DERIVATIVES OF THIAZOLIDINE-4-CARBOXYLIC ACID

To my parents,

Diniz and Lucinda

STRUCTURAL STUDIES OF DERIVATIVES OF THIAZOLIDINE-4-CARBOXYLIC ACID

by

MARIA DE LURDES MARTINS

A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfilment of the Requirements

for the Degree

Master of Science

McMaster University

September 1986

MASTER OF SCIENCE (1986) McMASTER UNIVERSITY
(Chemistry) Hamilton, Ontario

TITLE: Structural Studies of Derivatives of Thiazolidine-4-carboxylic Acid

AUTHOR: Maria de Lurdes Martins, B.Sc. (University of Toronto)

SUPERVISOR: Professor C.J.L. Lock

NUMBER OF PAGES: ix, 167

ABSTRACT

A series of derivatives of thiazolidine-4-carboxylic acid was prepared from two sulfur containing aminoacids, cysteine and D-penicillamine. Cysteine is very easily oxidized to a disulfide, while penicillamine is less susceptible to oxidation of the sulfhydryl group because of greater steric hindrance. Sulfhydryl aminoacids react readily with aldehydes and ketones to give thiazolidine rings with varying degrees of substitution.

Many of the compounds prepared were studied in solution and in the solid state by means of nmr, vibrational spectroscopy, mass spectra and X-ray crystallographic data. Thiazolidine-4-carboxylic acids contain a free carboxyl group and a secondary amino group, both of which can be ionized. Infrared spectra and X-ray crystallography are useful in detecting ionization and hydrogen bonds. An example is given of a compound that can exist in both the zwitterion and the non ionized state depending on the solvent of recrystallization.

From previous work in our group we were predicting that increasing steric crowding in the thiazolidine ring in close proximity to the ionizable groups would decrease the tendency of these molecules to ionize. No such simple relationship could be found.

ACKNOWLEDGEMENTS

I am very grateful to Drs. Colin Lock and Helen Howard-Lock for their continuing encouragement, help and support throughout the duration of this work.

Many thanks to Dr. Russell Bell for his expert and friendly advice on synthetic chemistry and nmr analysis.

I would also like to extend my gratitude to Mary Turner, Mary Duarte and all the members of the group in SS206 for the interesting discussions of all aspects of student life, and especially to Brenda Brown for all her help in the last year, informing me of deadlines and handing in thesis revisions A through Z for me.

My thanks go to Romolo Faggiani for his help in this thesis, not only with the X-ray work but equally so for the interesting ideas about human psychology and life in general.

I must thank McMaster University and the Department of Chemistry for financial support of this research.

Finally I am thankful to Dave who kept telling me that a graduate student's thesis is always between being just started or almost finished but it is never really finished until graduation day. Thanks for the well meaning criticism.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

I. INTRODUCTION

I.1. The Importance of Imaging in Medicine

Imaging has been a very important diagnostic tool in medicine since the discovery of X-rays in 1895 because it allows detection of abnormalities from the outside of the body without surgery. There are two main types of diagnostic imaging: X-rays and gamma-rays. The most serious objection to routine use of X-rays arises because patients are exposed to high levels of ionizing radiation.

Nuclear medicine has played an increasingly important role in the last few decades, both in cancer treatment by irradiating rapidly growing tissues and in diagnosis through imaging. Nuclear medicine techniques require the administration of a radiopharmaceutical that often distributes itself non-selectively throughout the body and eventually ends up in the excretory system.

The problems associated with these diagnostic techniques are (i) the image obtained has low resolution and (ii) high doses of the radiopharmaceutical are required and consequently a considerable radiation dose is given to the patient, although this is greatly reduced compared to X-rays. In order to reduce the doses administered and increase the spatial resolution of radioimaging, a higher

concentration of the imaging agent is needed only in the organ of interest. Our intention at the beginning of this project was to develop the synthesis of a potential heart-specific technetium-99m imaging agent.

