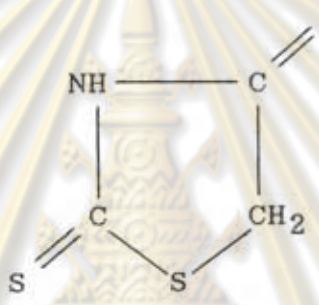
CHAPTER II

HISTORY

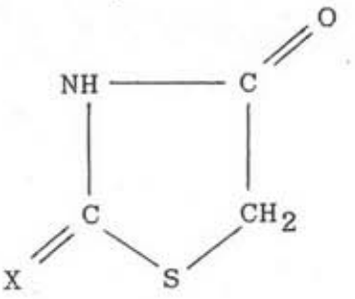
Rhodanine (I) is a derivative of thiazolidinone with a thio group and a carbonyl group in the 2- and 4-positions respectively.



I

Its chemical name is 2-Thio-4-thiazolidinone or 2-Thio-4-ketothiazolidine, but it is also commonly known either as rhodanic or rhodaninic acid (26).

Substituents in the 2-, 3-, and 5-positions may be varied, but main difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position (X in formula II).



II

A : X = O

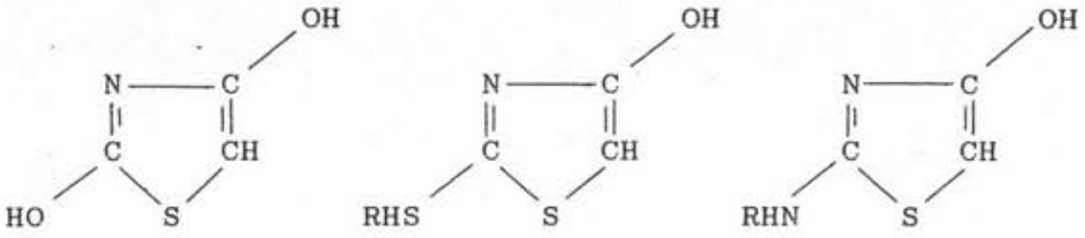
B : X = S

C : X = NR

D : X = $NN=CR_1R_2$

Such groups include alkyl or aryl, oxygen (IIA : 2,4-thiazolidinedione, which frequently called " Senfolessigsaure " in the early German literature), sulfur (IIB : rhodanine), imino (IIC : pseudohydantoin, although compounds in which alkyl or aryl groups replace the hydrogen atoms are named as derivatives of 2-imino-4-thiazolidinone), and hydrazino(IID : named as the 4-oxo-2-thiazolin-2-ylhydrazones of the aldehyde or ketone).

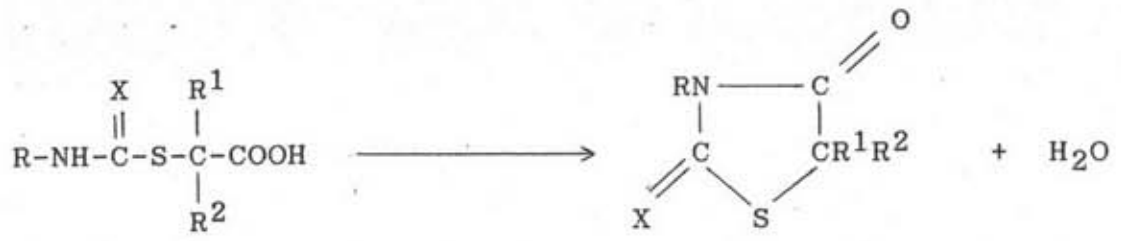
The presence of a thiazole ring in a tautomeric forms of 2,4-thiazolidinedione (III_a), in rhodanine (III_b) and in pseudothiohydantoin (III_c) indicate the close relationship in structure among the three substances (24).



