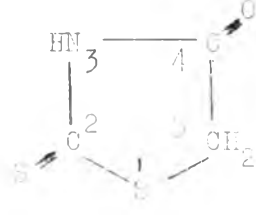
CHAPTER II

History

Rhodanine [I] is a derivative of thiazolidine, with a thio and a carbonyl group in the 2 and 4 positions respectively.

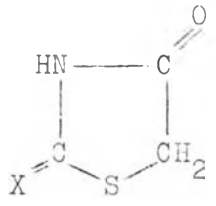


[I]

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(51).

There is considerable confusion concerning the structure of rhodanine in the early literature. It was first thought to have a noncyclic formula, α-CH_2-CO-SCN(56). However, recognition of mercaptoacetic acid as a primary product of the hydrolysis of 3-Phenyl-2-phenylimino-4-Thiazolidinone led to the choice of as cyclic formular, and by analogy a cyclic formula [II B] was proposed for rhodanine in 1879 (57, 58).

By varying the substituents in the 2 position of 4-thiazolidinone compounds, a number of related compounds can be obtained [II] :



(II)

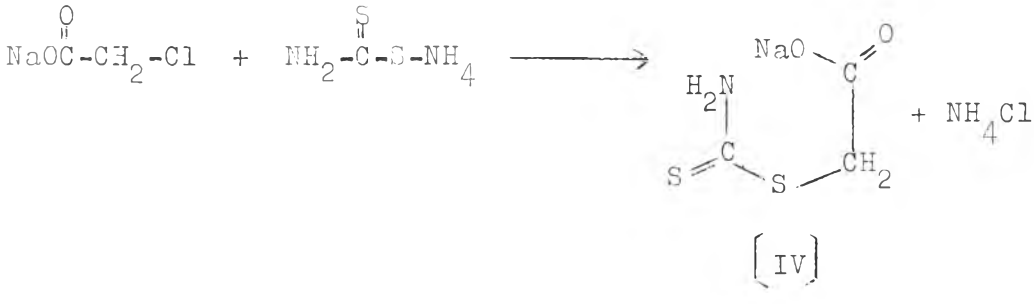
A	X	=	O
B	X	=	S
C	X	=	NR
D	X	=	NN=CRR'

Formula II A - where X is oxygen - is 2,4-Thiazolidinedione, which is frequently called "Senfölessigsäure" in the early German literature. Formular II B - where X is sulfur - is rhodanine. Formula II C - where X is imino - is pseudothiohydantoin, and Formula II D - where X is hydrazino - is the 4 - Oxo - 2 - Thiazolin-2-ylhydrazones of the aldehyde or ketone. The presence of a thiazole ring in a tautomeric form [III] of 2,4-thiazolidinedione in rhodanine and in pseudothiohydantoin indicated a close relationship in structure among the three substances, (59).

(II) (III)

Rhodanine and its derivatives can be synthesized by the cyclization of acyclic compounds or by interconversions among appropriately substituted thiazolidine derivatives. In the cyclization reaction, the acyclic intermediate(which is not usually

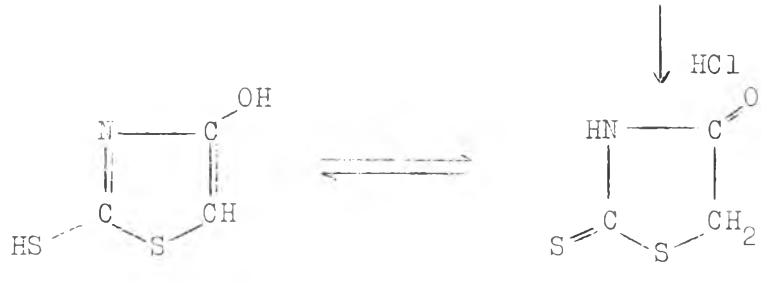
isolated) is either the salt or the ester of an appropriately substituted alkanoic acid. In general, sodium chloroacetate, as an α-haloalkanoic acid, reacts with ammonium dithiocarbamate to give an acyclic intermediate - thiocarbamyl thioglycolic acid or S - carboxymethyl dithiocarbamate [IV] . This intermediate can be made to cyclize after the addition of a strong acid, such as hydrochloric acid, sulfuric acid or acetic acid, after which the solution must be kept for 12 - 24 hours at room temperature before the rhodanine is produced. The reactions can be shown as follows :