I.2. Brief Survey of Imaging Techniques

X-RAYS: This is the oldest imaging technique, it is very useful for bone examination. A body section is exposed to X-rays; the camera detects radiation which is not absorbed by bone or other dense tissues. A problem with the technique is that the difference in absorption by different body components is not great, that is, there are problems with contrast. This can be improved by the use of contrast agents. For instance X-rays of the gastro-intestinal tract involve taking a large dose of $BaSO_4$ (1). X-ray pictures are of low resolution: only changes of shape and size are detected. A most serious problem is the exposure of the patient to relatively high doses of ionizing radiation. This can be very detrimental, especially in pregnancy where it can cause physical or mental birth abnormalities.

CAT: X-ray Computed Axial Tomography: The X-ray data recorded from many different directions are reconstructed mathematically to yield cross-sectional views of selected areas of the body. The X-ray dose can be lowered because of extensive computer handling and in addition the resolution is increased. The disadvantages, though decreased, are

similar to the conventional X-rays. Pathological lesions are not detected because the X-ray absorption is similar to that of surrounding tissue, unless the lesions are large enough to change the size or shape of the organ (2).

ULTRA-SOUND: This technique is widely used in pregnancy to observe the fetus. It has been useful in detecting the early stages of cancer because of density variations between normal and diseased tissue (2). A beam of very low energy ultrasonic waves is directed at the tissue; sound waves move at different speeds through different materials. The scattered waves are integrated by computer to create an image on a screen.

NMR IMAGING: This is a non-invasive technique in which the water distribution in the body is monitored. Nuclear magnetic imaging neither requires the injection of radioactive nuclides nor does it induce radioactivity into the patient's tissues. When the patient is placed in an intense magnetic field a small fraction of the hydrogen nuclei in the body is partially aligned with the field. A pulse of the appropriate radiofrequency for protons is applied, and is of very low energy compared to X-rays or even visible light. Thus nmr has been claimed to be powerless to disrupt molecules in living tissue (3). The radiofrequency exposure hazard may be related to direct tissue heating, and the high magnetic field, both static and time varying, may be harmful in yet undetected ways because

of induced voltages and currents (4,5). Field uniformity, necessary for spatial resolution, is achieved with superconducting magnets, which are very expensive. Nmr imaging shows increased differentiation between healthy and diseased tissue, compared to X-rays. Paramagnetic ions, such as Mn^{2+} and Fe^{2+}, cause a shortening of the proton relaxation time, T_1. Thus changes of T_1 rates can be used to show relative permeability or tissue perfusion. Paramagnetic "contrast agents" can be used in this manner to improve the contrast in selected organs.

Nuclear medicine imaging techniques show poor resolution compared to radiographic imaging, but their strength is in that they permit evaluation of regional physiology and metabolism (6). Radioimaging techniques depend on injecting into the body a radiopharmaceutical, the distribution of which can be determined through detection of emitted radiation. The radioactivity is detected by a gamma camera, which by a series of computer calculations produces an image on a screen.

PET: Positron Emition Tomography: A radioimaging agent with a positron-emitting radionuclide such as carbon-11, nitrogen-13 or oxygen-15 must be used. The positron interacts with the tissue by displacing an electron from the outer shell of an atom. As the electron and positron annihilate each other, a pair of gamma-rays is released each going in opposite directions. Coincidence recording and

detecting computers can locate the site of radionuclide activity more accurately than with single photons. The technique is useful in detecting tumours and degenerative diseases, and it can reveal anatomic and functional information (1). The main disadvantage is that a particle accelerator (cyclotron) is needed on site to produce the short-lived radioisotopes along with a sophisticated detection system, and the cost is too high for most hospitals.

SPECT: Single Photon Emitting Cross-Section Tomography: In this technique the three-dimensional distribution of a radioactive tracer in the body is reconstructed. Readily available radionuclides such as technetium-99m are used with a rotating gamma camera or a multidetector system. The principles of scanners and scintillation cameras and the technique of reconstruction tomography are explained elsewhere (7). All common radioisotopes, including Tc-99m, emit gamma-rays one at a time--single photon emitters.

Computed tomography in general is a good diagnostic tool for tumour detection (8, 9), its principal disadvantages being inadequate sensitivity, high dose of the radiopharmaceutical required and consequent high radiation exposure.

