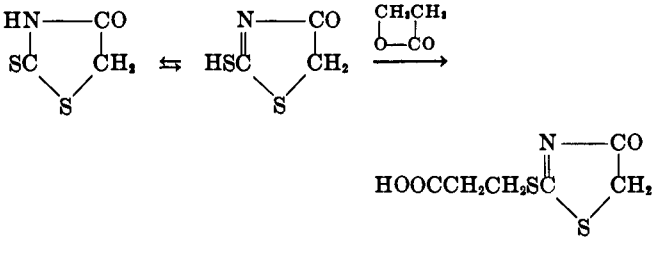
(403). *N*-Methylation has been accomplished by the use of diazomethane (333, 334, 369) or dimethyl sulfate in alkaline solution (563). The *N*-substituted derivative is obtained if 2,4-thiazolidinedione or its 5-alkyl or 5-alkylidene derivatives are treated with trichloromethyl sulfenyl chloride (143, 217, 367, 405).

A Mannich reaction takes place between 2,4-thiazolidinedione, formaldehyde, and amines. With the secondary amines morpholine, piperidine, or dimethylamine, the product is the 3-aminomethyl-2,4-thiazolidinedione, while a similar reaction with methylamine gives *N,N* - bis(2,4 - thiazolidinedione - 3 - ylmethyl)-methylamine (75).



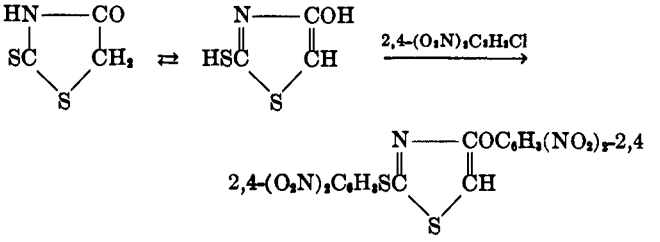
4. Alkylation of rhodanines

While 2,4-thiazolidinedione is alkylated on the nitrogen atom, rhodanine and its 5-substituted derivatives usually give products with the alkyl group attached to the sulfur atom of the 2-thione group. The sodium salt of rhodanine reacts with β-propiolactone at room temperature, producing the *S*-(β-carboxyethyl) derivative (282), and with a sultone, forming the *S*-(ω-sulfoalkyl) derivative (290). 5-Alkylidenerhodanines, such as 5-benzylidenerhodanine or 5-anilinomethylenerhodanine, dissolve in sodium hydroxide and on treatment with benzyl chloride form the *S*-benzyl derivatives (147).

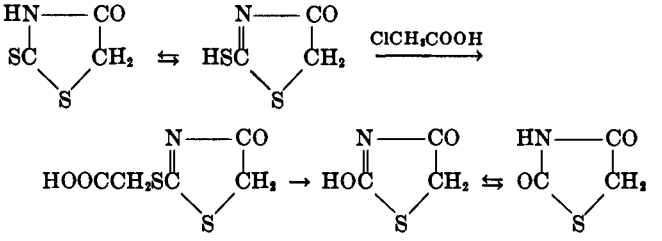


Refluxing rhodanine with two moles of 2,4-dinitrochlorobenzene in the presence of sodium acetate yields a compound which is formulated as the *O,S*-diaryl derivative of thiazole (409).

S-Alkylation is the basis of one method of converting the 2-thione group of rhodanine into the 2-oxo group. Refluxing rhodanine or its 5-alkylidene derivatives



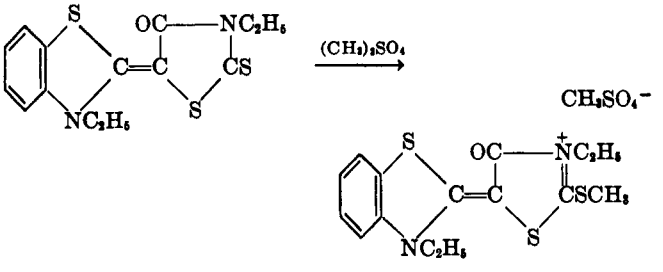
with chloroacetic acid in alcoholic solution converts them into the corresponding 2,4-thiazolidinediones (143, 218). The reaction is believed to proceed through the intermediate formation of the *S*-carboxymethyl derivative.



The insolubility of 5-arylidenerhodanines in aqueous chloroacetic acid prevents the use of this method in the synthesis of 5-arylidene-2,4-thiazolidinediones from the former (651).

Certain alkylating agents produce the *N*-methyl derivative. Diazomethane reacts with 5-benzylidenerhodanine, forming 5-benzylidene-3-methylrhodanine, whose structure was confirmed by independent synthesis (177), while 5-ethyl- and 5-phenylrhodanines on treatment with allyl bromide in alkaline solution give the 3-allyl derivatives (211). Further treatment of the latter with allyl bromide in alkaline solution introduces a second allyl group. Xanthydrol reacts with rhodanine to form a xanthyl derivative in which the xanthyl substituent is assigned to the 3-position (447).

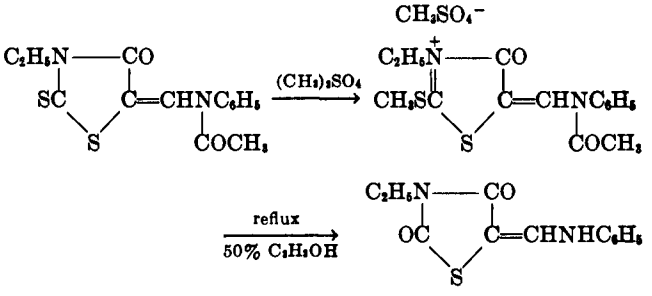
Merocyanine dyes, which may be considered as 3,5-disubstituted rhodanines, are converted into quaternary ammonium salts by reaction with dimethyl sulfate or methyl *p*-toluenesulfonate.



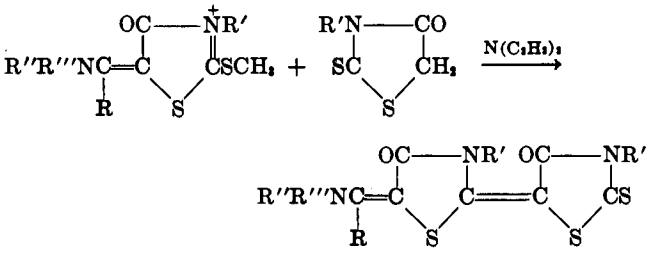
Substituents attached to the 5-position of the rhodanine affect this reaction. No examples of the isolation of quaternary salts were found among the 3-substituted rhodanines with two hydrogen atoms attached to the carbon atom in the 5-position, although in one instance the quaternary salt of 3-(*p*-ethoxyphenyl)rhodanine must have been formed (651). The 5-(1-ethoxyalkyli-

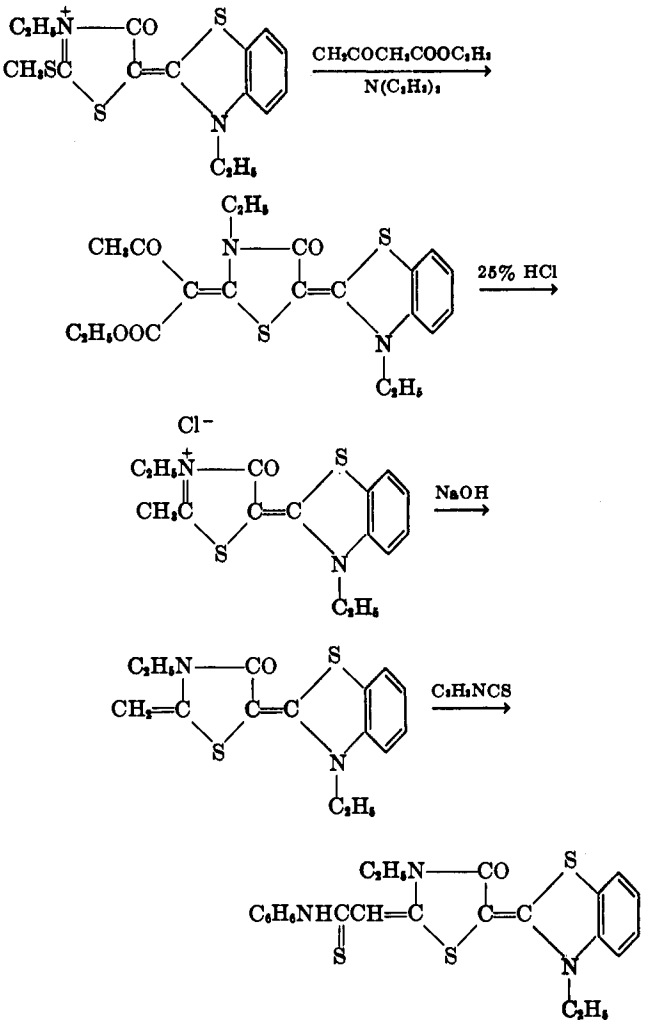
dene)-3-substituted rhodanines are not converted into quaternary salts, while 5-(1-aminoalkylidene)-3-substituted rhodanines form quaternary salts less rapidly than if the amino group is a part of a heterocyclic ring, as in a merocyanine dye (372).

When 5-acetanilinomethylene-3-ethylrhodanine is converted to its quaternary salt and refluxed in 50 per cent ethanolic solution for 1 hr., the methylthio group and the acetyl group are hydrolyzed while the thiazolidine ring remains intact (588). This reaction also takes place with 5-benzylidene-3-phenylrhodanine and gives a high yield of 3-phenyl-2,4-thiazolidinedione (651). With 5-benzylidenerhodanine, *N*-methylation occurs in addition to hydrolysis of the methylthio group. Provided quaternization of the rhodanine is possible, this reaction forms an additional method of converting rhodanines into the corresponding 2,4-thiazolidinediones.



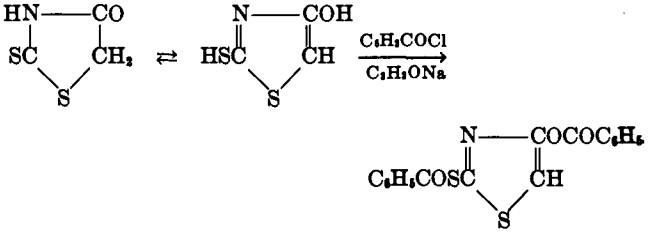
The positive charge on quaternary nitrogen confers pronounced electrophilic activity upon the adjacent carbon to which the alkylthio substituent is attached and reaction takes place with nucleophilic centers. The latter may be present as the active methylene groups of noncyclic compounds such as acetoacetic ester (168, 186) or of cyclic compounds such as rhodanine derivatives (372). In the reaction the alkylthio group is displaced, the molecule loses HX, and a 2-methylene derivative is formed. On acid hydrolysis of the 2-methylene derivative from acetoacetic ester, the quaternary salt of the 2-methyl derivative is formed. Neutralization of the salt by sodium hydroxide results in the removal of HX and the formation of the 2-methylene base, which can attack the electrophilic carbon atom of phenyl isothiocyanate or carbon disulfide. Acid chlorides react less readily (188).