[IV]

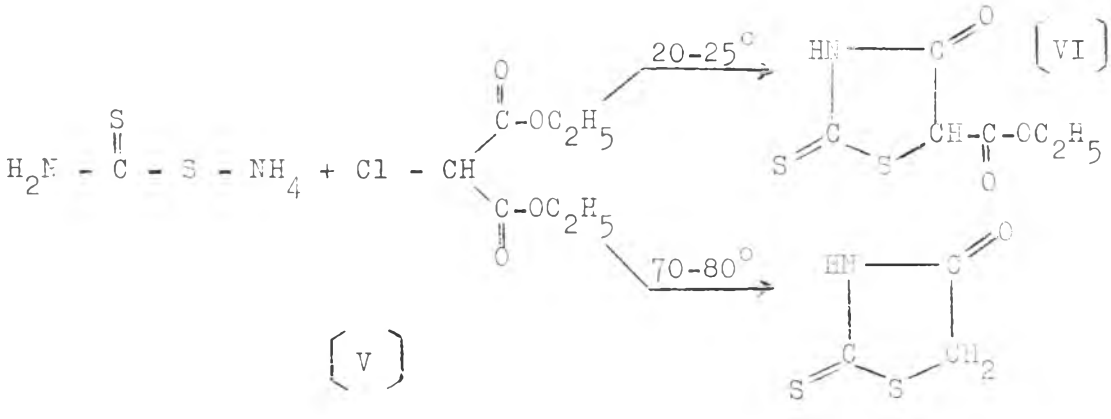
Thiocarbamylthioglycolic acid or

S-carboxymethyl dithiocarbamate



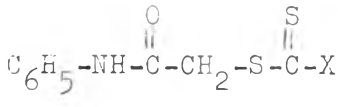
Julian and Sturgis (60) have reported a valuable modification in connection with improvement on this procedure. Using diethyl chloromalonate [V] as the α - haloalkanoic acid ester, the final product will depend on the temperature of the reaction. At room

temperature or below, 5-carbethoxy rhodanine [VI] is obtained, while refluxing the reaction mixture causes saponification and decarboxylation, yielding rhodanine (61,62).



In addition, the cyclization of S-carboxymethyl dithiocarbonate to rhodanine was found to be a monomolecular reaction and had a velocity constant of $c = 0.19 \times 10^{-3}$ with the time being measured in minutes (63)

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 [VII A] nor the 2-trithiocarbonate [VII B] of acetonilide can be cyclized as a result of losing ethanol or ethanethiol :



[VII]

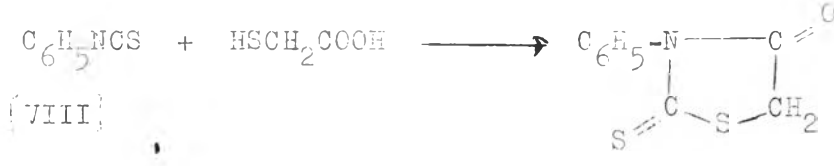
A : $X = OC_2H_5$

B : $X = SC_2H_5$

C : $X = NH_2$

Also the cyclization of the amides of S - carboxymethyl dithiocarbamate [VII C] by heating the compound with dilute sulfuric acid yielded rhodanine and aniline rather than 3-phenyl rhodanine and ammonia (64).