I.3. Radioimaging Agents

A radionuclide for use in radioimaging should ideally have the following characteristics: it should (a) be easily

produced, (b) have a high yield of gamma-rays of about 150 keV of energy, ideal for detection by a gamma camera but sufficiently low to avoid causing excessive tissue irradiation, (c) have a high organ specificity to allow small administered dose with high photon flux for imaging, (d) have no physiological or toxic effects in the doses required for imaging, (e) have a short physical and biological half-life. Among the radioisotopes used in radioimaging, metals are preferred because of the relative ease of coordination once the ligand is available. There is a possible problem: at great dilution in the blood the chelated metal may or may not remain chelated under physiological conditions, because of competition with metal binding proteins (10).

Technetium-99m labeled radiopharmaceuticals will be discussed here because this isotope is the best suited for imaging and it is currently used in over 80% of all nuclear medicine scans taken in the U.S.A.. Technetium-99m is conveniently available from a generator via the Molybdenum-99/Technetium-99m decay scheme as follows:

$$\text{Mo-99} \xrightarrow{\beta,\,66\ \text{hr}} \text{Tc-99m} \xrightarrow{\gamma,\,6\ \text{hr}} \text{Tc-99} \xrightarrow{\beta,\,2.13\cdot10^{5}\ \text{yr}} \text{Ru-99}$$

The disintegration characteristics of Tc-99m are excellent: short half-life of six hours, low gamma-ray emission energy of 140 keV which minimizes radiation exposure but is in the right energy range for gamma camera detection. Another

essential property of technetium is the formation of stable complexes with a variety of ligands containing donor atoms such as O, N, S, P, As (11). The literature dealing with Tc-99m radiopharmaceuticals is very extensive, although it is relatively new, considering that radioimaging is itself a recent development. The chemistry of technetium has been reviewed recently by Deutsch, Davison and coworkers (11-15), who are currently among the most active researchers in the field.

I.3.1. Large Molecule Radiopharmaceuticals

Proteins and peptides labeled with a radionuclide have been used in radioimaging for cancer diagnosis (16). These biologically active molecules are in some cases chemically modified by attaching a chelating functionality such as EDTA (17), which can coordinate the radioactive metal. It is expected that the extra functionality and the metal will not alter biospecificity so that the original molecule and the labeled derivative should have the same biodistribution. Poor results have been obtained due to lack of specificity and poor cell permeability except in tissues that require such proteins or peptides in their metabolism. If the metal ion is bound to the protein active site, the protein becomes inactivated, and its only purpose is to be a carrier for the radioactive metal.

I.3.2. Small Molecule Radiopharmaceuticals

Small molecule radiopharmaceuticals are of three types: (i) compounds which are foreign to the body and cannot be metabolized, (ii) compounds which the body recognizes as metabolic precursors or intermediates, and (iii) compounds which can not be used in metabolism but possess structural features similar to a compound the tissue absorbs specifically. All these complexes are referred to as "Tc-essential radiopharmaceuticals" (12, 17) because the metal ion determines the overall charge and stereochemistry of the complex, and as a consequence the biodistribution of the complex is dependent on the metal.

Bifunctional ligands have been used to prepare Tc-99m complexes, and these were expected to accumulate in the same target tissues as the ligands. It has often been found (15) that small Tc-labeled molecules with expected biodistribution no longer have any specificity because the complex was rapidly removed from circulation by the kidney--if the ligand is hydrophilic--or by the liver, in the case of lipophilic ligands.

Some complexes dissociate at blood pH and therefore are not stable long enough to permeate cell membranes. The radioactive ion is released into the bloodstream and is quickly eliminated through the excretory system. For example $^{99m}TcO_4^-$ has been tested as a potential brain imaging agent (18). It is characterized by high diffusion

rates in and out of brain cells and the retention time within cells is too short for imaging. Pertechnetate shows lack of specificity and yields low resolution images.