(a) (b) (c)

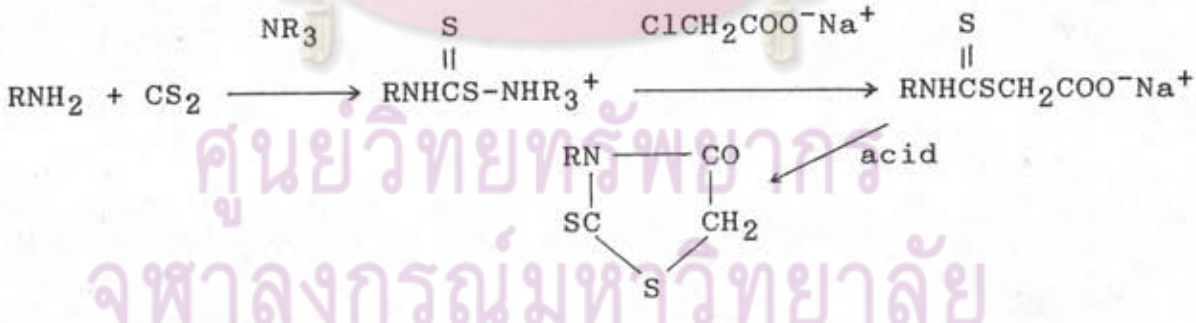
III

Rhodanine and its derivatives can be synthesized by cyclization of acyclic compounds or by interconversions among appropriately substituted thiazolidinone derivatives. 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 intermediates, which usually not isolated, are an appropriately substituted alkanoic acids and their salt or esters. The ring closure occurs between the acid group and the hydrogen attached to the nitrogen, i.e. between atoms 3 and 4 of the thiazolidinone ring, for example cyclization of S-carboxymethyl dithiocarbamate (IV: R = R_1 = R_2 = H; X = S) to rhodanine. The reaction is monomolecular with velocity constant C = 0.19×10^{-3} (time measured in minutes) (27). The ester of this acid, which can be isolated if its synthesis is performed at low temperature, cyclization can be obtained by refluxing in alcoholic or aqueous solution (24).



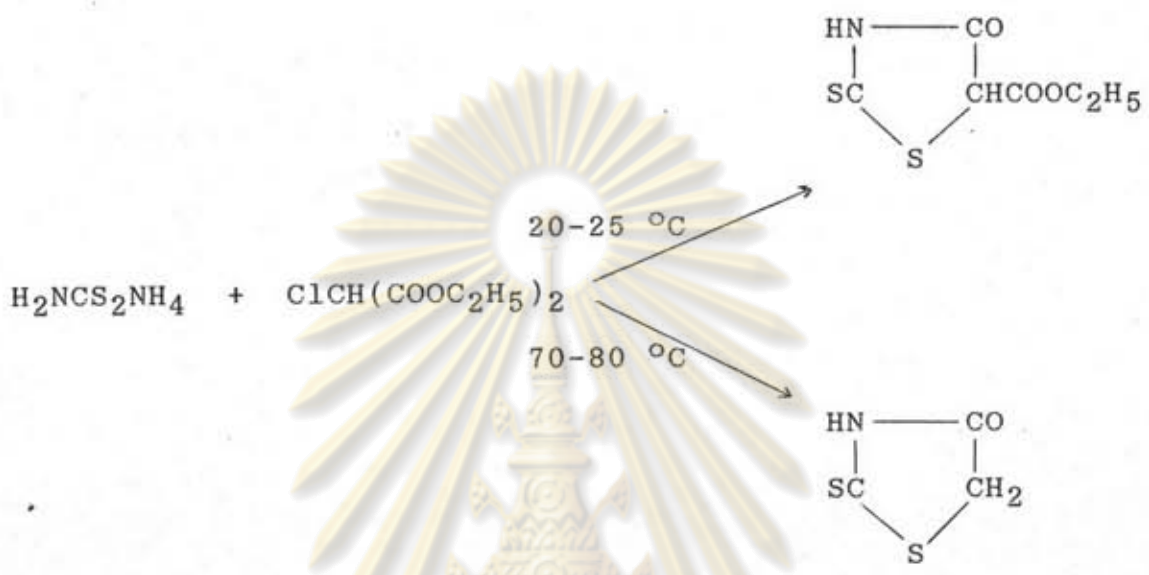
IV

Dithiocarbamates, formed by the reaction of ammonia or primary amines with carbon disulfide in the presence of base, are the source of the hetero atom of the 4-thiazolidinone ring (28), the thiocarbamate may be either as its sodium salt or S-carboxymethyl ester (29). 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 hrs at room temperature has been recommended (29).

