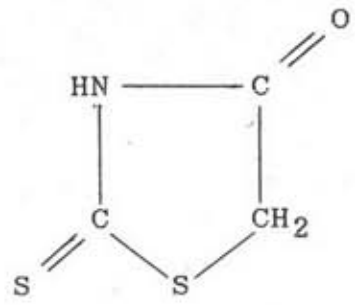
CHAPTER I

INTRODUCTION

The number of chemotherapeutic agents continues to increase annually. Many of new agents were obtained by modifying from known basic drug structures, thus improving some profiles as efficacy, pharmacokinetics, or reducing toxicity.

Rhodanine (2-Thio-4-thiazolidinone, I) and its derivatives were developed for years. They were reported to exhibit antibacterial (1-3), antituberculous (4-7), antimalarial (8), antifungal (1,9,10), insecticidal (9), pesticidal (11) and antiparasitic (12-14) activities. Eggers and his co-workers (15) found that rhodanine was a selective inhibitor of the multiplication of echovirus type 12 by inhibiting some step in the reproductive sequences of echovirus type 12 after virus adsorption. This activity was found to be selective only echovirus type 12 with non-toxic concentration for host cells. Moreover, rhodanine also inhibited the development of virus-induced morphologic changes through the inhibition of viral capsid protein synthesis (15).



I

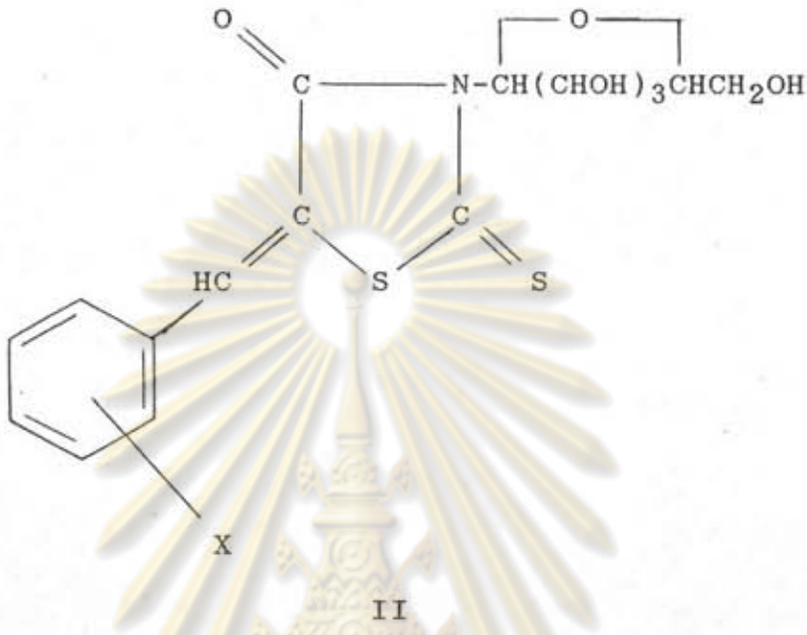
Haskell and his co-workers (16) reported that the hydrolysis products of rhodanine derivatives, ∝ - mercapto acrylic acids, and their disulfides acted as neuraminidase inhibitors of influenza virus and myxovirus. The neuraminidases or sialidases are enzymes of diverse biological origin which selectively cleave the terminal sialic acid moieties from sugar in oligosaccharide chains in glyco and mucoprotein. Therefore, a neuraminidase inhibitor prevents a myxovirus from being desorbed by the protective mucoproteins found in epithelial surfaces of the respiratory tract and can be envisioned as an enhancer of body's defence mechanisms.

The precised mechanism of antibacterial activity of rhodanine and its derivatives is unknown. Since Brockman and his co-workers (17) studied the correlation between structure of heterocyclic thiosemicarbazones, inhibition of ribonucleotide reductase and inhibition of

DNA virus. They found that the thiosemicarbazones which had the $-CH=N-NH-C(=S)NH_2$ moiety affixed to the heterocyclic ring system in the position alpha to the ring nitrogen were active inhibitors of reductase and of the DNA viruses. The inhibitor appeared to be interfering with an intracellular process essential for virus replication. Foye and his co-workers (3) proposed that rhodanine and its derivatives possibly acted as analogs of purine bases in nucleic acid synthesis, in addition the presence of a sugar moiety attached to the rhodanine ring might also provide rhodanines with less toxicity. The nucleoside derivatives with glucose (3), ribose (18) and simulated ribose moiety (19) at ring nitrogen were also reported.