In summary, most of the presently available radioimaging agents show poor organ specificity, low stability, or insufficient intracellular retention. Relatively high doses of the radioimaging compound are required causing some degree of radiation exposure. The radiation hazards in living tissue are mutations in DNA, which can result in faulty proteins that may be the cause of serious metabolic problems, and the formation of free radicals that can catalyze a chain of detrimental reactions. In order to reduce the dose administered and increase the resolution in the organ of interest, a higher concentration of the imaging agent is needed only in the organ to be imaged.

I.3.3. Need for New Organ Specific Radiopharmaceuticals

It is easy to make radiolabeled complexes which when injected into an animal will most likely result in a more or less even body distribution, eventually ending up in the excretory organs (liver and kidney), so that the dose administered must be high. The challenge lies in producing labeled complexes which are specifically absorbed by certain organs: the initial distribution takes place via the circulation, but the radiolabeled compound is rapidly cleared from other tissues. It is a well known fact that metabolic substrates such as aminoacids are necessary in the

pancreas for protein synthesis and in the heart because of rapid metabolism.

Much effort has been put into developing organ specific radiopharmaceuticals (19-21), with adequate intracellular retention time. A bifunctional ligand is needed with a chelating end and an antibody or cellular recognition site at the other end, for cell binding or for active transport recognition by the tissue of interest. Only the organ of interest would receive any significant radiation exposure. A lower dose of the imaging agent would be required, resulting in a decrease of background radiation from the surrounding tissues and an increase in the sensitivity of the method.

A number of Tc-99m complexes have been studied which fall in the "Tc-99m-essential" type of radiopharmaceuticals; these are divided into five groups as follows:

--Group I: Following distribution in the extracellular fluid, these complexes are rapidly removed from the circulation by the kidneys. For example, Tc-99m-penicillamine complexes, some of undetermined structure, have been found useful in kidney imaging (22-24). Other aminothiol ligands prepared by Davison and coworkers (25-27) promise to be useful in evaluating kidney function.

--Group II: Complexes of this type are used in obtaining structural information about the kidneys. These complexes exhibit longer retention of activity in the

kidneys, perhaps caused by ligand exchange and formation of more stable complexes in the glomerular tubules.

--Group III: Myocardial perfusion agents for normal heart tissue are generally lipophilic monocations; they are thought to be specifically extracted from the blood by the Na/K ATPase transport system.

--Group IV: Tc-99m phosphates have been found to have bone specificity. The ligating atoms are usually oxygens (Deutsch et al.) (13).

--Group V: Hepatobiliary agents are removed from the blood by the liver and are excreted in the bile.

I.3.4. Myocardial Imaging Agents

Technetium-99m complexes such as diphosphines, isonitriles and arsine halogenides have been shown (17, 28) to accumulate in normal myocardium much more effectively than in other body tissues. Most potential radioimaging agents have in common the fact that they are lipophilic monocations. They may consist of an amphoteric organic moiety with a long chain fatty acid and a hydrophilic end--the cationic functional group. The high extraction rate from the blood and the prolonged retention in heart tissue suggest that a pumping system is involved in actively transporting into the cells these cations. The Na/K ATPase system may be involved but the lack of specificity indicates that another transport mechanism is operating.

Studies of nitrogen-containing ligands which were expected to have enhanced heart uptake but did not, show that parameters such as size and charge and stereochemistry of the complex are not sufficient to develop heart specific imaging agents (29). The most important feature of an organ specific radiopharmaceutical is its ability to bind to specific receptor sites.

For heart imaging one can try to synthesize a bifunctional ligand such that the radioisotope is attached to one end of the ligand, and the recognition site with high affinity for receptors is left at the opposite end of the molecule. Because of the high energy requirement of heart tissue there is an active transport mechanism operating in heart cell membranes that selectively carries fatty acids and other lipids into myocardial tissue. Therefore a labeled fatty acid derivative is expected to accumulate in healthy heart tissue, while infarction damaged tissue will only take any such molecules by free diffusion through cell membranes. It has been shown by labeled antibiotics, however, that damaged tissue results in increased membrane permeability and nonselective entry of extracellular molecules into the damaged cells (17).