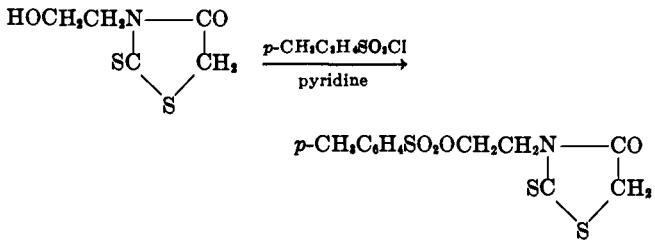
E. ACYLATION

At temperatures below 0°C. benzoyl chloride reacts with rhodanine in the presence of sodium ethoxide in a manner similar to that of 2,4-dinitrochlorobenzene. The product is formulated as a derivative of the isomeric 2-mercapto-4-oxythiazole (273). 5-Benzylidenerhodanine, whose carbonyl group cannot tautomerize, is monobenzoylated in alkaline solution (273). If the

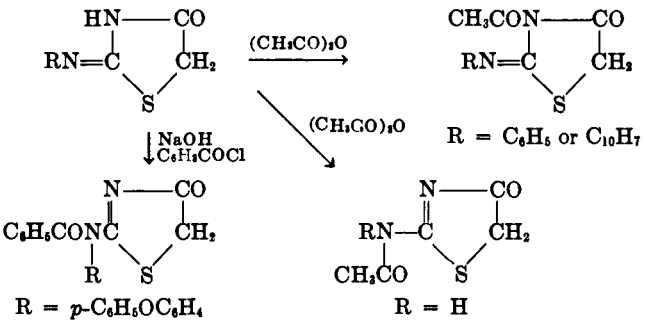


rhodanine contains substituents such as alcohol or amino groups which react readily with acid halides, the reaction takes place with the substituent group (362, 589).

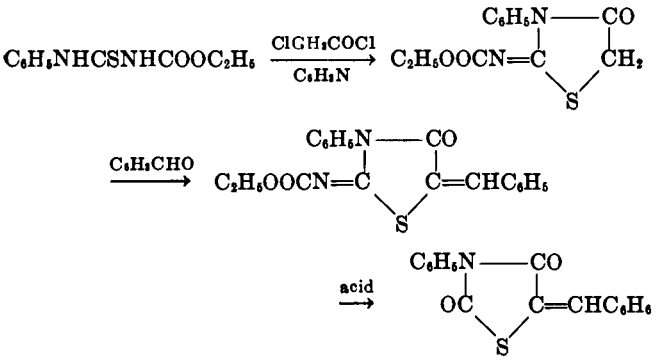
Acylation is a characteristic reaction of 2-imino-4-thiazolidinones which contain hydrogen atoms attached to either nitrogen atom. The derivatives with



an unsubstituted 2-imino group react with acetic anhydride (145) and with the aromatic sulfonyl chlorides (171, 320, 448), forming amide groups attached to the 2-carbon atom. With aromatic substituents replacing the hydrogen of the 2-imino group, acylation produces a compound in which the acyl or benzoyl group is attached to the 3-position or to the 2-amino position. Acetic anhydride reacts with 2-phenylimino-4-thiazolidinone (667) and with 2-naphthylimino-4-thiazolidinone (339), forming the easily hydrolyzed 3-acetyl derivative, while benzoylation of the sodium salt of 2-(*p*-phenoxyphenylimino)-4-thiazolidinone yields 2-(*p*-phenoxyphenylbenzoylamino)-2-thiazolin-4-one (507).



2-Carbalkoxyimino-4-thiazolidinones are synthesized from the thioallophanic ester and chloroacetyl chloride (181). The structure is assigned on the basis of acid hydrolysis of the 5-benzylidene derivative to the corresponding 2,4-thiazolidinedione (198).



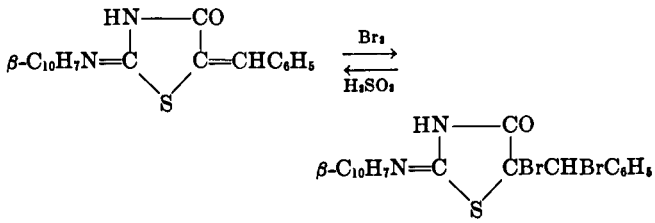
F. OXIDATION

The effect of an oxidizing agent on a derivative of a 4-thiazolidinone depends not only on the groups attached to the thiazolidine ring but on the chemical nature of the oxidizing agent and the conditions under which it attacks the heterocyclic compound.

With sufficiently drastic reaction conditions, the ring is destroyed and inorganic products are obtained. Nitric acid acts in this manner. The hydrochloride of pseudothiohydantoin yields a mixture of sulfuric and hydrochloric acids (414) and 2,4-thiazolidinedione forms sulfuric and nitric acids (368), while actithiazic acid [2-(5)carboxypentyl-4-thiazolidinone] is converted to sulfate ion, ammonia, and a mixture of dibasic aliphatic acids (429).

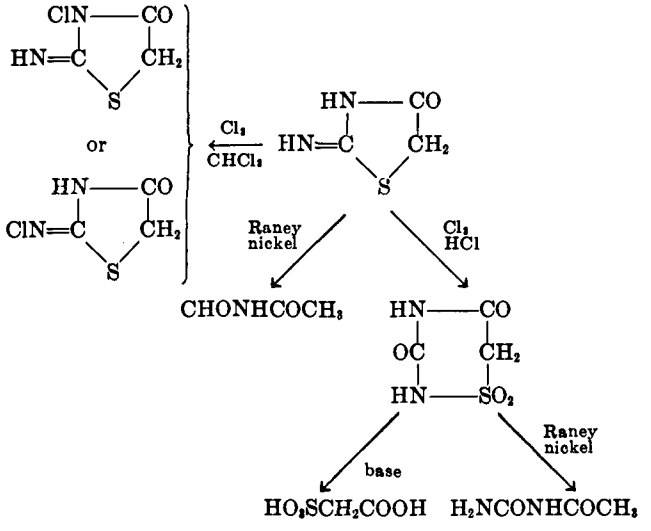
1. Oxidation of 2-imino-4-thiazolidinones

The addition of bromine to a hydrochloric acid solution of pseudothiohydantoin produces a compound which analyzes for a dibromo-2-imino-4-thiazolidinone. Although no proof other than elemental analysis was given, the bromine atoms were assumed to replace the hydrogen atoms in the 5-position. The substance is unstable in the presence of water, and oxalic acid was found in the mother liquor (384, 449). With 2-imino-5-methyl-4-thiazolidinone, two atoms of bromine are added to the compound, but on the addition of dilute sulfurous acid the original compound is restored (26). 3-Aryl-2-arylimino-4-thiazolidinones behave similarly, but with these compounds there is the possibility of brominating the aromatic portion of the molecule (3, 131, 228). The 5-arylidene derivatives form dibromides which on treatment with sulfurous acid revert to the original compound. In these compounds the bromine is assumed to add to the double bond conjugated with the carbonyl group (512).

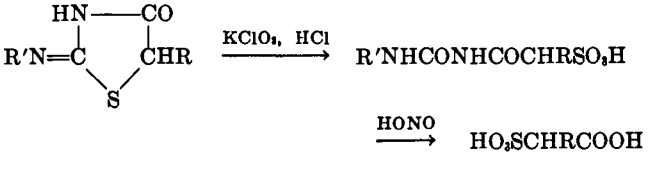


Bubbling chlorine gas into a chloroform solution of pseudothiohydantoin at room temperature forms a compound containing positive chlorine, but if the reaction is run in dilute hydrochloric acid at 0–5°C. oxidation and rearrangement occur (515). Under the latter conditions the sulfur of the thiazolidine ring is oxidized to sulfone, the ring is broken, and subsequent cyclization forms the six-membered 1,2,4-thiadiazene-3,5-dione 1,1-dioxide. The same compound was obtained earlier by the same procedure but was assigned a different structure (384). Evidence for the present structure is its hydrolysis with base to sulfoacetic acid and its conversion to acetylurea by Raney nickel, whereas pseudothiohydantoin forms *N*-formylacetamide. The same type of reaction is possible with 2-imino-5-methyl-4-thiazolidinone, but electron-attracting groups in the 5-position cause explosive reactions with the loss of sulfur as sulfate ion. The experimental conditions

are critical; if they are not followed precisely, the molecule is decomposed into sulfuric acid, hydrochloric acid, acetic acid, and urea (135).

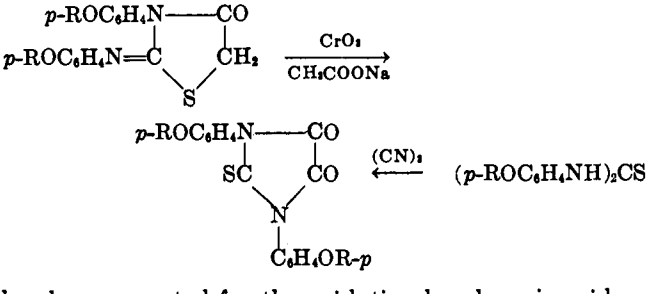


If potassium chlorate in hydrochloric acid solution is used instead of chlorine and the experimental conditions are carefully controlled, the product is sulfoacetylurea (R = R′ = H), which is converted by nitrous acid into sulfoacetic acid (R = H) (18, 20). 5-Substituted-2-imino-4-thiazolidinones yield a homolog of sulfoacetic acid (25, 26, 34), while 2-substituted-imino-4-thiazolidinones form a substituted urea (386). Hydrogen peroxide in potassium carbonate solution

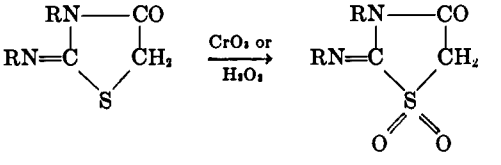


oxidizes pseudothiohydantoin to sulfoacetylurea (366).