A derivative of rhodanine can also be produced using α-mercartoalkanoic acid with isothiocyanate, [VIII] (64,65) :



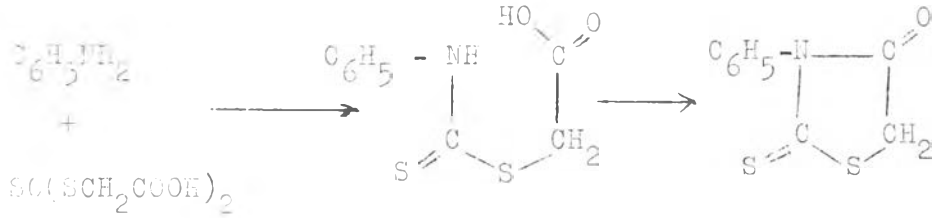
[VIII]

In a variation of this method, the isothiocyanate is heated with an acetic acid solution of methylthiocyanoacetate [IX] in the presence of a catalytic amount of lead acetate, until the evolution of carbon dioxide from the decomposition of cyanic acid is complete, giving 3-substituted rhodanine [X] (66).

[IX] [X]

Certain 3-substituted rhodanines have also been prepared using the reaction of di(ω-carboxylalkyl) trithiocarbonates [XI]

with primary amines (67). In this case, the primary amines attack the carbon atom of the thiono group of di-carboxymethyl-trithiocarbonate, and eliminate the anion of mercaptoacetic acid. The cyclization of the S-carboxymethyl dithiocarbamate then produces the desired product :



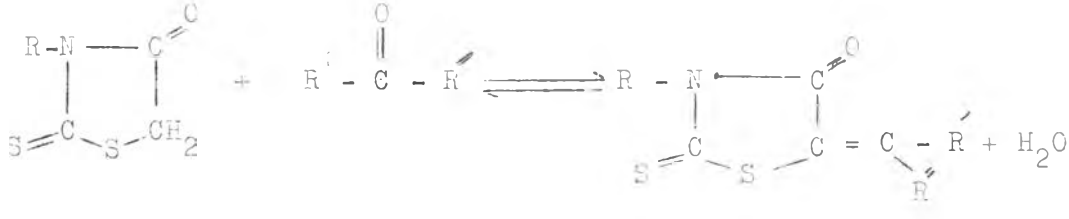
[XI]

In addition, several methods are available for the conversion of 2-substituted 4-thiazolidinones into compounds with other substituted groups at the 2-position. Thus corresponding rhodanine was converted from 2-imino-4-thiazolidinone when heated for 6 hours at 180°C with carbon disulfide (63).

Rhodanine has a solubility of 2.25 gram per litre at 25°C (63). The 3-unsubstituted rhodanines are usually solid, but the attachment of an alkyl group to the nitrogen atom lowers the melting point. Polymorphism occurs with 3-aminorhodanine (69). Crystallographic data, density and indices of refraction have been reported (70). The dipole moment of rhodanine has been given as 2.20 D (71), and of 3-ethyl rhodanine as 1.75 D (72).

Rhodanine is a weak acid, the ionization constant being 1.69×10^{-5} at 20°C (73). In addition, 5,5-disubstituted rhodanines show little difference in their values for ionization constants from the unsubstituted compounds. The acidity is attributed to the hydrogen atom attached to nitrogen (74).

Since rhodanine has an active methylene group at 5 position, it can undergo aldol condensation with the carbonyl group of an aldehyde or ketone, followed possibly by loss of water. The product (XII) of the reaction contains an α - β - unsaturated carbonyl group.

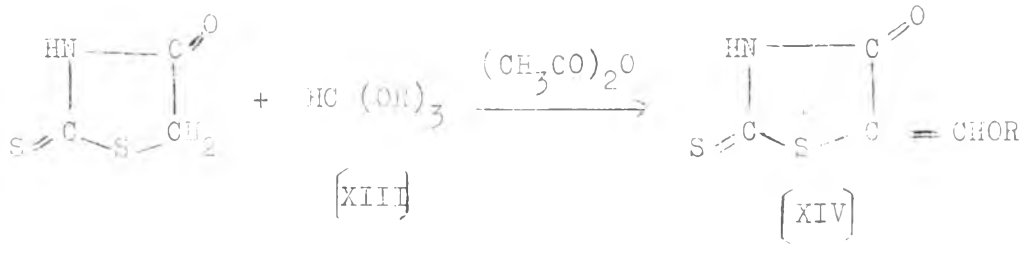


(XII)