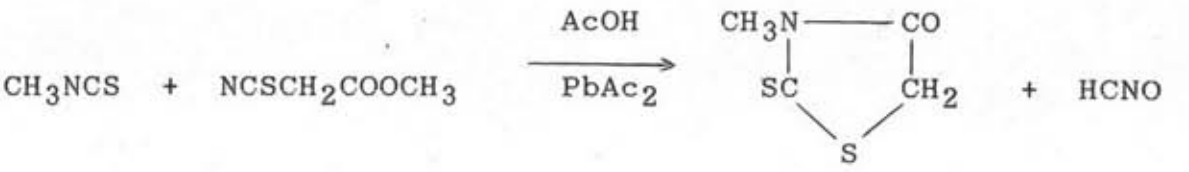


With diethyl chloromalonate as the ∝ -haloalkanoic ester, the final product depends on the temperature of the reaction. At room temperature or below, 5-carbethoxy

rhodanine is obtained, while refluxing the reaction mixture at 70-80 °C causes saponification and decarboxylation, yielding rhodanine (30,31).

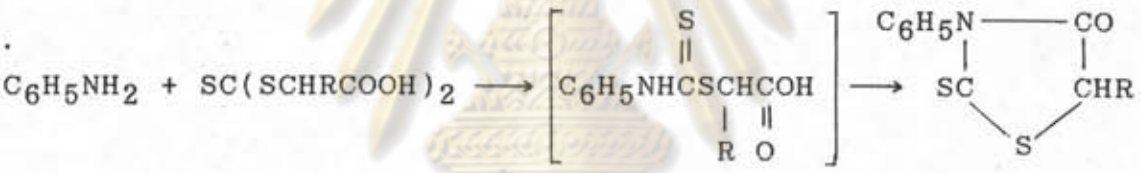


Moreover, rhodanine and its derivatives can be synthesized by reacting ∝-mercaptoalkanoic acids with isothiocyanate. The isothiocyanate is heated with acetic acid solution of methylthiocyanoacetate in the presence of a catalytic amount of lead acetate until the evolution of carbon dioxide, from the decomposition of cyanic acid, has stopped (24,32).



isothio cyanate — methylthio cyanoacetate — 3-methyl-2-thio-4-thiazolidinone — cyanic acid

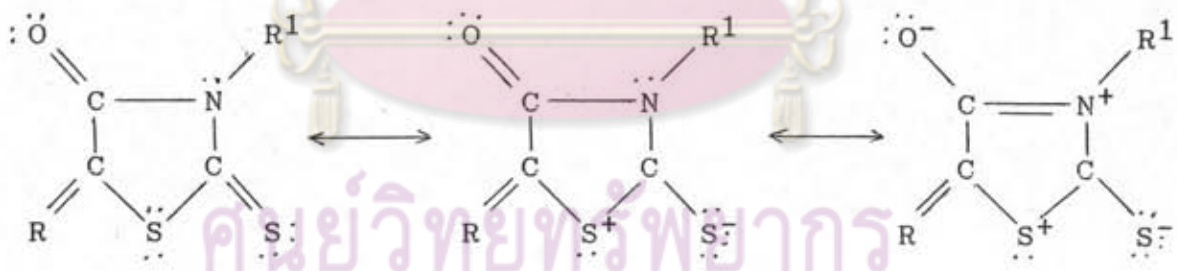
A useful method of preparing certain 3-substituted rhodanines involves the attack of a primary amine on the carbon atom of the thiono group of dicarboxymethyl trithiocarbonate with elimination of the S-carboxymethyl dithiocarbamate (29).