Oxidizing agents, such as chromic oxide or selenium dioxide, convert 3-(*p*-alkoxyphenyl)-2-(*p*-alkoxyphenylimino)-4-thiazolidinones into the 1,3-dialkoxyphenyl-2-thioparabanic acids (443). The structures of the products were confirmed by independent synthesis from 1,3-di(*p*-alkoxyphenyl)thiourea and cyanogen. Oxidation is therefore accompanied by opening the thiazolidine ring and recyclization. Sulfone formation



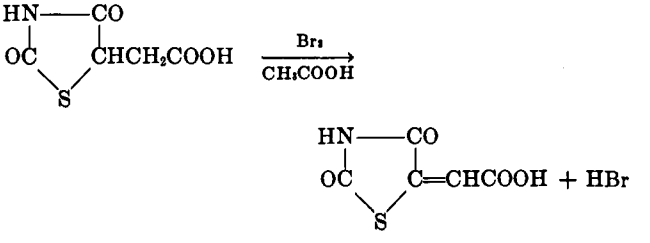
has been reported for the oxidation by chromic acid or hydrogen peroxide of 3-aryl-2-arylimino-4-thiazolidinones, in which the aryl groups are hydrocarbon (64, 66, 67). It should be noticed that the empirical formulas of the 1,3-diaryl-2-thioparabanic acid and of the corresponding 3-aryl-2-arylimino-4-thiazolidinone 1,1-dioxide differ from each other by one molecule of water.



2. Oxidation of 2,4-thiazolidinediones

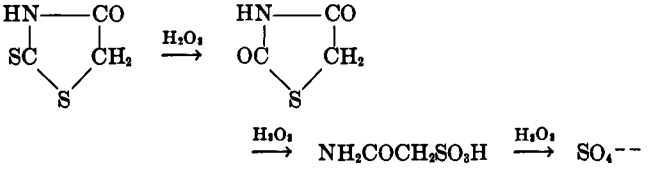
2,4-Thiazolidinedione is oxidized to sulfoacetamide by hydrogen peroxide in potassium carbonate solution (366), while sulfones are reported from the oxidation of 3-substituted 2,4-thiazolidinediones by potassium permanganate in acetic acid solution (69, 73).

Refluxing 2,4-thiazolidinedione-5-acetic acid with bromine in acetic acid solution causes the evolution of hydrogen bromide and yields 5-carboxymethylidene-2,4-thiazolidinedione (166).



3. Oxidation of rhodanines

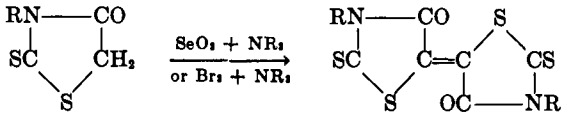
With rhodanine (366), or its 5-alkylidene derivatives (599), the first point of attack by hydrogen peroxide is the thione group, which is converted to the carbonyl group. This reaction forms a method of synthesizing 2,4-thiazolidinedione. An excess of hydrogen peroxide oxidizes the latter, eventually to sulfate ion.



Selenium dioxide reacts with 3-ethylrhodanine in boiling butanol and in the presence of a catalytic amount of a tertiary amine. Oxidation and condensation take place and a quantitative yield of the dimer is obtained (541). Sulfur monochloride, or at higher temperatures sulfur dioxide, produces the same indigo-type product.

3-Substituted 5-unsubstituted rhodanines yield the same type of compound on treatment with bromine in chloroform solution, followed by triethylamine (381). With this oxidizing agent the unstable 5-bromo derivative can be isolated, while the base facilitates the loss of hydrogen bromide and the formation of the dimer. The evidence is insufficient to determine whether

the reaction proceeds by α-elimination and the formation of a carbene followed by dimerization, or by an attack of the anion of the 3-substituted 5-bromo-

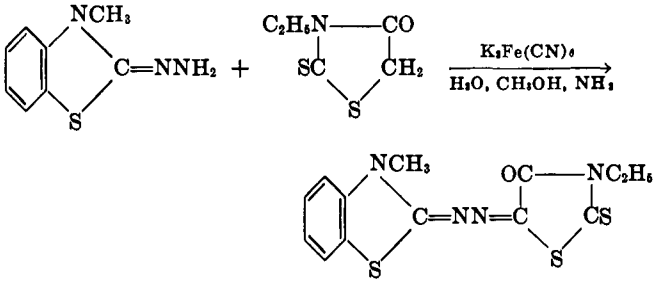


rhodanine on another molecule of the 3-substituted 5-bromorhodanine, followed by β-elimination of hydrogen bromide.

The bromination of 3-phenylrhodanine gives a bromine-containing product whose structure was not determined (33), while a similar reaction with 3-(*p*-tolyl)rhodanine gives a compound which was assumed to be the 5-bromo derivative, since it is different from 3-(2-bromo-4-methylphenyl)rhodanine (497).

Oxidizing agents, such as iodine or ferric chloride, convert rhodanine into a dye called "rhodanine red" (461). Later investigation showed that with ferric chloride the methylene group in the 5-position is involved, since 5-benzylidenerhodanine is not affected and 3-phenylrhodanine gives a similar dye (273, 281). It was assumed that the dyes are related in structure to the indigo dyes, although the analyses fit the trimer structure more closely than that of the dimer formed during oxidation with selenium dioxide or bromine in the presence of a base. 3-Phenylrhodanine red acts as a vat dye, since it can be reduced by sodium hydrosulfite and the reduced form oxidized by air.

2-Hydrazino-3-methylbenzothiazalone undergoes an oxidative coupling reaction with phenols, aromatic tertiary amines, and compounds with active methylene groups including 3-ethylrhodanine (47, 323). Potassium ferricyanide in an aqueous methanolic ammonia solution is the oxidizing agent. The hydrazone component has the structure of an amidrazone or its vinylog (324), and the evidence indicates that the reaction

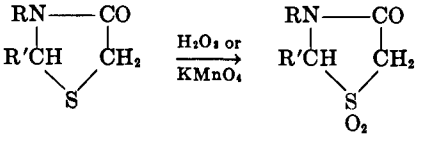


does not proceed through the intermediate formation of a diazonium ion (322). The product is a diazamerocyanine dye in which =N—N= replaces the =CH—CH= group.

Two types of products have been reported for the bromination of 3-substituted 5-arylidenerhodanines. 5-Benzylidene-3-phenylrhodanine is converted into the corresponding 2-oxo compound (33), while 5-benzylidene-3-(*p*-tolyl)rhodanine is reported to give a dibromide analogous to that obtained from 2-arylimino-5-benzylidene-4-thiazolidinones (497).

4. Oxidation of 2,3-dialkyl(or diaryl)-4-thiazolidinones

Sulfones are formed during the oxidation of 2,3-disubstituted 4-thiazolidinones with hydrogen peroxide in acetic anhydride and acetic acid (630), or by potassium permanganate in aqueous acetic acid solution at 30–35°C. (578, 581, 583, 584).



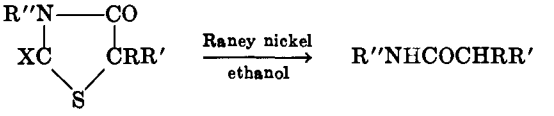
Actithiazic acid on treatment with hydrogen peroxide in acetic acid solution gives the sulfone, which on short refluxing with hydrochloric acid liberates sulfur dioxide, ammonia, and pimelaldehydic acid (429), products similar to but not as completely oxidized as those produced by nitric acid. Pimelic acid has been identified as an oxidation product of actithiazic acid with hydrogen peroxide in acetic acid (537).

G. REDUCTION

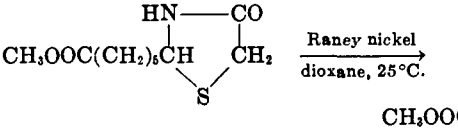
1. Reduction by Raney nickel

Raney nickel has been used to desulfurize 4-thiazolidinones and establish their structure. The product depends upon the conditions under which the Raney nickel reacts. In refluxing ethanolic solution, the four types of 2-substituted 4-thiazolidinones are desulfurized and converted to amides, while in aqueous alkaline solution hydrolysis to an α-mercapto acid precedes desulfurization.

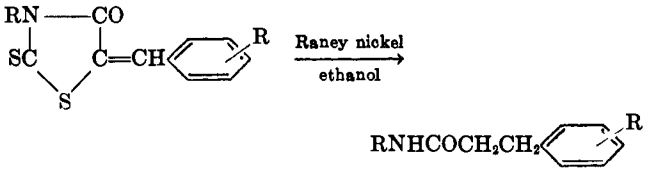
Pseudothiohydantoin (328), and its derivatives 3-phenyl-2-phenylimino-4-thiazolidinone (515) and the 5-amidomethyl-2-imino-4-thiazolidinones or its 2- and 3-substituted derivatives (420), on refluxing for several hours with Raney nickel in ethanol eliminate both the sulfur and the carbon atom in the 2-position of the 4-thiazolidinone ring and form an amide. Actithiazic acid (429) and 5,5-diphenyl-2,4-thiazolidinedione (158) under the same conditions also form amides.



Under milder conditions, as in dioxane solution at room temperature, the methyl ester of actithiazic acid loses the sulfur but retains the 2-carbon atom with its substituents (429).

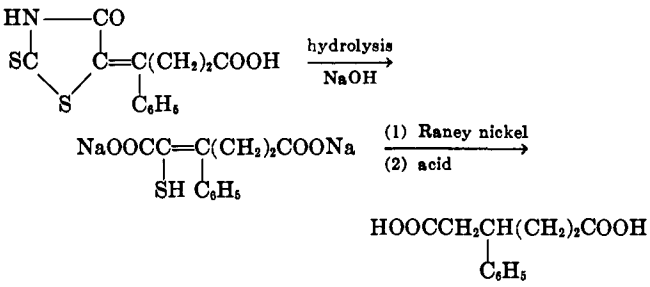


5-Arylidenerhodanines with Raney nickel in a refluxing alcoholic solution give good yields, usually above 75 per cent, of the amide of the corresponding hydrocinnamic acid (56).



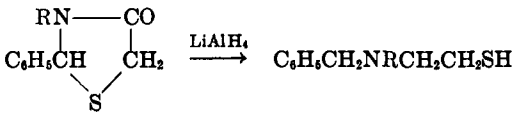
Reducible groups, such as nitro, attached to the benzene ring are also reduced.

In aqueous solution Raney nickel hydrolyzes and reduces rhodanine to ammonia and acetaldehyde (328). 5-Substituted alkylrhodanines (81) and 5-alkylidenerhodanines (11) are hydrolyzed to α-mercapto acids from which the mercapto group is eliminated and replaced by hydrogen. A double bond attached to the carbon atom with the mercapto group is also reduced.



2. Reduction by lithium aluminum hydride

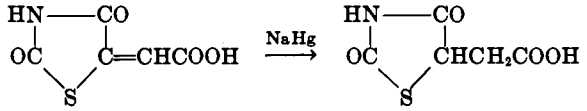
Lithium aluminum hydride in refluxing ether reduces 3-(*n*-alkyl)-2-phenyl-4-thiazolidinones (544). The carbonyl group is reduced to a methylene group and the heterocyclic nucleus is broken between the sulfur atom and the 2-carbon atom. The structure of the product was confirmed by independent synthesis of the β-mercaptoethylamine.