I.4. Purpose of the Thesis

In view of the need for organ specific imaging agents, the purpose of this work was to develop a synthetic approach

for a Tc-99m labeled radiopharmaceutical for heart imaging, with a derivative of D-penicillamine as a ligand. This breakdown product of penicillin was chosen because its effects in the human body are well known, and it can form stable complexes with technetium. D-Penicillamine is prescribed in the treatment of some serious diseases like cystinuria (30), Wilson's disease (31), rheumatoid arthritis (32), and heavy metal poisoning. The chemistry of D-penicillamine has been reviewed by Weigert et al. (33).

D-Penicillamine is a good metal chelating species, with three possible chelating sites (thiol, amino and carboxyl groups). It is a better chelator than cysteine, which in the presence of traces of oxygen forms cystine, which does not chelate Tc-99m very effectively. Complexes of D-penicillamine with Tc-99m have been prepared (24, 34) and characterized by vibrational spectroscopy and X-ray diffraction. Of the two D-penicillamine molecules bound to a technetium atom, one is tridentate and the other is bidentate with the thiol and amine as the chelating groups.

The goal in this project was to synthesize a heart specific radioimaging agent containing a fatty acid moiety covalently bound to D-penicillamine through an ether linkage. Heart cell membranes are thought to have an active transport system for fatty acids and other complex lipids such as digitoxin (35). It is also possible and desirable that, since D-penicillamine is a non-metabolic aminoacid,

its derivatives may not be readily attacked by intracellular enzymes, and the complex with technetium should be stable long enough in the tissue for data collection by the radioimaging system.

I.4.1. Revised Scope of Thesis

The particular synthetic approach taken did not succeed in yielding a radiopharmaceutical, either starting with D-penicillamine to make thiazolidine ring compounds, or through protection of the reactive groups of the starting aminoacid, because of the high steric hinderance and consequent low reactivity of the functional groups of D-penicillamine towards reducing agents and sterically hindered protecting groups. There was a very large amount of preparative and characterization work carried out on the thiazolidines and their derivatives having various degrees of substitution. It was therefore decided to limit the scope of this thesis to the synthesis, spectroscopy and characterization, and a detailed discussion of the physical and chemical properties including some X-ray crystal structures of thiazolidine compounds, which have potential usefulness in the preparation of Tc radiopharmaceuticals.

I.5. Thiazolidine Ring Compounds

I.5.1. Biological and Medicinal Aspects

The formation of thiazolidine compounds by condensation

with aldehydes and ketones occurs readily both with L-cysteine and with D-penicillamine. The study of these compounds is important in understanding the therapeutic action of penicillamine, since many such carbonyl compounds are present in the body. This type of condensation is postulated (33) to be the basis for the inhibitory action of vitamin B_6 by D-penicillamine through reaction with the aldehyde group of pyridoxal-5'—phosphate. Recent work in our group has shown, however, that there is no difference in the *in vitro* chemistry of the reaction of vitamin B_6 with D- or L-penicillamine. In the solid state only the (RR) and (SS) products are found, but in solution they epimerize to form the four possible diastereomers. The *in vivo* inhibitory reaction may be caused by a stereospecific enzyme.

Excess ethanol in the body is oxidized into acetaldehyde which is very toxic. D-Penicillamine may be useful to counteract ethanol intoxication, through the formation of 2,5,5-trimethylthiazolidine-4-carboxylic acid (36).

Insoluble precollagen, characteristic of rheumatoid arthritis, probably results from enzymic oxidation of the side chain amino groups of lysine to aldehyde groups followed by crosslinking via aldol condensations. D-Penicillamine reacts with the aldehyde groups of soluble collagen to form thiazolidines and thus inhibits