This reaction was first observed with rhodanine and benzaldehyde or acetaldehyde, using sulfuric acid as the condensing agent (75). Later, sodium hydroxide in ethanolic solution (76), sodium ethoxide in ethanolic solution (77), anhydrous sodium acetate in acetic acid (60), anhydrous sodium acetate, acetic anhydride, and acetic acid (78), ammonia and ammonium chloride in ethanolic solution (79,80,81), ammonium hydroxide in ethanolic solution (82), diethanolamine (83) and piperidine (84, 85)

were used as condensing agents.

With sulfuric acid as the condensing agent, the aldehyde diacetate can be used instead of the aldehyde (80). In addition, alkoxy-orthoformates [XIII] can condense with rhodanine, using acetic anhydride as the condensing agent, yielding 5-alkoxymethylene rhodanine [XIV] (80).



[XIII] [XIV]

Most aromatic and heterocyclic aldehydes condense with rhodanine and produce a good yield (87,88,89). Aliphatic aldehydes condense with rhodanine after being refluxed for several hours in acetic acid solution(64), or by using either sodium acetate in acetic acid or ammonium chloride and ammonia in ethanolic solution(90). 3-substituted rhodanines in anhydrous sodium acetate and acetic anhydride give the desired product but it is sometimes necessary to heat the reagents in an autoclave (91).

If the aldehyde exists predominantly in the enol form, its sodium derivative [XV] reacts with rhodanine in pyridine solution and produces the tautomer of the aldol - condensation product (92).

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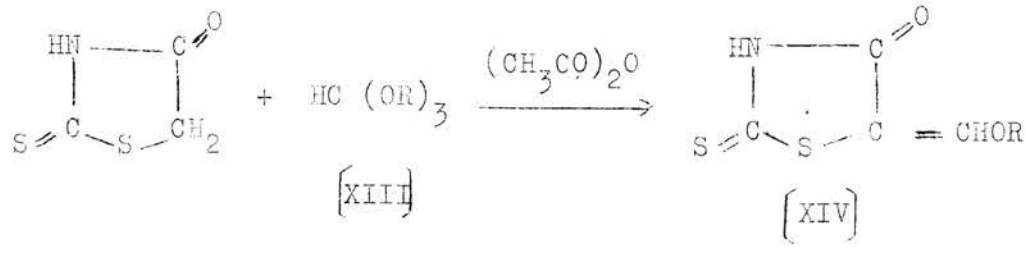

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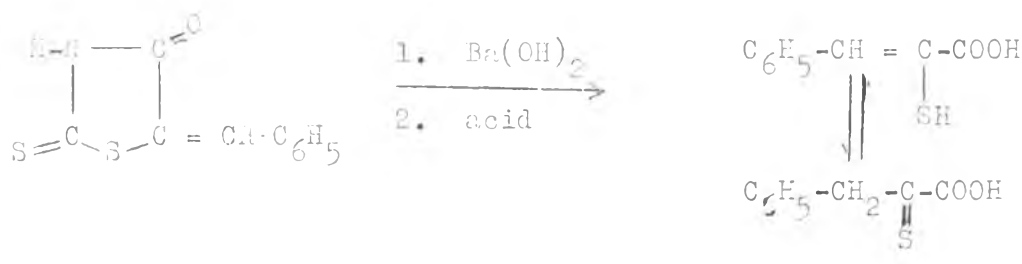
Alkaline hydrolysis of 5-arylidene rhodanine, the condensation product of rhodanine and aldehyde, give the corresponding β-substituted-α-mercaptoacrylic acid which can exist in two tautomeric forms(76,98)



Chemical reactions have been used to prove the existence of the two tautomer forms (96). In addition, ultraviolet spectra show that the ene-thiol structure is the predominant form (99).