3. Reduction by other reducing agents

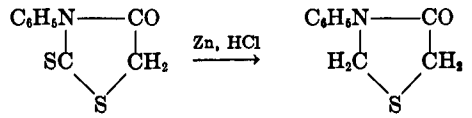
Other reducing agents are less effective in giving good yields of an organic product.

Sodium amalgam reduces 5-benzylidene-2-imino-4-thiazolidinone to the 5-benzyl derivative (210) and 5-carboxymethylidene-2,4-thiazolidinedione to 5-carboxymethyl-2,4-thiazolidinedione (166). Reduction of 2,4-thiazolidinedione with sodium amalgam, sodium in



boiling ethanol, or phosphorus and hydrogen iodide results in the formation of hydrogen sulfide, acetic acid, and ammonia (44).

3-Phenylrhodanine and 5-benzylidene-3-phenylrhodanine on reduction with metals (zinc or tin) and hydrochloric acid liberate hydrogen sulfide and give a small yield of the corresponding 2-methylene compound (35). Under the same conditions rhodanine is hydrolyzed to thioglycolic acid.

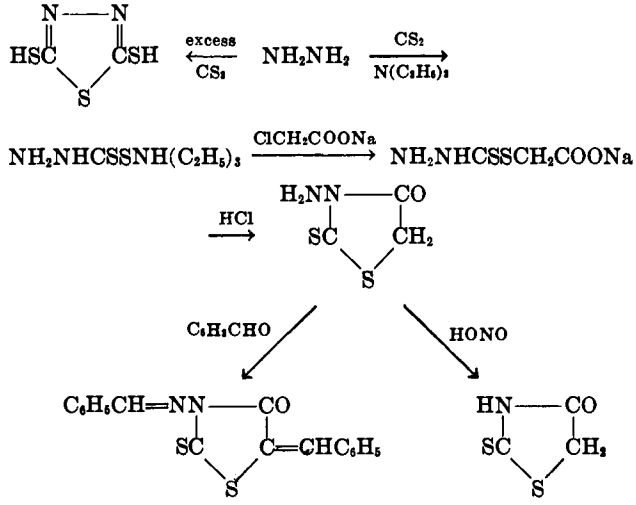


3-Phenylrhodanine

VII. 4-Thiazolidinones with Atoms Other Than Carbon or Hydrogen Attached to Nitrogen

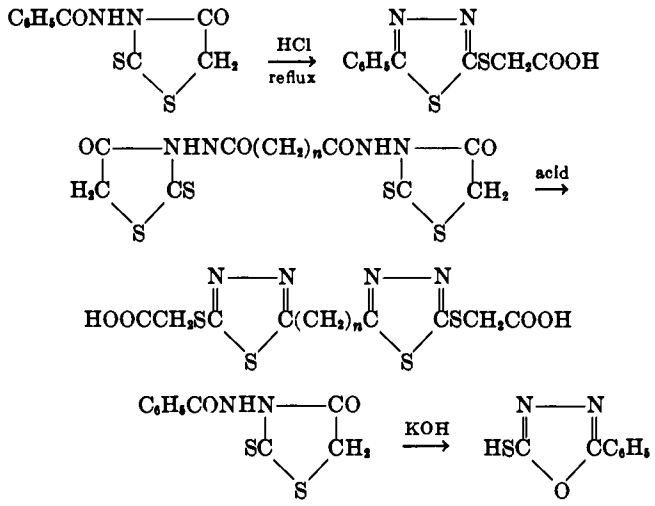
The chief atoms other than carbon or hydrogen attached to the nitrogen of the 4-thiazolidinone ring are nitrogen, sulfur, or oxygen. Of these possibilities, the 3-amino-4-thiazolidinones have been investigated most widely.

The replacement of the primary amine in the synthesis of dithiocarbamates by equimolar quantities of hydrazine or phenylhydrazine to carbon disulfide yields the corresponding dithiocarbazates. Such compounds react with α-halo acids and after cyclization form 3-aminorhodanines (28, 29, 310). They have also been formulated as derivatives of 2-mercapto-1,3,4-thiadiazenes (77, 423), but chemical evidence (including deamination with nitrous acid and the formation of a dibenzylidene derivative (526)) and ultraviolet and infrared spectroscopic evidence (101) support the structure of 3-aminorhodanine. Substituted 3-phenylhydrazines are converted into the corresponding 3-substituted anilinorhodanines (101). With hydrazine and excess carbon disulfide, the reaction product is 2,5-dimercapto-1,3,4-thiadiazole (104).

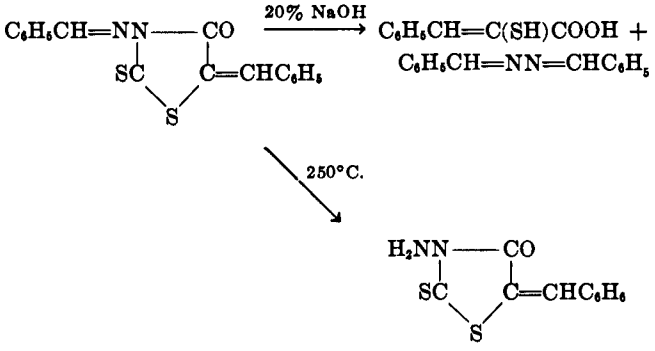


Benzoylhydrazine can be used instead of hydrazine and forms 3-benzoylaminorhodanine (530, 572). Boiling

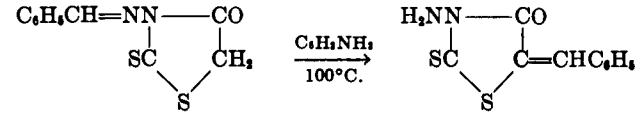
the latter compound with hydrochloric acid hydrolyzes the amide portion of the 4-thiazolidinone ring. Subsequent ring closure forms a derivative of 1,3,4-thiadiazole (530). The same type of reaction occurs on acid hydrolysis of compounds containing two 3-aminorhodanine moieties joined by amide linkages to a dibasic acid (641). No reaction takes place when 3-formylaminorhodanine is heated with 48 per cent hydrobromic acid, and under the same conditions 3-acetylaminorhodanine is deacylated. 3-Benzoylaminorhodanine on being heated with potassium hydroxide solution forms 2-mercapto-5-phenyl-1,3,4-oxadiazole (530).



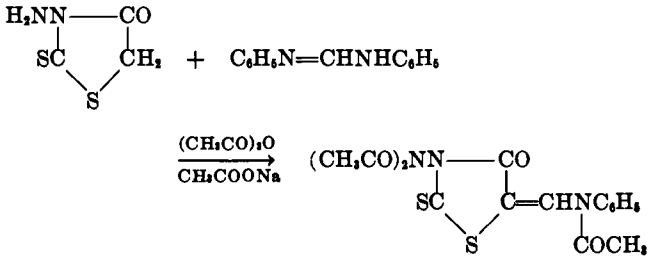
3-Aminorhodanine forms Schiff bases with aldehydes if a trace of hydrochloric acid is added to the ethanolic solution or if the reaction is run in acetic acid. In the presence of sodium acetate and acetic acid or of an ethanolic solution of ammonia and ammonium chloride, an aldol condensation occurs (391, 526, 639). 5-Arylidene-3-arylidineamino derivatives can also be formed. The latter on alkaline hydrolysis are converted into α-mercaptoacrylic acids and azines of the aldehyde (640), while heating 5-benzylidene-3-benzylideneaminorhodanine to 250°C. eliminates the 3-benzylidene group (639).



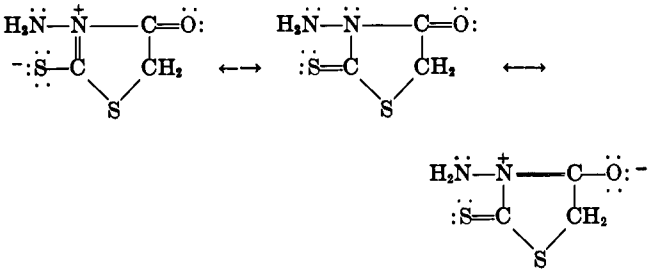
3-Benzylideneaminorhodanine, if heated with aniline at 100°C., rearranges into 3-amino-5-benzylidenerhodanine (640).



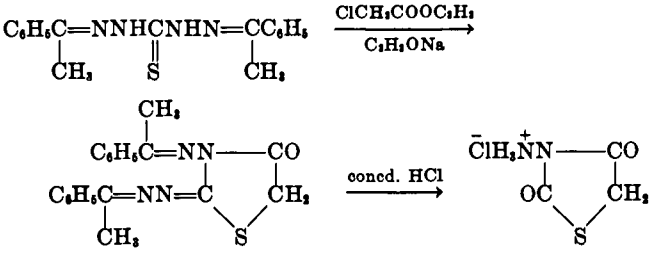
In the presence of acetic anhydride and sodium acetate, 3-aminorhodanine reacts with diphenylformamidine in the expected manner (589).



The basic properties of 3-aminorhodanine are so slight that the free base forms in the presence of hydrochloric acid. The low basicity has been explained by resonance structures which put a positive charge on the nitrogen of the ring and therefore attract the unshared pair of electrons of the amino nitrogen (528).

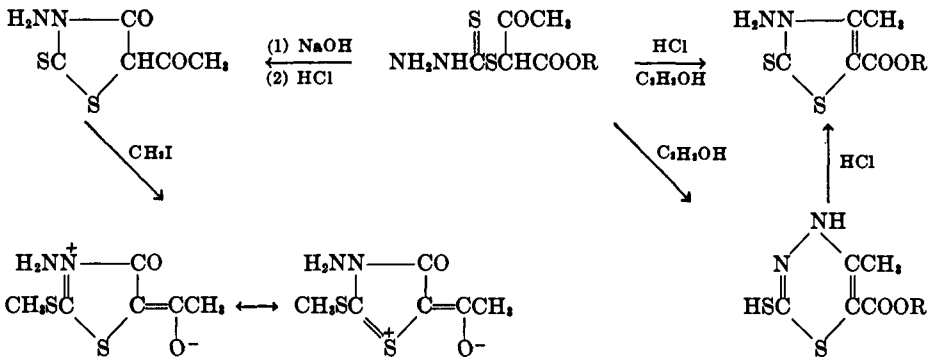


The resonance involving the thione group must be more important than that with the carbonyl group, since 3-amino-2,4-thiazolidinedione is isolated as a very deliquescent hydrochloride (569). The latter compound is obtained by the reaction of the thiocarbazone of acetophenone and ethyl chloroacetate in the presence of sodium ethoxide, followed by hydrolysis with concentrated hydrochloric acid.