Several methods are available for the conversion of 2-substituted 4-thiazolidinones into compounds with other substituent groups at 2-position. Carbon disulfide, if heated for 6 hrs at 180 °C with a 2-imino-4-thiazolidinone yields the corresponding rhodanine (24).

Rhodanine has a water solubility of 2.25 g per liter at 25 °C (27). Crystallographic data density and indices of refraction of rhodanine have been reported(33). Dipole moment of rhodanine is 2.20 D (44) and of 3-ethyl

rhodanine is 1.75 D (35). The ultraviolet spectra of rhodanine, its 3-substituted derivatives and its 5-alkyl derivatives have shown 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 and to the dithio ester group, and (b) to the thione and amide groups (24). Unsaturation at position 5 causes a bathochromic shift of the position of the peaks in rhodanine (36). Introduction of vinyl groups between the rhodanine and aromatic moieties of 5-benzylidene rhodanine causes a further bathochromic shift of 25 mμ per vinyl group in the high-intensity peak of 375 mμ (24). The bathochromic shift in 5-benzylidenerhodanine has been ascribed to resonance forms in which the sulfur of the 4-thiazolidinone ring acquires a positive charges (24).



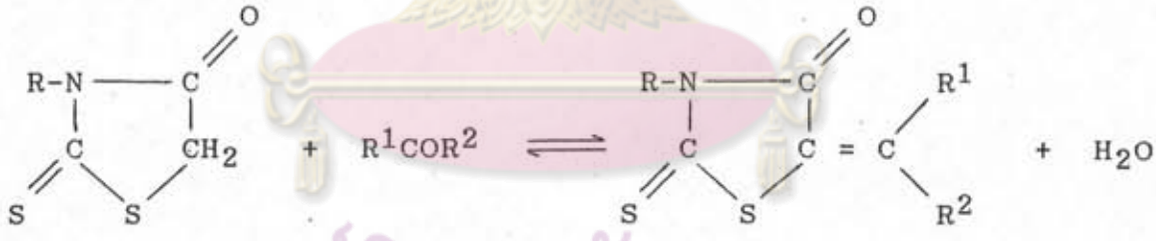
The infrared spectra of the 4-thiazolidinones has shown the carbonyl peak, usually found between 1760 cm^{-1} and 1655 cm^{-1}, is strong and characteristic. With rhodanine derivatives a saturated alkyl group in the 5-position does not have a significant effect on the

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 (37). 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 is usually found between 1580 cm^{-1} and 1450 cm^{-1} (37,38). With the rhodanine derivatives strong band, 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 (24).

The methylene carbon atom at 5-position of 4-thiazolidinone possesses nucleophilic activity and attacks an electrophilic center. Most frequently, the reaction occurs in the presence of 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 depends 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 (39). The electron attraction of sulfur of 2-thione group is greater than that of the oxygen of 2-carbonyl group.

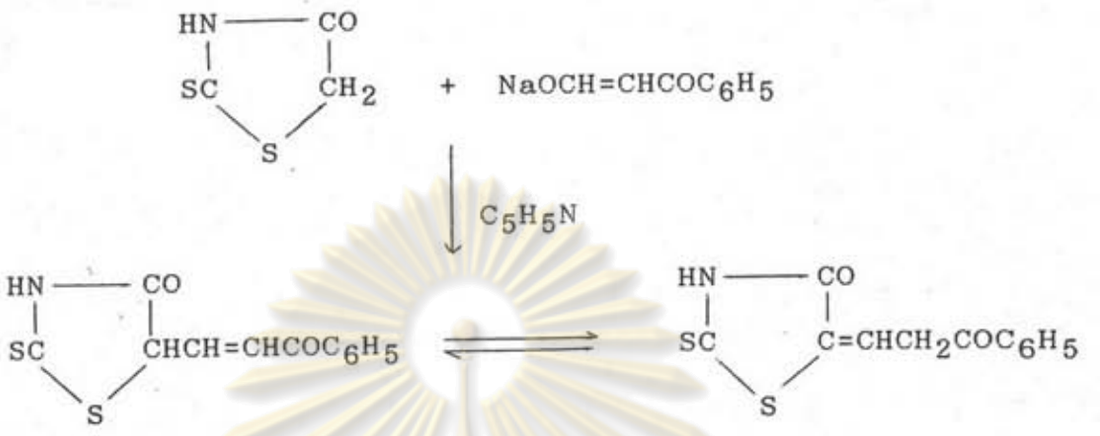
The first reaction of this type to be investigated and one that has received much attention is the aldol