Rhodanine and its derivatives have been used for various purposes. In quantitative analysis they have been used as analytical reagents(100,101) on account of their ability to form complex with heavy metals such as silver, gold, copper, mercury and palladium.

The reaction with heavy metals has been found to result in the formation of a complex rather than a simple salt formation (102). In addition, rhodanine derivatives with alkyl or aryl groups attached to the nitrogen do not bind silver ions as does rhodanine itself (103), and it is thought that the imido hydrogen is the one which causes this reaction. However, studies on the complexation of rhodanine and various metals, with the assistance

of IR and NMR, indicated that the coordination takes place via the thiocarbonyl group of the ligand, and the IR spectrum of Cu (3-allylrhodanine) Cl complex suggests that the copper was bonded through the thiocarbonyl group and the olefinic double bond of the ligand (41, 104)

A spectrophotometric procedure using 5-(p-dimethylamino-benzylidene) rhodanine is available for the quantitative determination of silver in a 25-ml. sample containing $2x10^{-8}$ to $2x10^{-7}$ moles of silver (105). Ascorbic acid can also be determined with such derivatives in the presence of copper sulfate and sodium pyrophosphate (106).

As regards the biological activity, certain 3-aroyl aminorhodanines are effective in inhibiting the in vitro growth of Microbacterium tuberculosis at a concentration of 0.5 mg/ml. (107) ; and 3,5-dimethyl-and 3-ethyl-5-methylrhodanine have been found to be bacteriostatic (108).

Rhodanine itself shows antifungal activity against Alternaria tenuis and Botrytis alli (46). 5-substituted rhodanines, especially 5-(p-chlorobenzylidene) rhodanine and 5-(2-thienylmethylene) rhodanine, have been proved to be fungistatic and mildew preventing agents (46, 109-111). 5-(p-dimethylamino-benzylidene) rhodanine inhibits the growth of the fungus Neurospora silaphila (112). Rhodanine and those of its derivatives with hydrogen attached to nitrogen have been patented as a

fungicide (113). Derivatives with a hydrocarbon residue attached to a nitrogen atom have been patented because of their value as insecticides and fungicides(114).

Certain 3-phenyl rhodanines and their derivatives have been shown to have a weak but demonstrable antimalarial activity against Plasmodium berghei (45). In addition, such derivatives including 3-(p-chlorophenyl)-5-methyl rhodanine and 3-(p-chlorophenyl)-5-ethylrhodanine have been found to be effective insecticides and nematocides(115). The sodium salt of 3-phenyl-5-(o-sulfobenzylidene)rhodanine has been found to be an effective nothicide(116), and 3-methyl-5-[(p-nitrophenyl) azo] rhodanine has been used as an anthelmintic agent (49).

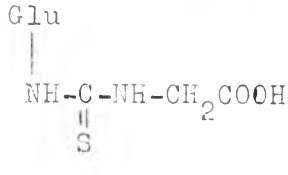
In pharmacological testing, 3-(p-Arylethyl rhodanines have been synthesized with the expectation that the similarity of its structure to adrenaline might produce useful compounds. However, the compounds were too insoluble to be of practical use (117). 5,5-Diethyl rhodanine exhibited a narcotic action slightly greater than that of 5-5 diethylbarbituric acid (118), but its therapeutic value is also restricted by its solubility. 3-(α-methyl-β-phenyl)-ethylrhodanine has been found to exhibit psychostimulating action (119).

5-(2-Thienylmethylene) rhodanine and 5-(2-pyrrolylmethylene) rhodanine have been found to increase blood glucose in the Charles River rat (54).