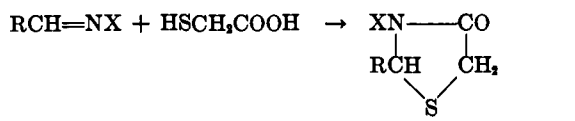


The reaction of ammonium dithiocarbazate with ethyl α-chloroacetoacetate gives the *S*-alkyldithiocarbazate (527). Three cyclization products are possible and all were obtained. Heating the uncyclized product in ethanolic hydrochloric acid brings about cyclization between the ketone and the —NH— groups, forming 3-amino-5-carbethoxy-4-methyl-2-thione-4-thiazoline. In neutral ethanolic solution some of the same

compound is obtained, but the chief product is the six-membered ring compound, ethyl 2-mercapto-1,3,4(4*H*)-thiadiazene-6-carboxylate. Heating with ethanolic hydrochloric acid converts the latter compound to the 4-thiazoline derivative. When the *S*-alkyldithiocarbazate is dissolved in dilute sodium hydroxide and the solution immediately neutralized with hydrochloric acid, the product is 5-acetyl-3-aminorhodanine, which can be alkylated to a mesoionic compound.

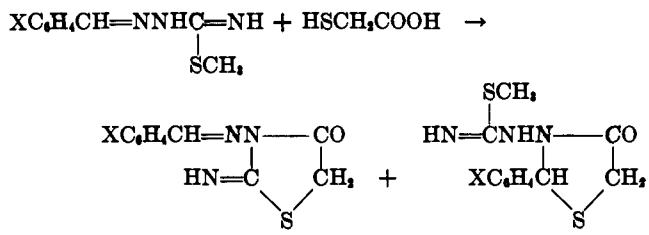


Mercaptoacetic acid reacts with several aldehyde derivatives in the same manner in which it adds to anils (Section II,A,2(d)). With semicarbazones the products are 2-aryl(or alkyl)-3-ureido-4-thiazolidinones (237, 582, 583). Differences in reactivity are attributed to differences in polarity of the $\diagdown C{=}N- \diagup$ linkage and susceptibility of the carbon to attack by the sulfur of the mercaptoacetic acid. 2,4-Dinitrobenzoylhydrazones (236), isonicotinylhydrazones (239), and thiobenzoylhydrazones (314, 315) react analogously. With phenylhydrazones, the products are 3-anilino-2-aryl-4-thiazolidinones (235, 244, 446, 539); with azines, 2-aryl-3-arylideneamino-4-thiazolidinones (244); and with oximes, 2-aryl-3-hydroxy-4-thiazolidinones (538), which are the only recorded examples of 3-oxy derivatives of 4-thiazolidinones.



X = —NHCONH₂, —NHCOR, —NHCSR, —NHR, —N=CHR, or —OH.

The *S*-methyl ether of an aldehyde thiosemicarbazone contains two groups which can react with mercaptoacetic acid. Displacement of the *S*-methyl group by mercaptoacetic acid and cyclization yields 3-arylideneamino-2-imino-4-thiazolidinone, while addition of the mercaptoacetic acid to the $\diagdown C{=}N- \diagup$ linkage, followed by cyclization, forms 2-aryl-3-methylisothioureido-4-thiazolidinone (238). The former is the chief product with equivalent amounts of reactants, but an excess of mercaptoacetic acid increases the yield of the 2-aryl derivative.

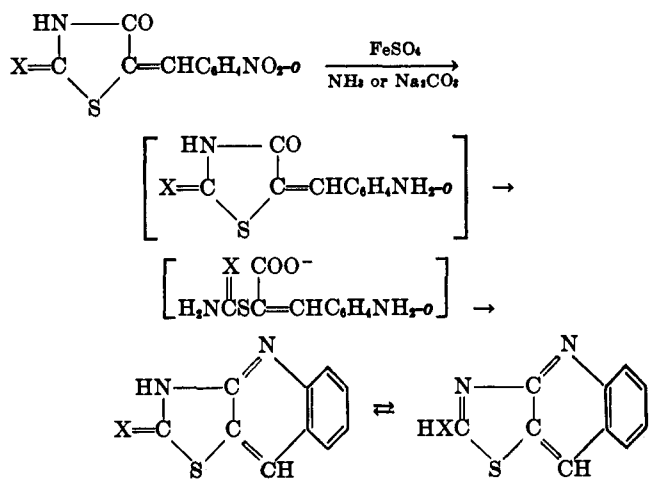


2,4-Thiazolidinedione and its 5-substituted derivatives are alkylated with trichloromethyl sulfenyl chloride. The products contain the trichloromethyl group attached by a sulfur atom to the nitrogen of the 4-thiazolidinone ring (Section VI,D,3).

VIII. Condensed Compounds Related to 4-Thiazolidinones

A. Cyclizations involving atoms 4 and 5

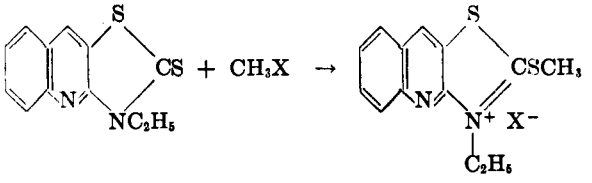
Reduction of 5-(*o*-nitrobenzylidene)rhodanine with ferrous sulfate and a weak base such as soda or ammonia, reagents which convert *o*-nitrobenzaldehyde to *o*-aminobenzaldehyde, gives a condensed ring compound which is formed by loss of water (280). The same series of reactions takes place with 5-(*o*-nitrobenzylidene)-



X = S, O, NR.

2,4-thiazolidinedione (595) and with 2-arylimino-5-(*o*-nitrobenzylidene)-4-thiazolidinones (161), while with 2-imino-5-(*o*-nitrobenzylidene)-4-thiazolidinone reduction of the nitro group to the amino group is not followed by ring closure by acetic anhydride (595). It has been postulated with the rhodanine derivative that the 4-thiazolidinone ring is hydrolyzed and that recyclization occurs, giving a product different from the 5-(*o*-aminobenzylidene)rhodanine (280). An alternate synthesis of the 2-mercapto derivative of thiazolo[4,5-*b*]quinoline, originally called quinrhodanine, is the reaction of 2-amino 3-mercaptoquinoline with carbon disulfide in basic solution (596).

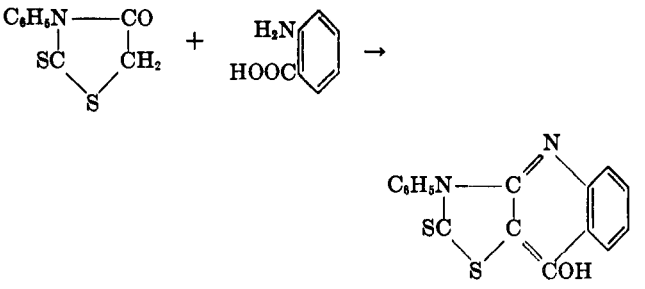
3-Substituted rhodanines condense with *o*-aminobenzaldehyde in acetic acid solution, forming *N*-substituted quinrhodanines (280). Certain 3-methyl- or 3-chlorophenyl-5-(*o*-nitrobenzylidene)rhodanines have been reduced and cyclized by heating with zinc and acetic acid (520). These compounds can be quaternized and converted to cyanine dyes (87).



2-Mercaptothiazolo[4,5-*b*]quinoline is soluble in 20 per cent sodium hydroxide solution, from which it can be recovered by the addition of hydrochloric acid, but heating the compound with 50 per cent sodium hydroxide hydrolyzes it to 3-mercapto-2-quinolone. The mercapto groups of both compounds can be alkylated to thio ethers and oxidized to disulfides by potassium ferricyanide (280). On careful oxidation with potassium permanganate (room temperature, pH 8), the mercapto group of 2-mercaptothiazolo[4,5-*b*]quinolone is oxidized to the sulfonic acid group (595). Treatment of the same 2-mercapto derivative with chlorine in acetic acid solution replaces the mercapto group with a chlorine atom (598). Both the sulfonic acid group and the chlorine are extremely labile and are converted to the 2-hydroxy derivative by alkali and to the 2-amino derivatives by ammonia or amines.

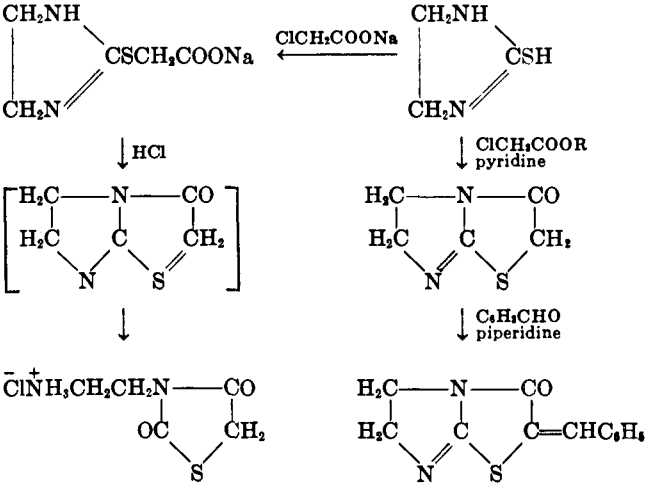
In agreement with the *N*-methylation observed with 2,4-thiazolidinediones (Section VI,D,3), methylation of 2-hydroxythiazolo[4,5-*b*]quinoline with dimethyl sulfate, diazomethane, or methyl iodide with the sodium salt leads to *N*-methylation rather than *O*-methylation (597). The structure of the compound was confirmed by reduction and cyclization of 3-methyl-5-(*o*-nitrobenzylidene)-2,4-thiazolidinedione.

Fusion of 3-phenylrhodanine and anthranilic acid at 150°C. in the presence of sodium acetate gives a product insoluble in sodium bicarbonate but soluble in sodium hydroxide, which is formulated as having a phenolic group attached to the carbon of the middle ring (520).



B. CYCLIZATIONS INVOLVING ATOMS 2 AND 3

Certain cyclizations involving positions 2 and 3 of the 4-thiazolidinone ring are possible, and the resulting compounds may be considered as derivatives of 2-imino-4-thiazolidinones. In alcohol solution 2-mercaptoimidazoline reacts with ethyl chloroacetate (569), or sodium chloroacetate (643), forming a derivative of thioglycolic acid, while in pyridine solution the same components give a small yield of a compound whose nitrogen analysis indicates that the imidazole and thiazole rings are fused (569). If, after refluxing the above components for 5 hr., benzaldehyde and piperidine are added, the benzylidene derivative is obtained (643).



Refluxing the intermediate 2-carboxymethylmercaptoimidazoline with hydrochloric acid forms 3-(β-aminoethyl)-2,4-thiazolidinedione hydrochloride, which is assumed to proceed via the formation and acid hydrolysis of the bicyclic heterocyclic compound (644). The structure of the 3-(β-aminoethyl)-2,4-thiazolidinedione is supported by the preparation of amide and quaternary salt derivatives of the amino group, benzylidene derivatives of the 5-methylene group, and ultraviolet absorption spectra.