condensation of the methylene group with the carbonyl group of an aldehyde or ketone followed, if possible, by loss of water. The reaction was first performed with rhodanine and benzaldehyde or acetaldehyde, using sulfuric acid as the condensing agent, and the isolation of a product was believed to support an open-chain formula for rhodanine, $HSCH_2COSCN$. Later, sodium hydroxide in ethanolic solution, sodium ethoxide in ethanolic solution (40), anhydrous sodium acetate in acetic acid (41), anhydrous sodium acetate, acetic anhydride and acetic acid (42), ammonia and ammonium chloride in ethanolic solution (43-45), ammonium hydroxide in ethanolic solution (46), diethanolamine (47) and piperidine (48,49) were used as condensing agents.

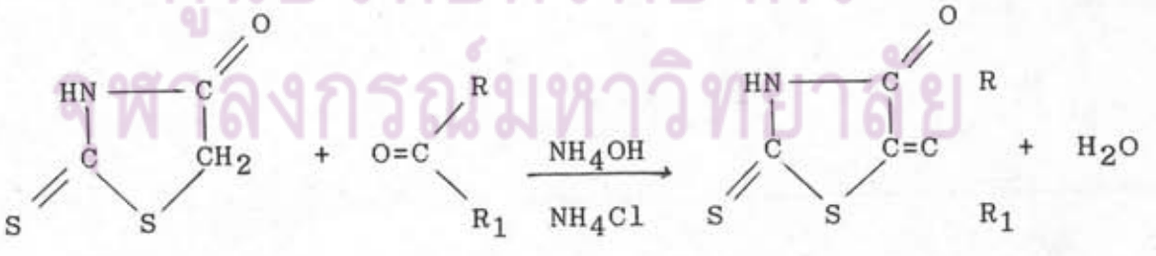


With most aromatic and heterocyclic aldehyde, the yields in reaction with rhodanine are above 75 % and the reaction is used to prepare derivatives of the aldehyde (50-52). If the aldehyde exists predominantly in the enol form, its sodium derivative reacts with rhodanine in pyridine solution and produces the tautomer of the

aldol condensation product (53).