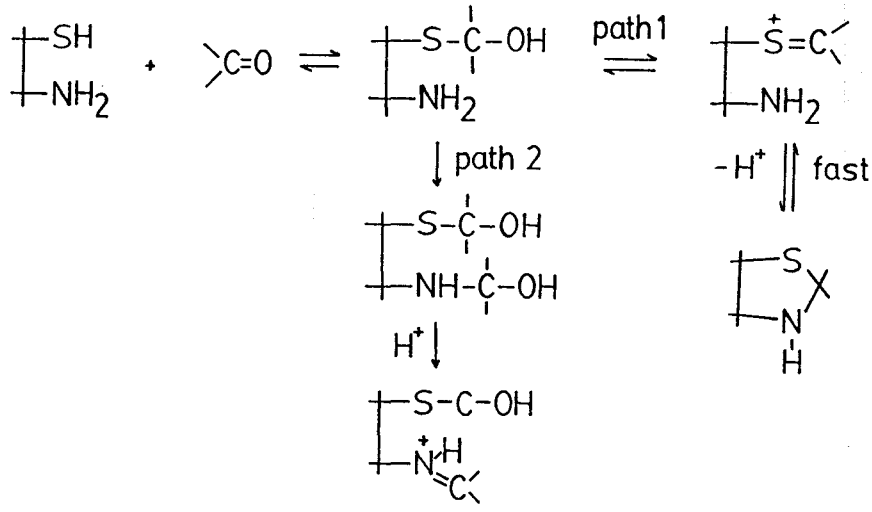
crosslinking in living systems.

I.5.2. Mechanism of Formation of the Thiazolidine Ring

Thiazolidines have been known since the 1930s. Ratner and Clarke published the first thorough study of the thiazolidine formed by the reaction of cysteine with formaldehyde in 1937 (37), including the preparation of derivatives, stability of the ring to acid and base, and possible mechanism of formation.

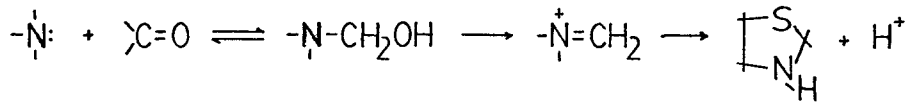
The formation of thiazolidines is useful for protection of aminothiols by carbonyl compounds in synthetic work. For example in 2,2-dimethylthiazolidine-4-carboxylic acid the isopropylidine group (derived from acetone) protects the thiol from oxidation and from interfering with other reactions. Since formation of the thiazolidine-4-carboxylic acid from cysteine and acetone involves an equilibrium, the isopropylidine group can be readily removed in the presence of water.

Thiazolidine ring formation has been suggested (38) to occur through a Schiff base intermediate resulting from the carbonyl and aminothiol precursors. A possible alternate mechanism (39a) involves nucleophilic attack by the sulfur atom on the carbon of the carbonyl group to form a sulfonium ion intermediate, followed by cyclization (Scheme 1, path 1):



Scheme 1

Careful mechanistic studies (39a,b) indicate that the hemithioacetal of cysteine is formed before the N-hydroxymethyl and the cationic Schiff base intermediate (Scheme 1, path 2), if cysteine exists as the free thiol and there is excess formaldehyde in the reaction medium. The rate determining steps in path 2, Scheme 1, are the formation of the carbinolamine, which occurs in acidic medium, and its dehydration, originating the cationic Schiff base in an alkaline medium, see the equation below:



The dependence of the rate on the pH provides evidence for a change in the rate determining step with pH, but does not show which step is rate determining in each pH range. The carbinolamine dehydration step is acid catalyzed but the

rate of amine attack is not, therefore this slow step can be rate determining. There is kinetic evidence for the Schiff base imine but it has not yet been identified in solution by uv experiments.

I.5.3. Thiazolidine Ring Stability

A study of the decomposition in solution of a series of thiazolidines derived from L-cysteine was published in 1963 (40). The conditions required for decomposition of several substituted thiazolidine-4-carboxylic acids were investigated by taking the nmr spectrum of solutions of the compounds in varying acid or base concentration (41).

C(2) substituted aliphatic thiazolidine-4-carboxylic acids and those with no substitution showed no change in the nmr spectrum with time in strongly acidic conditions (several days in up to 8M HCl). However with C(2) substituted aromatic thiazolidines in strong acid solution, all proton resonances of the ring began to disappear.

In strongly basic solution, C(2) substituted aliphatic thiazolidines readily decomposed into cysteine or penicillamine and the aldehyde, except 4-carboxy-thiazolidine. The results obtained indicate that both aliphatic and aromatic C(2) thiazolidines are unstable in strongly basic solution. It is interesting to note that in moderately basic solution (0.5 to 1.0M NaOH) interconversion between the ring and the open form takes place at a rate

observable on the nmr time scale.