Instead of 2-mercaptoimidazoline, other mercapto-substituted heterocyclic compounds can be used, with 2-mercaptobenzimidazole as the most frequently studied

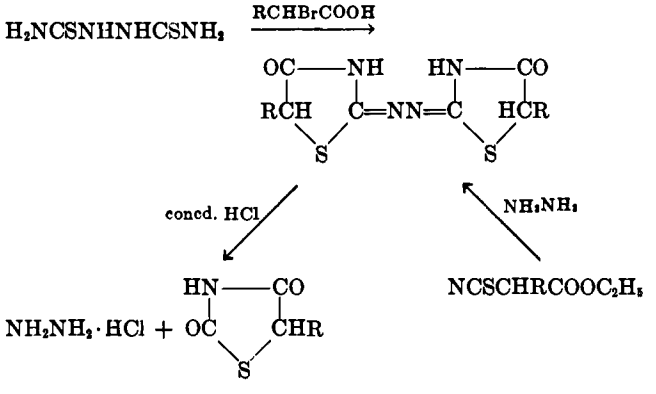
representative (356, 438, 569, 643). The presence of the active methylene group in the product is evidenced by condensation with aromatic aldehydes (438, 643) and the formation of merocyanine dyes with quaternary salts having electrophilic carbon atoms activated by thioether or acetanilinovinyl groups (358). Cyclization by thionyl chloride in pyridine solution produces a thioindigo-type compound (438). Mercapto heterocyclic compounds which condense with chloroacetic acid or its ester include: 3,4,5,6-tetrahydro-2-mercaptopyrimidine (643), methylthiouracil, 4-ketotetrahydro-2-thioquinazoline and 2-mercapto-5-methyl-1,3,4-triazole (356), and 2-methylhypoxanthine-8-thiol (203).

IX. Compounds with Two or More 4-Thiazolidinone Rings

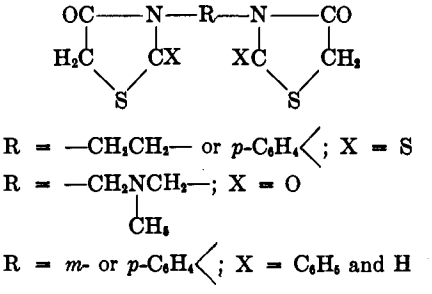
Several types of compounds with more than one 4-thiazolidinone ring are possible. In general, their synthesis follows standard methods of preparation, with the appropriate modifications necessary to produce bis derivatives.

The 4-thiazolidinone moieties may be joined by linkages attached to the carbon atoms in the 2- or 5-position or to the nitrogen of the ring structure. In a few cases the 4-carbonyl group is involved in the linkage of the heterocyclic rings (Section VI,A,2). Such combinations yield the following types of compounds:

1. 2,4-Thiazolidinedione-2-azines: These compounds, which can be synthesized from hydrazodithiodicarbonamide and ethyl chloroacetate (253, 570) or by the reaction of hydrazine with ethyl thiocyanatoacetate (253, 257), were originally believed to have the structure of 3,3-bis(pseudothiohydantoin) (253), but the isolation of 2,4-thiazolidinedione and hydrazine hydrochloride as the products of acid hydrolysis established the azine structure (257, 570).

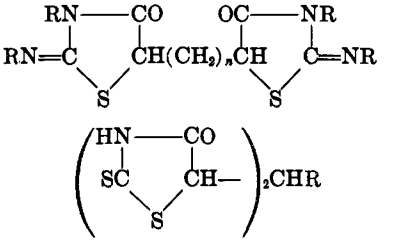


2. Bis(4-thiazolidinon-3-yl)alkanes or -benzenes: The use of a diamino compound, such as ethylenediamine (142, 456) or *p*-phenylenediamine (361, 459), in place of compounds with one amino group gives di(4-thiazolidone) structures attached through the nitrogen atoms. Schiff bases, prepared from *m*- or *p*-phenylenediamine and benzaldehyde, react with mercaptoacetic acid forming *m*- or *p*-bis(2-phenyl-4-thiazolidinon-3-yl)-benzene (422a). The product of a Mannich reaction between a primary amine, formaldehyde, and 2,4-thiazolidinedione (Section VI,D,3) belongs to the same class.



The reaction of a substituted 1,2-dithioureideëthane with ethyl chloroacetate gives a bis(4-thiazolidinone) derivative, as shown by its analysis and alkaline hydrolysis to mercaptoacetic acid, but insufficient experimental evidence was given to decide whether the ethylene group is attached through the 2-imino nitrogen or the nitrogen of the 4-thiazolidinone ring (456).

3. Bis(4-thiazolidinon-5-yl)alkanes: The use of esters of α,α'-dibromodicarboxylic acids with thioureas forms bis(pseudothiohydantoins) in which the heterocyclic rings are attached at the methylene carbon to the α,ω-positions of the alkane chains (45, 470, 471). The Michael-type reaction of 5-alkylidenerhodanines with rhodanine (Section VI,B,1,(a)) gives compounds with both 4-thiazolidinone structures attached to the same carbon atom of the alkane chain.

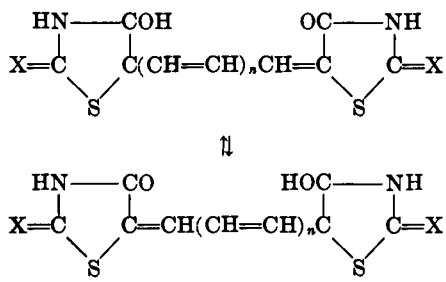


4. 5-Methylidenebisrhodanines: Aromatic compounds with two or more aldehyde or ketone groups undergo multiple aldol condensation reactions and form bis- or polyrhodanine compounds. The dialdehydes that have been used include: isophthalaldehyde (31), 5-nitroisophthalaldehyde (337), *o*-phthalaldehyde, terephthalaldehyde, and 2,6-dialdehydopyridine (9), while condensations with 2,4,6-tri(formylphenoxy)-1,3,5-triazines give trirhodaninyl derivatives whose molecular weights are in the range 700 to 1100, and which contain 51–62 per cent of the molecule as a rhodanine moiety (6). Of the diketones which have been investigated, one mole of phenanthraquinone reacts with two moles of rhodanine (105), while only one carbonyl group per molecule of acenaphthenequinone (281), isatin (278), 5-nitroisatin (342), 5-methyl- and 1,5-dimethylisatins

(344), 1-(2-cyanoethyl)isatin (176), and biacetyl (373) reacts with rhodanine or its 3-substituted derivatives. Compounds with two acetanilinovinyl groups react with two moles of 3-ethylrhodanine (412).

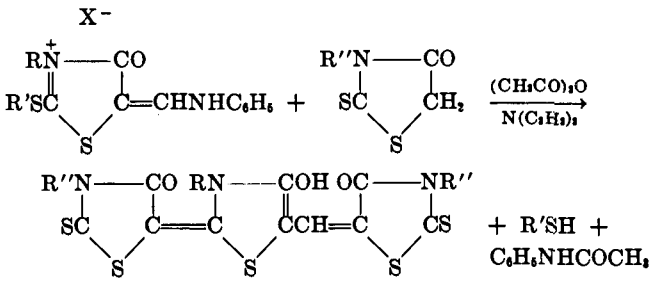
5. Azanol dyes: In one tautomeric form, nitrogen atoms form an integral part of the conjugated chain connecting the 5,5′-atoms of the 4-thiazolidinone moieties (Section VI,B,2,(c)).

6. Oxonol and merocyanine dyes (Section VI,B,2(g)): Oxonol dyes are joined through the 5,5′-positions of the 4-thiazolidinone nuclei. A conjugated system is present and tautomerism is possible, with either of the 4-carbonyl groups being present in the enolic form (293). With merocyanine dyes, the attachment of the two 4-



thiazolidinone nuclei will be from the 5-carbon atom of one ring to the 2-carbon atom of the other.

Complex merocyanine dyes containing more than two 4-thiazolidinone moieties become possible through repetition of the synthetic steps involved in their formation (372). With an appropriately substituted quaternary salt and at least two moles of the rhodanine derivative in the presence of acetic anhydride and triethylamine in pyridine solution, the dye obtained contains three 4-thiazolidinone moieties and has both a merocyanine and an oxonol structure (586).



X. Uses of 4-Thiazolidinones

A. Use in Qualitative and Quantitative Analysis

Early investigation of the properties of rhodanine (461) and of pseudothiohydantoin (653) showed that they form precipitates with the heavy metals and that this property is also characteristic of 5-methylene (462) and of 5-oximino (416) derivatives of rhodanine. The use of rhodanine and its derivatives as analytical reagents in spot testing for silver, gold, copper, mercury, and palladium has been reviewed (661), and the use of 5-(*p*-dimethylaminobenzylidene)rhodanine ("Feigl's reagent") in the detection of the same ions has been described (230). 5-(*o*-Sulfobenzylidene)rhodanine divides salts of metallic ions into three categories on the basis of the rapidity with which precipitates are formed (7). Thorium may be determined by using 3-(4-carboxyphenyl-3-hydroxy)rhodanine (509), while titanium(IV) compounds form colored complexes with 5-(3,4-dihydroxybenzylidene)rhodanine and its 2-oxo and 2-imino analogs (263). 5-(3-Indolylmethylene)- and the three 5-pyridylmethylenerhodanines have been investigated as reagents in the determination of certain metallic ions by paper chromatography (463).

The reaction with heavy metals is considered to be the formation of a complex rather than simple salt formation (633, 662), although in the range of concentration studied in the determination of the solubility product of the silver derivative of the 5-(*p*-diethylaminobenzylidene)rhodanine (S.P. = 8×10^{-19} at 20°C. in 20 per cent ethanolic solution of 0.05 ionic strength) there is no evidence of the formation of complex ions such as AgR_2^- or Ag_2R^+ (523).

Since rhodanine derivatives with alkyl or aryl groups attached to the nitrogen do not bind silver ions as does rhodanine (560), the imido hydrogen is considered to be the one involved in the reaction. Among the 5-substituted methylene derivatives, the sensitivity of the reagent increases with increasing dipole moment caused by the substituent attached to the methylene group (387, 388).

A colorimetric procedure using 5-(*p*-diethylaminobenzylidene)rhodanine is available for the quantitative determination of extremely small quantities of gold (522). In absolute sensitivity the method is intermediate between the usual fire assay and the very sensitive method developed by Haber to determine the amount of gold in sea water. The method is suitable for the determination of gold in biological specimens.

The same reagent and general procedure are useful for the quantitative determination of silver and can detect 0.05–0.10 p.p.m. in 10-ml. samples (525). As the acid concentration affects the concentration of the 5-(*p*-diethylaminobenzylidene)rhodanine negative ion and therefore the solubility of the silver compound, it was necessary to determine ionization constants for the organic substance (Section III).