Foye and Tovivich (3) synthesized a series of N-tetraacetyl-D-glucosyl derivatives of 5-arylmethylene rhodanines and screened for antiviral and other biological activities. It was reported that N-Gluco pyranosyl-5-(4-nitrobenzylidene)rhodanine(II) exhibited antiviral activity by inhibition of RNA synthesis. None of the rhodanines exhibited inhibitory activity against *Aspergillus niger* and *Candida albicans*. Only rhodanine and o-nitrobenzylidenerhodanine exhibited activity against *Escherichia coli*. Many of the 5-substituted rhodanine derivatives were active against *Staphylococcus aureus*, but

in general the tetraacetylglucosyl derivatives were not. Exceptions were found with the tetraacetyl derivatives

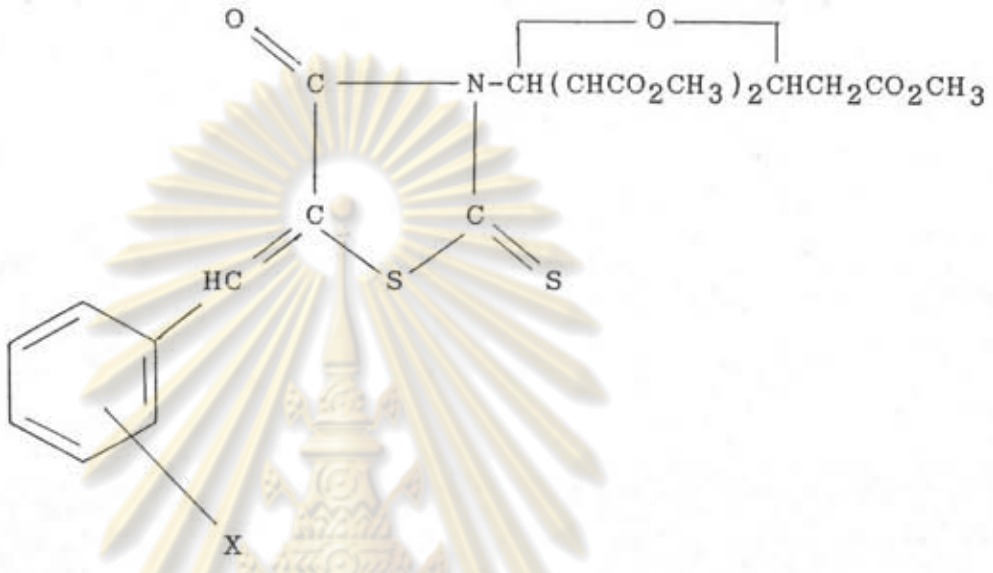


II

of 5-(5-bromothienylmethylene)rhodanine and 5-(1-naphthylidene)rhodanine. With the benzylidene derivatives, electron-withdrawing substituents increase activity, whereas electron-releasing substituents decrease activity. Methyl substitution at the methylene side chain either decreases or removes inhibitory activity (3).

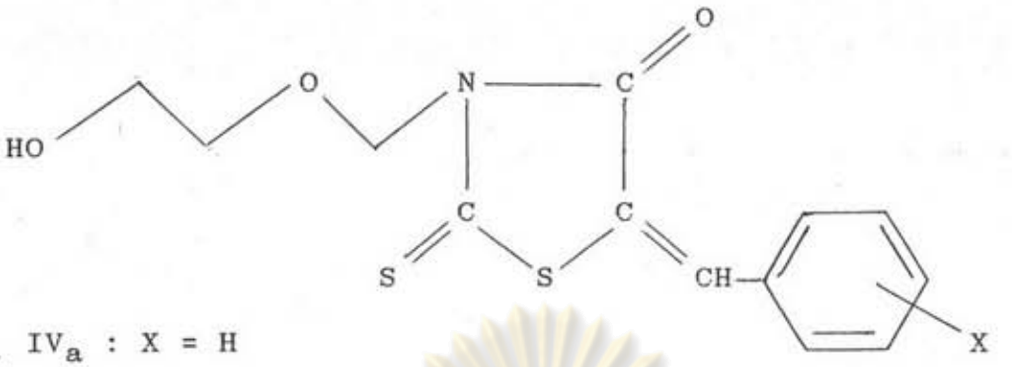
Foye and An (18) found that N-(2,3,5-Tri-O-acetyl-B-D-ribofuranosyl)rhodanine (III) was active against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* , *Candida albicans* and *Aspergillus niger*, however, possibly because of *in vivo* hydrolysis of the

acetyl groups. While the corresponding 5-benzylidene derivatives were active against *Staphylococcus aureus* and *Candida albicans* only.



III

Moreover, ribose analogs of rhodanine e.g. N-(2-Hydroxyethoxymethyl)-5-benzylidenerhodanine (IV_a), N-(2-Hydroxyethoxymethyl)-5-(2,6-dichlorobenzylidene)rhodanine (IV_b) and N-(2-Hydroxyethoxymethyl)-5-(4-nitrobezylidene rhodanine (IV_c) had antibacterial activities against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Candida albicans* (19).