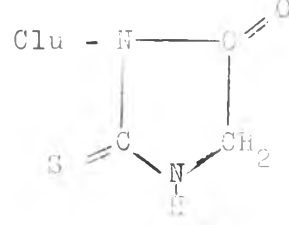
As far as the antiviral effect is concerned, some derivatives of rhodanine have been tested. Piperonylidene rhodanine has shown activity against Columbia SK Virus in mice (120). Rhodanine has been found to inhibit the multiplication of ECHO 12 virus (38). According to Egger's report, there is 95 % inhibition of the virus growth in monkey kidney cells at 17 μg/ml. Furthermore the cellular RNA synthesis and morphological appearance are also unaffected at 150 μg/ml. However, all 5-substituted rhodanines have been found to be inactive, or only slightly active, and are generally more toxic than the parent compound. In addition, N-β-D glucopyranosyl-5-(p-nitrobenzylidene) rhodanine have been shown to have definite antiviral activity against vesicular stomatitis virus growth by inhibition of the viral RNA synthesis (54).

In general, the rationale for the design and synthesis of a drug is patterned on the chemical structure of a metabolite which participates in the target-cellular activity. As antiviral agents, nucleoside analogues hold a prominent position. Moreover while viruses make extensive use of the biosynthetic machinery of the host cell, they retain some specificity with respect to the formation of their nucleic acid. For this reason, attention has been given to the use of glycosides and nucleosides as antiviral agents. Nitrogenous glucoside was first made in 1930, when Hilbert and Johnson (121) successfully synthesized 3-glucosidouracil by the interaction of 2,6-dimethoxypyrimidine and acetobromo-

-glucose, and produced the acetyl derivative. After hydrolysis using an ethanolic hydrochloric acid solution the desired nucleoside was obtained. Hilbert (122) failed to prepare Glucosidocytosine by applying a similar reaction to the preparation of Glucosidouracil. Fischer (123) also failed in his attempt to prepare glucosides of both uracil and cytosine in his experiments to test the reactions of tetraacetylbromoglucose on the silver salt of these two pyrimidines. Recognizing the limitations of such methods, acetobromoglucose was used for making nitrogenous glucoside, sugar isocyanates and corresponding ureas being used as starting materials. Fischer used tetraacetylglucose isocyanate and the corresponding isothiocyanate in making tetraacetylglucoside (123). Haring and Johnson (124), using Fischer's sugar isocyanate procedure, prepared four new glucoside ureides, d-glucosidothichydantoic acid (XVIII), N-1-d-glucosido-2-thichydantoin (XIX), d-glucosidohydantoic acid (XX), and N-1-d-glucosidohydantoin (XXI),



(XVIII)



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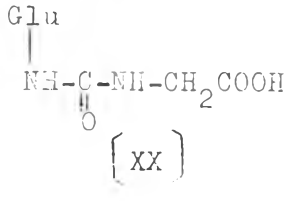

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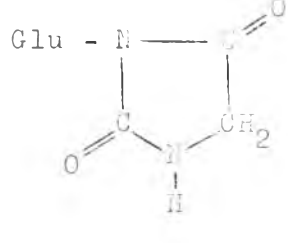

(XXI)

Nevertheless, the glucosides of pyridazones and thiopyridazones have been successfully synthesized via the reaction of acetobromoglucose and certain aglycones, resulting is Tetra-O-acetyl-β-D-Glucopyranosyl derivatives, which were deacetylated by sodium methoxide (125). Glucoside of 4-ethoxypyridine (126) and phenol (127) have also been reported.

Only a few glycosides of rhodanine derivatives have been reported in the literature for 1966. Bognar and Wieniawski (53), synthesized N-Tetra-O-acetylglucosyl derivatives of 5-isopropylidene, 5-benzylidene and 5-anisylidene rhodanines. They established chemically that the sugar moiety is attached to the nitrogen atom. However, they were unable to remove the acetyl groups without decomposing the rhodanine nucleus. Foye and Tovivich (54) have recently reported the synthesis of a series of Tetra-O-acetyl glucopyranosyl-5-aralkylidene rhodanine and the deacetylation was successfully carried out by acidic hydrolysis with hydrochloric acid in methanol to obtain N-β-D-glucopyranosyl-5-aralkylidene rhodanine.

The present study is based on the methods described by Foye and Tovivich (54) and reports an attempt to synthesize some new glucosylated rhodanines so that the biological activities of these compounds and the related intermediates can be tested in the future.