A spectrophotometric procedure using 5-(*p*-dimethylaminobenzylidene)rhodanine is available for the quantitative determination of silver in 25-ml. samples containing 2×10^{-8} to 2×10^{-7} moles of silver (125). In the absence of thiocyanate ion, ten samples run at different times gave a standard deviation of 1.5 per cent. The same reagent and general method are used for the microdetermination of gold (139). When precise experimental procedures are followed, 10 μg. of gold can be determined with a mean deviation of ±1 per cent. 5-(*p*-Dimethylaminobenzylidene)rhodanine acts as an

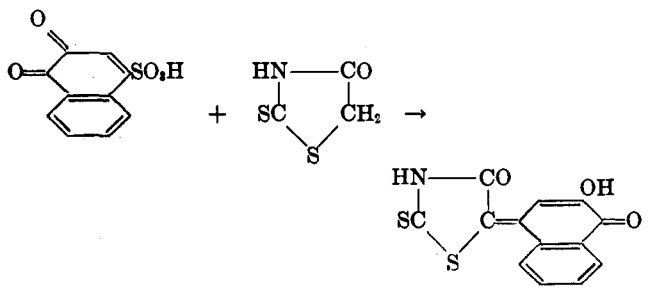
indicator in the titration of cyanide ion (514) and of chloride or bromide ions (271) with silver nitrate. It can be used as an indicator in anhydrous acetic acid solutions (307).

Small amounts of easily oxidized substances such as ascorbic acid can be determined with 5-(*p*-dimethylaminobenzylidene)rhodanine in the presence of copper sulfate and sodium pyrophosphate (233). The ascorbic acid is oxidized, and the cupric ion is reduced to cuprous ion, which forms an insoluble red precipitate of cuprous 5-(*p*-dimethylaminobenzylidene)rhodanine.

Colored solutions or precipitates in the presence of certain metallic ions or organic reagents distinguish the various types of 4-thiazolidinones (193, 634).

Certain reactions are used for spot tests for rhodanine and its derivatives. Compounds which contain a thiono or thiol group catalyze the reaction of sodium azide with iodine, in which the evolution of nitrogen is the indication of a positive test. The presence of 0.1–10 p.p.m. of rhodanine and several of its derivatives can be determined by this method (229).

Another test uses 1,2-naphthoquinone-4-sulfonic acid, which condenses with the nucleophilic carbon atom of rhodanine, forming in acid solution a red precipitate which turns blue-violet in the presence of base (517). When used in spot tests, this method will indicate the presence of 0.6 γ of the compound (231). Substances which participate in the synthesis of 4-thiazolidinones



can, by the addition of the appropriate reagent, be detected by this test (232). The procedure gives a positive color test with 5 γ haloacetic acid, 10 γ ammonium thiocyanate, 2.5 γ thiourea, or 6 γ cyanamide.

B. USE IN PHOTOGRAPHIC FILM

The outstanding use of the 4-thiazolidinones is in the synthesis of merocyanine dyes which extend the sensitivity of silver halide emulsions to wavelengths within the visible region of the spectrum. This use has been reviewed extensively (14, 86, 292).

Certain rhodanine derivatives act as antifoggants, which decrease the reduction of unexposed silver halide in the development of the film (352, 363, 547, 560). Formation of an insoluble silver salt of rhodanine and chelation are considered as possible mechanisms of the antifogging effect. On the other hand, pseudothiohydantoin, as its copper salt, makes the photographic film unusually sensitive to traces of thiosulfate and increases the fogging of the film (568).

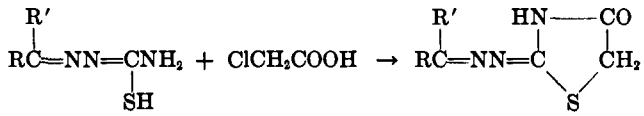
Several 3-substituted-5-arylidene-2-phenylimino-4-thiazolidinones protect light-sensitive photographic film from the harmful effects of ultraviolet radiation (531, 532, 533, 534, 535). Groups which can be present in the 3-position include phenyl, benzyl, cyclohexyl, and alkyl ranging in size from hexyl through cetyl and rosyl, while the phenyl nucleus of the 5-arylidene moiety often contains relatively large substituents.

The formation of a polymeric acetal by the addition of 3-(2,2-diethoxyethyl)-2-phenyl-5-(*o*-sulfobenzylidene)-4-thiazolidinone to polyvinyl alcohol gives a compound which absorbs ultraviolet radiation (645), and the reaction of polyacrylic anhydride with 3-(2-aminoethyl)-5-arylidene-2,4-thiazolidinediones produces polymeric compounds which protect photographic films from ultraviolet radiation (435).

Certain 3-substituted rhodanines, including 3-dodecylrhodanine, 3-(*p*-dimethylaminophenyl)rhodanine, and the alkylenebis(3,3′-rhodanines) act as antikinking agents for x-ray films (343). 3-Octadecylrhodanine increases the grain size of the silver halide emulsion (472).

C. USE AS ANTIMICROBIAL, INSECTICIDAL, AND PARASITICIDAL AGENTS

The frequent occurrence of the group —NHCSNH— or its tautomer in compounds possessing *in vivo* tuberculostatic activity has been noted (255). Many of the tuberculostatic aldehyde or ketone thiosemicarbazones which possess the thioureide group can be converted into the corresponding 2-hydrazone of 2,4-thiazolidinedione (265, 502) in which a part of this structure is present in the heterocyclic portion of the molecule. In a comparison of the derivatives of the



same carbonyl compound, the thiosemicarbazone is usually active at a lower concentration than the 4-thiazolidinone prepared from it but the former causes greater fatty degeneration and hemorrhage in the livers of mice and rats (117, 120).

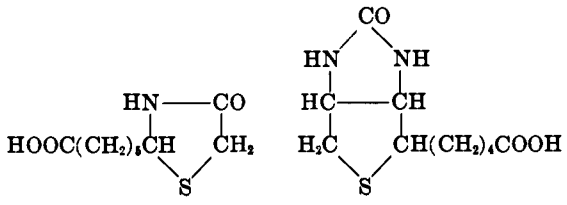
In an investigation of the effect of variation of the R group (R′ = H) in the hydrazone moiety, the *o*-hydroxyphenyl group showed strong activity (602, 604, 607, 608, 610, 649) and inhibited the growth of *Mycobacterium tuberculosis* at concentrations of 0.5–1 γ/ml. The activity of the *o*-hydroxyphenyl group is enhanced by the presence of an additional hydroxy group in the para position and either a chlorine atom or an ester group (256). Conversion of the phenolic group to an allyl ether (609) or replacement of

R′ = H by R′ = methyl (611) or of the hydrogen attached to nitrogen in the 4-thiazolidinone moiety by an alkyl or aryl group (612) decreases the activity.

As certain 1,3-bis(thiocarbanilides) show pronounced antituberculous activity, the corresponding 3-aryl-2-arylimino-4-thiazolidinones were synthesized and tested (441). An alkoxy substituent containing three to six carbon atoms attached to the phenyl group, such as isoamoxyphenyl, produces a substance with good *in vivo* activity, while the corresponding 3-aryl-2,4-thiazolidinediones are inactive (204, 442).

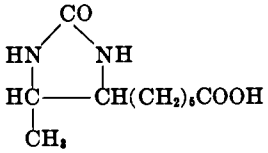
A comparison of the activity toward *M. tuberculosis* of the 2-(*p*-aminobenzenesulfonylhydrazino)-4-thiazolidinone with 2-(*p*-aminobenzenesulfonylimino)-4-thiazolidinone indicates that the former is more effective (616). In otherwise similar compounds, the 2-hydrazino group is more effective than the 2-imino-, the 2-thiono-, or the 2-oxo group (601); nevertheless, 2-phenylhydrazino-4-thiazolidinone is less active than isonicotinoyl hydrazide (647). Among the 2-aroylhydrazino-4-thiazolidinones that have been investigated, the most active contains an aromatic substituent which is 4-chlorophenyl or 4-pyridyl (619). Certain 3-aroylaminorhodanines in which the aryl group is phenyl, *p*-nitrophenyl, or 4-pyridyl are effective in inhibiting the *in vitro* growth of *M. tuberculosis* at concentrations of 0.5 mg./ml. (572). The *in vitro* tuberculostatic activity of arylidene derivatives of 3-aminorhodanine has been tested (566). The most active compounds are 3-(*o*-hydroxybenzylideneamino)rhodanine and 3-amino-5-(4-hydroxy-3-methoxybenzylidene)rhodanine, but they are ineffective when tested against experimental tuberculosis in mice.

Actithiazic acid (page 471) is an antibiotic isolated from a species of *Streptomyces* (289, 558). The compound has high specific *in vitro* activity against *M. tuberculosis*, but is inactive *in vivo*. Biotin, which contains some structural features similar to actithiazic acid reverses the activity of the antibiotic (289, 487), although biotin deficiency, induced in the rat by administration of raw egg white, was not changed significantly by the addition of actithiazic acid (175).



Actithiazic acid

Biotin



Dethiobiotin

It has been suggested that actithiazic acid bears a closer structural relationship to dethiobiotin than to biotin and that the former may be a more effective inhibitor of the antibiotic (642). The synthesis and testing of similar compounds show that certain functional derivatives of the acid, such as esters, retain activity but that a change in the number of carbon atoms between the acid group and the 4-thiazolidinone moiety produces compounds with little or no activity (440, 484).

3,5-Dimethyl- and 3-ethyl-5-methylrhodanines are bacteriostatic (669), and some 2-aryl(or 2-furyl)-3-substituted-4-thiazolidinones exhibit moderate activity against several pathogenic bacteria (237, 240).

The antibacterial activity of sulfanilamide and its derivatives suggested the introduction of this group into the 4-thiazolidinones. 2-Sulfanilamido 2-thiazolin-4-ones with various alkyl groups attached to the methylene carbon atom are active against *Streptococci*, *Pneumococci*, and *Staphylococci* (138, 448). It seems probable that activity in these compounds is caused by the sulfanilamide moiety.

The usefulness of 5-(*p*-dimethylaminobenzylidene)-rhodanine in precipitating traces of heavy metals suggested that such compounds might be bacteriostatic by precipitating traces of metals essential in the metabolism of the bacteria (291, 545). Although the compound was active against several pathogenic bacteria at concentrations of 50 p.p.m., no definite correlations could be drawn between the bacteriostatic activity and chelation with heavy metals. Chosen in a series of tests because of its ability to bind heavy metals, 5-(*p*-dimethylaminobenzylidene)rhodanine was found to inhibit the growth of the fungus *Neurospora sitophila*. Increasing the concentration of pyridoxine in the culture medium eliminated the inhibition (2).

