CHAPTER I

Introduction

The present state of the art of antiviral chemotherapy is similar in many ways to that of antibacterial chemotherapy in the late 1930s. With only one or two drugs in current use and a great deal of research being done to find more effective agents. In fact, antiviral chemotherapy has now been in existence for more than a decade, yet one could say that whereas the problem of the treatment of bacterial infection has been virtually solved, the specific treatment of virus diseases is still embryonic.

A virus is so much simpler in its constitution than a bacterium that many of the points of attack on the latter are just not possible with the former. A virus lacks a muramic acid type cell wall and the enzymes associated with such a structure, and consists only of a single nucleic acid molecule either ribonucleic (RNA.) or deoxyribonucleic (DNA.), protected from external attack by a protein coat.

In order to cover all the possibilities of influenzing virus infections or their sequelae, the term "antiviral agent" has been comprehensively defined as,"a substance other than a virus, a virus containing, a vaccine or a specific antibody, which can produce either a protective or therapeutic effect to the clear, detectable advantage of the virus infected host.

Any material that can significantly enhance antibody formation, improve antibody activity, improve non-specific resistance, speed convalescence or depress symtoms would also be considered an antiviral agent, despite the fact that such an agent has no direc action on the invasion, synthesis or migration of the virus." (1) Most workers in the field would restrict themselves to the first sentence of this definition, but they would not deny that the drugs which would enhance any of the five factors in the second sentence may be very useful in the therapy of virus diseases.

There have been several general reviews of antiviral chemotherapy(1 - 22). More specialized reviews have also appeared on controlling viral infections by means of vaccines (23) and interferon (24 - 30); the mechanism of viral multiplication and mode of action of antiviral agents (31); the pharmacology of viruses especially on sites of inhibition by antiviral agents (32), the prevention and treatment of influenza (33), and the evaluation of antiviral drugs in volunteers(34). Antiviral substances of both microbial and synthetic origin have been reviewed by Thompson (5) and Swallow (35). Two conferences were helded by the New York Academy of Sciences in December,1964 (36) and June, 1969 (37).

Rhodanine (2-Thio-4-Thiazolidinone) has shown some antiviral properties. Eggers and his co-workers have found that rhodanine inhibit the multiplication of ECHO 12 virus, one of

the enteric RNA viruses, which has been found to prevent viral protein coat synthesis (38). Also, in various other viruses, hydrolysis products of rhodanine derivatives, α-mercaptoacrylic acids and their disulfides, act as inhibitors of neuraminidases (39) enzymes which are involved with the entry and release of virus particles in the host cells (40). Rhodanine and its derivatives also have the ability to form a complex with iron and other metals (41). This enables the rhodanine to inhibit the ribonucleoside diphosphate reductase enzyme system, which requires iron as a cofactor, and thereby inhibit the synthesis of DNA(42). Such inhibition apparently serves as the basis of antiviral activities.

In addition, Rhodanine and its derivatives have also exhibited antibacterial (43), antitubercular (44), antimalarial (45), antifungal (46), insecticidal and pesticidal (47), and antiparasitic activities (48). Nitrodan, 3-methyl-5-p-nitrophenylazorhodanine has been used as an anthelmintic agent (49).

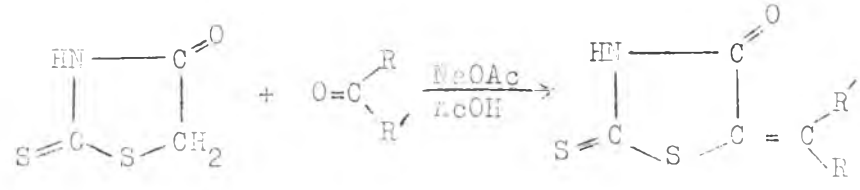
Thousands of compounds, including non-glycosylated rhodanine derivatives, have been evaluated for antiviral activity (50), and it has been found that all substances which are active against viruses in cell culture are toxic to the cell, if the concentration is sufficiently high. However, Foye and his coworkers (51,52) have shown that the glucose moiety decreases the toxicity of some antitubercular agents. Since the basic antiviral action

of rhodanine may act as an analogue of a purine base in nucleic synthesis, and thus glucosylated derivative may be more effective inhibitors.

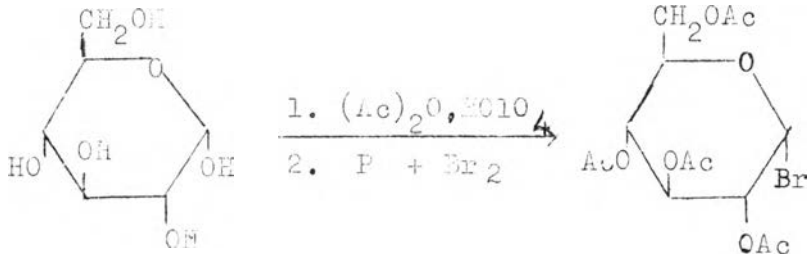
The first few glycosylated rhodanines were made by Bognar and Wieniawski (53), who prepared the N-tetraacetyl-glucosyl derivatives of the 5-isopropylidene, 5-benzylidene and 5-anisylidene rhodanines. Although they were unable to remove the acetyl group without decomposition, they were able to show that the sugar moiety was attached to the nitrogen atom of the rhodanine. Nevertheless, Foye and Tovivich (54) have made a series of N-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5-aralkylidene rhodanines and the acetyl groups were removed to give N-β-D-glucopyranosyl-5-aralkylidene rhodanines, without cleavage of the rhodanine ring, by means of acid hydrolysis. Alkaline hydrolysis with ammonia in methanol resulted in cleavage to N-glucosylthiourea, providing further evidence for N-glycoside formation. They also reported that N-β-D-glucopyranosyl-5-(4-nitrobenzylidene) rhodanine showed antiviral activity by inhibiting viral RNA synthesis.

The present work reports an attempt to synthesize some N-β-D-glucopyranosyl-5-arylmethylene rhodanines as potential antiviral agents. The scheme of synthesis can be drawn as follows:

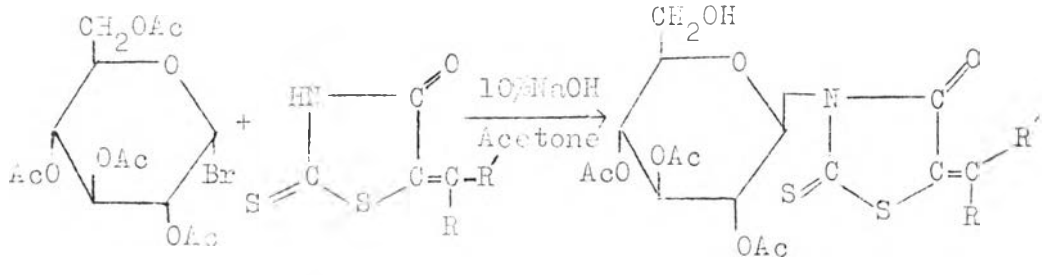
1. Preparation of 5-arylmethylene rhodanine



2. Preparation of Acetobromoglucose



3. Prepartion of N-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5-arylmethylene rhodanine



4. Preparation of N-β-D-glucopyranosyl-5-arylmethylene rhodanine