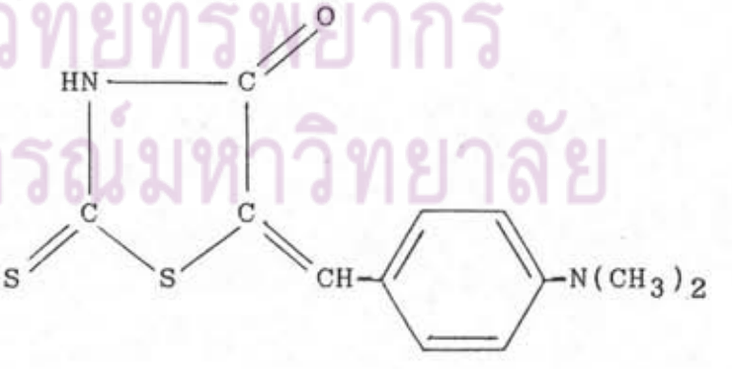


. IV_a : X = H

IV_b : X = 2,6-dichloro

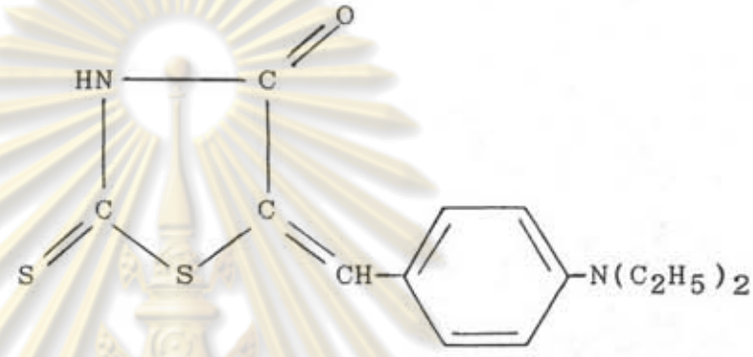
IV_c : X = 4-nitro

Nevertheless, there are several evidences indicate that the inhibitory mechanism of rhodanine and its derivatives might be metal complexation related. Rhodanine and its derivatives have the ability to complex heavy metal ions e.g. silver, mercury, gold, palladium, platinum and copper (20-23). p-Dimethylaminobenzylidene rhodanine (V) has been used as analytical reagent for detection of copper, gold, mercury, palladium, platinum and silver and also for determination of gold, mercury and silver (20).

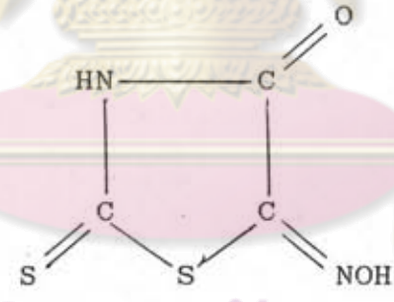


V

p-Diethylaminobenzylidenerhodanine (VI) has been used for determination of silver, Isonitrosorhodanine (VII) has been used for detection of mercury and silver, and Rhodanine (I) has been used for detection and determination of silver (20).



VI



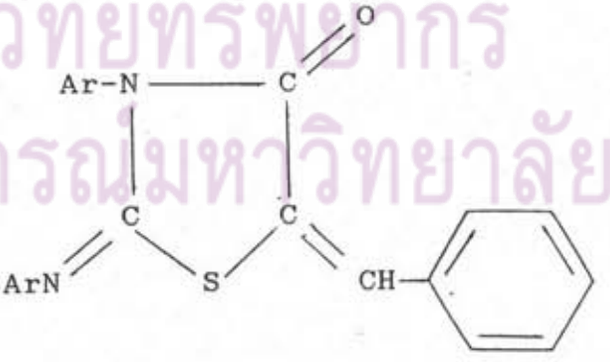
VII

It has been concluded that the coordination in the complexes takes place through the nitrogen and the thiocarbonyl groups of the ligand (20-23). This ability may enable rhodanine and its derivatives to complex with

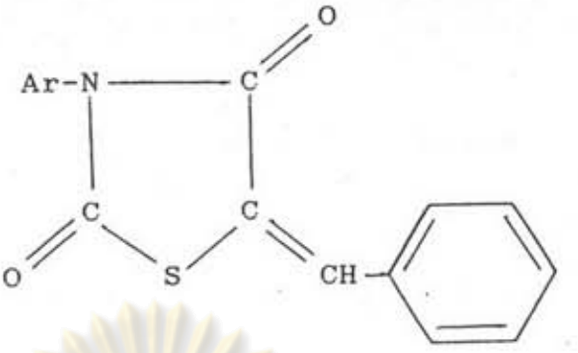
heavy metal ions which are required in bacterial metabolism (24). Hence, rhodanine and its derivatives exhibit the antibacterial activity.