Since rhodanine and its derivatives contain the dithiocarbamate structure present in many widely used organic fungicides, an extended study has been made of the fungistatic and mildew-preventing activity of the aldol condensation derivatives of rhodanine (93, 94, 95, 98). Of the large number of compounds investigated, two substances, 5-(*p*-chlorobenzylidene)-rhodanine and 5-(2-thenylidene)rhodanine, protected cotton cloth against four weeks' burial in soil, with less than 5 per cent deterioration in tensile strength taking place during this interval.

Rhodanine and its derivatives with hydrogen attached to nitrogen have been patented as fungicides (13), and other patents cover the use of rhodanine derivatives with a hydrocarbon residue attached to the nitrogen atom (132, 459).

3-Phenylrhodanine and some of its substituted phenyl derivatives inhibit the growth of certain fungi, including *A. niger*, *Botrytis cinerea*, *Penicillium italicum*, and *Rhizopus nigricans* (361).

Of twenty-six 3-phenylrhodanine compounds, twelve showed complete inhibition of the growth of *A. niger* at 250 p.p.m., with the most active having methoxy, chloro, bromo, or acetyl substituents in the para position of the benzene ring (99). While the 3-phenylrhodanines show little activity against the gram-positive bacteria, *B. subtilis*, or the gram-negative one, *E. coli*, 3-(*p*-chlorobenzyl)-, 3-(3,4-dichlorobenzyl)-, and 3-(2-methylthiobenzyl)rhodanines, which are relatively inactive as fungistatic agents, completely inhibit the growth of *B. subtilis* at 2.5 p.p.m., and 3-(*p*-fluorobenzyl)rhodanine inhibits the growth of *E. coli* at 5 p.p.m. (99).

It has been proposed that the active fungistatic compound is the corresponding isothiocyanate, which is formed from the rhodanine during the metabolic changes within the organism (361). Among a series of benzyl isothiocyanates, outstanding bacteriostatic properties are shown by 3,4-dichlorobenzyl isothiocyanate (428). 3-(*p*-Chlorobenzyl)thiazolidine-2-thione and 3-(3,4-dichlorobenzyl)thiazolidine-2-thione, which lack the carbonyl group at the 4-positions and would not be expected to be hydrolyzed to the isothiocyanate, do not prevent the growth of *B. subtilis* or *E. coli* at 250 p.p.m. (83). These facts support the theory that the active fungistat or bacteriostat is the isothiocyanate.

The same type of antifungal activity is exhibited by the 3-phenyl- and 3-benzyl-2,4-thiazolidinediones. On the basis of their activity towards *Alternaria solani* and *Sclerotinia americana*, 3-phenyl- and 3-(*p*-chlorophenyl)-2,4-thiazolidinediones have been patented as fungicides (576).

As would be expected from the lack of fungistatic activity of the 3-benzylrhodanines, various 3-substituted benzyl-2,4-thiazolidinediones exhibit low toxicity toward *A. niger* (83) and toward *Stemphylium sarcinaeform* and *Monilia fructicola* (403).

A comparison of the activity against *A. niger* of 5-(1-methylalkylidene)-2,4-thiazolidinediones with that of the corresponding rhodanines indicates that the peak of activity of the former series is reached when the number of methylene groups in the alkylidene chain is greater than with the rhodanines (97).

Efforts have been made to improve the fungicidal activity of certain rhodanines by bromination (497) and of some 2-arylimino-4-thiazolidinones by bromination (512) or by mercuration (444) of the aryl nucleus.

3-Trichloromethylsulfenyl-2,4-thiazolidinedione has been patented as being effective in preventing the growth of bacteria, fungi, and insects (367), while its alkyl or 5-alkylidene derivatives have been claimed as pesticides (405). Since other heterocyclic compounds with the trichloromethylsulfenyl group attached to nitrogen are also active, it is probable that the halogenated moiety is responsible for the toxic action.

Several rhodanine derivatives have been patented as insecticides or nematocides. These include 3-(*p*-chlorophenyl)-5-methylrhodanine (52), which has been used for soil in which tomato (318, 621) or strawberry (622) plants are growing, *S*-(β-carboxyethyl)rhodanine (282) and *S*-(γ-carboxypropyl)rhodanine (290). 3-(*p*-Chlorophenyl)-5-methylrhodanine is not as effective as 3,5-dimethyltetrahydro-2*H*-1,3,5-thiadiazene-2-thione in the control of the potato-root eelworm (74). The sodium salt of 3-phenyl-5-(*o*-sulfobenzylidene)-rhodanine is effective as a mothicide (8). 5-Ethylidenerhodanine (78) and 3-isobutyl-5-substituted benzylidenerhodanines (404) have been tested as insecticides.

Amoebicidal activity is exhibited by the 2-aryl-4-thiazolidinone 1,1-dioxides (584) and by 2-{[(arsenosobenzoyl)aryl]imino}-4-thiazolidinone (353), and anthelmintic activity by derivatives of 3-allylrhodanine (410, 411).

The effectiveness of paludrine as an antimalarial led to the synthesis of 2-substituted-imino-4-thiazolidinones with a biguanidine substituent in the 5-position (511).

D. PHARMACOLOGICAL USES

3-(β-Arylethyl)rhodanines were synthesized for pharmacological testing with the expectation that similarity of structure to adrenaline might produce useful compounds (103); however, the compounds proved too insoluble to be of practical use.

2-Aryl-4-thiazolidinones with an aminoalkyl group attached to the nitrogen atom are similar in structure to procaine and have local anesthetic properties (407, 579). The most promising ones have a higher anesthetic potency than procaine but are more toxic and somewhat more irritating.

Similarity in structure between 5,5-dialkyl-2,4-thiazolidinediones and the barbituric acid derivatives suggested an investigation of the narcotic properties of the former (211, 215). The most active compounds in this series are the 5,5-diethyl- and 5,5-dipropyl derivatives, which are comparable to 5,5-diethylbarbituric acid (209, 552). Undesired side effects accompany the intravenous injection of the sodium salts and limit their practical importance as drugs (185). Although 5,5-diethylrhodanine exhibits a narcotic action slightly greater than that of veronal, its therapeutic usefulness is restricted by its slight solubility in water and its ineffectiveness when administered orally (394). Narcosis, produced in mice by 5-phenyl-2,4-thiazolidinedione, is reversed by the barbiturate antagonist, 4-ethyl-4-methyl-2,6-piperidinedione (554). 5-Spirocyclohexyl-2,4-thiazolidinedione causes narcosis of shorter duration than that of amytal and exerts analgesic action less than that of morphine (341). The 3-methyl homolog is too insoluble in water for tests in solution, but injection of the liquid produces narcosis.

Sedative action is claimed for 3-methyl-5,5-diphenyl-2,4-thiazolidinedione (220), and for 5,5-disubstituted-2-imino-4-thiazolidiones (185, 223). While the 3-alkoxyphenyl-2-(*p*-alkoxyphenylimino)-4-thiazolidinones have antituberculous activity, similar compounds lacking the 3-aryl group are sedatives and spasmopreventives (227). Sedative action is also shown by the 2-dialkylamino-2-thiazolin-4-ones, which may be considered as alkylated derivatives of the tautomer of 2-imino-4-thiazolidinone (225).

Several 4-thiazolidinones have anticonvulsant properties. Against electrically induced convulsions, 3-methyl-2-phenyl-4-thiazolidinone and its 3-ethyl homolog give complete protection to cats with oral dosages of 100 mg./kg., but are much less effective at lower concentrations (130, 630). 3-Butyl-5,5-dimethyl-2,4-thiazolidinedione protects rats against electric shock, but the animals show noteworthy depression (627). As certain 2,4-oxazolidinedione derivatives protect against metrazole-induced convulsions and are used in the treatment of *petit mal* epilepsy (134), the corresponding thiazolidine analogs were examined and found to afford less protection (301, 421). 5-Phenyl-2,4-thiazolidinedione protects mice against metrazole-induced convulsions and also potentiates the hypnotic action of pentobarbital (554). Among the 3-alkyl-2-aryl-4-thiazolidinones which protect against metrazole-induced convulsions, 2-(*p*-chlorophenyl)-3-methyl-4-thiazolidinone is effective at an oral dosage of 125 mg./kg. Increasing the length of the alkyl group or oxidation of the sulfur to sulfone decreases the activity (208, 630).

The antithyroid activity of rhodanine, 2,4-thiazolidinedione, and pseudothiohydantoin is very slight in comparison with thiouracil or 6-methylthiouracil (270, 300, 425, 427), although there is evidence that the amount of antithyroid activity of rhodanine differs with various species of test animals (197).

Various 4-thiazolidinones cause slight activation or inhibition of the evolution of carbon dioxide from a 0.01 *M* yeast–glucose fermentation broth (250). Rhodanine injected in a rabbit at a concentration of 190 mg./kg. does not affect the level of blood sugar when measured before and after injections of glucose (426). Only rats with experimentally induced hypertension show a lowering of blood pressure on administration of pseudothiohydantoin (546), while at a dosage of 133 mg./kg. 5-benzylidenerhodanine produces a rise in blood pressure of 30 mm. which is of short duration (623).

E. MISCELLANEOUS USES

Before the merocyanine dyes were discovered, the red or yellow color of the 5-arylidene derivatives of rhodanine suggested their use as dyes, but instability to light prevented general usefulness (38, 273). However, the indigo-like oxidation product of rhodanine, called rhodanine red, is stable to light (273) and the 5-arylidene(or 5-arylimino)-3-phenyl-2-phenylimino-4-thiazolidinones are reported to give fast colors when dyed on wool (4).

Rhodanine derivatives have been patented as vulcanization accelerators in the production of synthetic rubber (156).

Polymeric substances containing a 4-thiazolidinone unit include a thermosetting polymer formed by the condensation of rhodanine and formaldehyde (681), and pseudothiohydantoin polymers prepared from proteins such as zein, casein, or soybean (327). The latter may also be condensed with phenol and formaldehyde, giving products which vary from thermoplastic solids to viscous fluids at high temperatures (325), and with anhydrides of dibasic acids (326).

Rhodanine has been considered as a possible source of mercaptoacetic acid in cold-wave preparations (302).

The incorporation of small amounts of rhodanine, 3-phenylrhodanine, or their 5-alkylidene or 5-arylidene derivatives in the bath used in the electrodeposition of copper (478) or silver (460) gives a smooth and bright deposit of the metal.

Rhodanine and its derivatives confer antiwear properties when incorporated in lubricating oils and greases (370, 395, 658). The inclusion of 0.025 per cent of rhodanine in stearic acid delays the first appearance of peroxides for 336 hr. (205), and the addition of 1 per cent of 5-benzylidene-3-hexadecyl-2-phenylimino-4-thiazolidinone to polyethylene gives excellent protection against weathering damage (594).

XI. REFERENCES

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