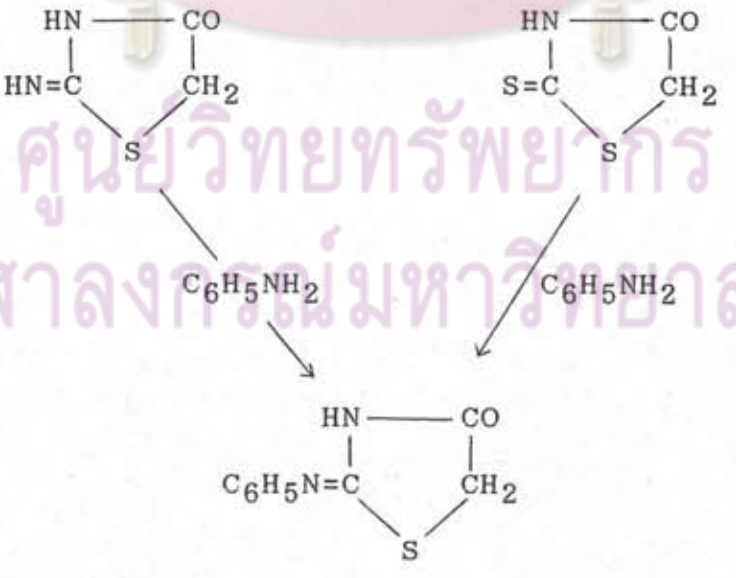


Schwarz (54) stated that condensations between rhodanine and ketone are possible, but neither descriptions of the physical properties nor analyses of this statement reaction have been made. However, certain derivatives of rhodanine with diketones have been reported (55-57). The method of making a rhodanine derivatives of ketone was suggested by Girard (45) who induced condensation in an ammonium hydroxide-ethanol medium containing ammonium chloride.

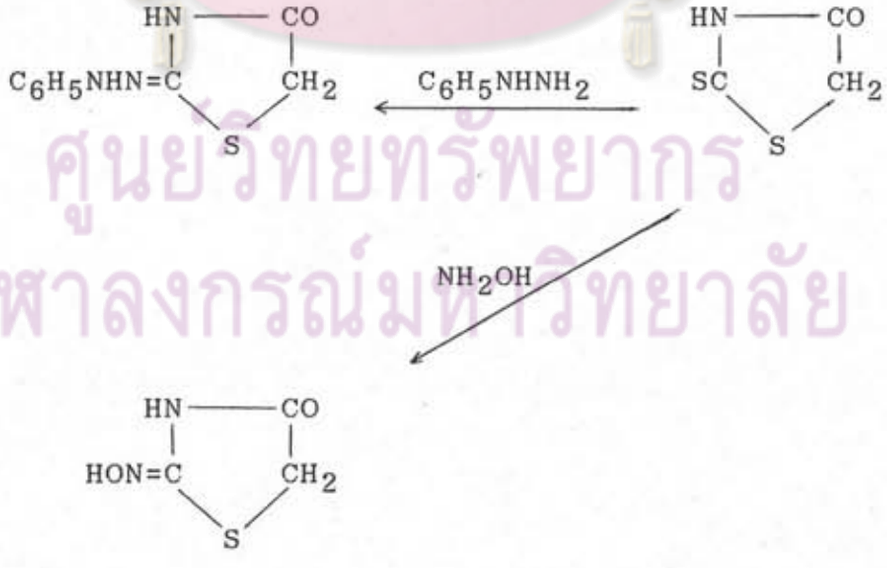


Many ketones whose carbonyl group is not markedly affected by steric hindrance yield the desired 5-disubstituted methylene derivatives (58). Ketones, including α - diketones such as biacetyl, condense with 3-substituted rhodanines if zinc chloride is added to the dioxane or methanol solution (39).

Many organic bases react with 4-thiazolidinones and attack the carbon atom at 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. 2-Phenylimino-4-thiazolidinone is formed on heating aniline with pseudohydantoin (59) or with rhodanine (60).



If 3-phenylrhodanine is heated with aniline for one hr at 160 - 170 ^{o}C, the attack at the thione group is followed by cleavage of the ring and thiocarbanilide is formed (24). The presence of substituents in the 5-position stabilizes the thiazolidine ring and aniline converts the sulfur of the thione group to the phenylimino derivative (60,61). Rhodanine and its derivatives react with phenylhydrazine and the product is the 2-phenyl hydrazone of the corresponding 2,4-thiazolidinedione (24). Hydroxylamine hydrochloride in the presence of sodium acetate (62) or barium carbonate (52) 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.



The use of rhodanine and its derivatives as analytical reagents in spot testing for silver, gold, copper, mercury, palladium and platinum has been reviewed (20). And the reaction with heavy metal ions is considered to be the formation of a complex rather than simple salt formation (63,21-23). The usefulness of rhodanine and its derivatives in complexation with traces of heavy metals suggested that such compounds might be bacteriostatic by complexing with heavy metal ions in the metabolism of bacteria (17,21-24).

The present study is based on the reactions of 4-thiazolidinones with organic bases and reports the attempt to synthesize some new rhodanine derivatives which are expected to provide the better antibacterial activity.