Taniyama and his co-workers (4) found that the modification at 2-positon of rhodanine still provided antibacterial activity. The 2-hydrazino-4-thiazolidinones was found to have the better activity against *Mycobacterium tuberculosis* than 2-imino and 2-oxo derivatives. It could be assumed that nitrogen atom in imino group and hydrazino group might be involved in the complexation with heavy metal ions.

Mizzoni and Eisman (7) investigated the antituberculous activity among various cyclic modification of 1,3-bis-thiocarbanilide structures. They found that 3-aryl-2-arylimino-4-thiazolidinones (VIII) possessed antituberculous activity but 3-aryl-2,4-thiazolidinediones (IX) were inactive.

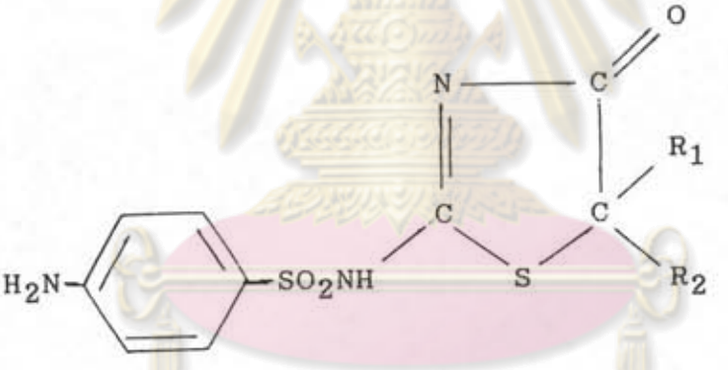


VIII

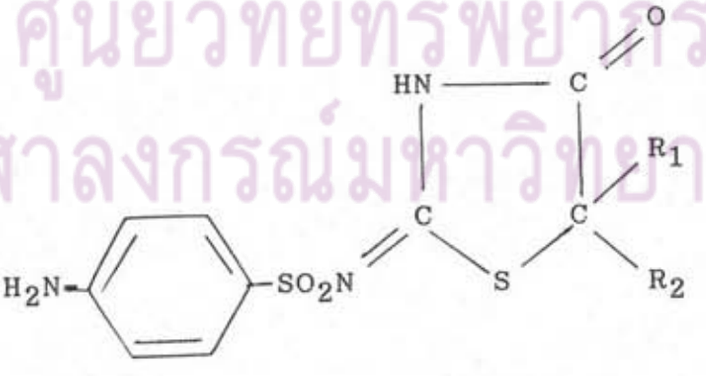


IX

In addition, Moore and Miller (25) found that acyl derivatives of 2-sulfanilamido-4-thiazolone (X_a or X_b) were active against *Streptococci* and *Pneumococci*.



X_a

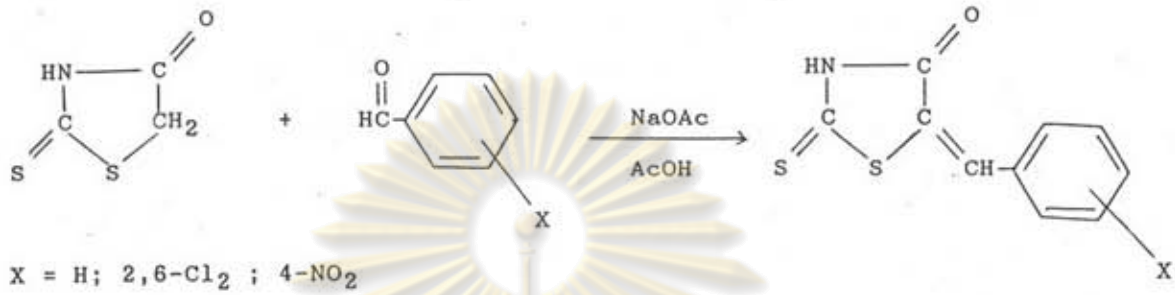


X_b

The present study reports an attempt to modify at 2-position of 5-arylmethylenerhodanines which were proven to be an antiviral agents by Foye and his co-workers. It could be expected that imino substituents e.g. imino, hydrazino or oximino groups may enhance the ability of rhodanine nucleus to complex with heavy metal ions. Therefore, the better antibacterial activity should be obtained.

The scheme of synthesis can be drawn as follows :

1. Synthesis of 5-arylmethylenerhodanines.



2. Synthesis of 2-imino-5-arylmethylene-4-thiazolidinones.