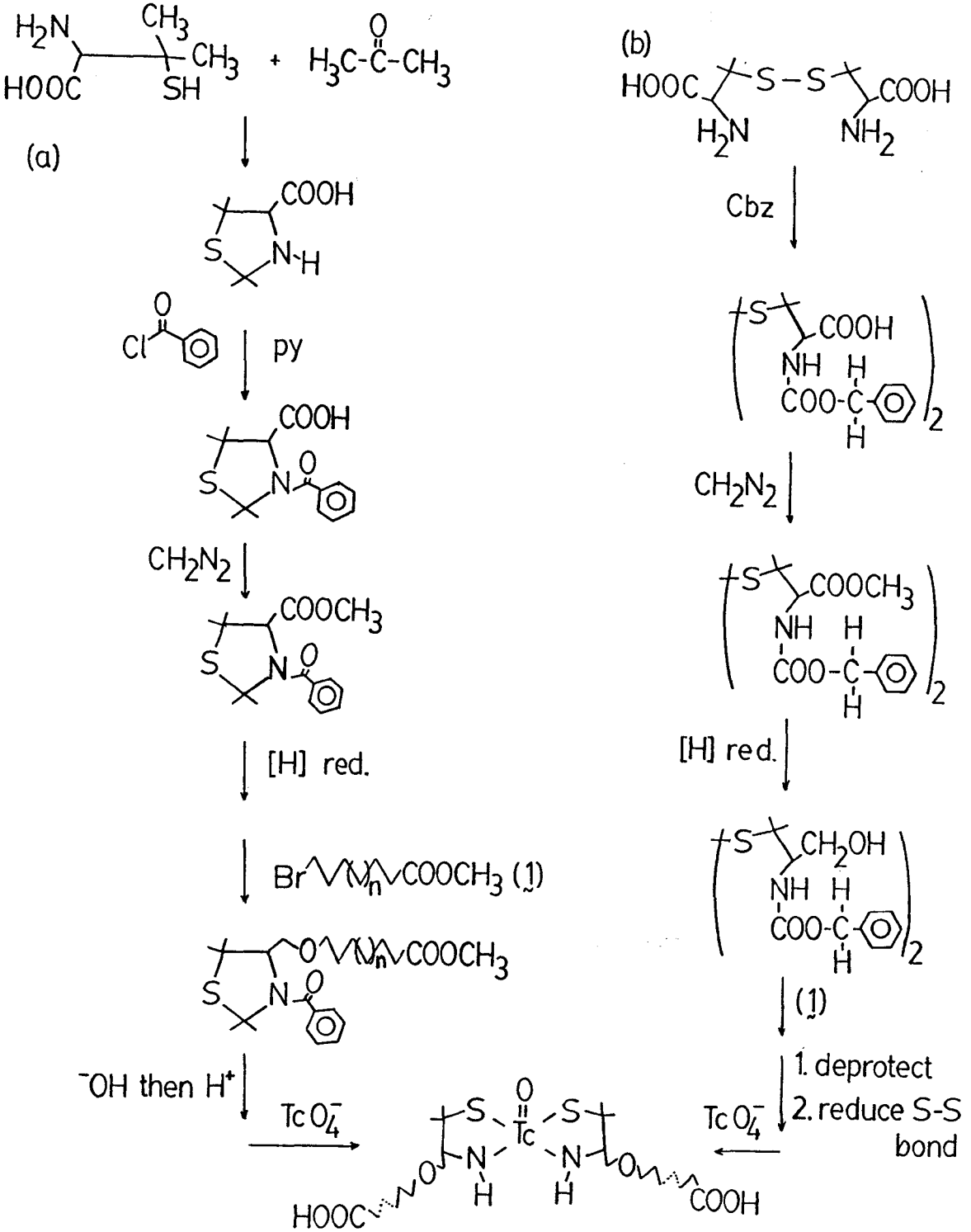
Stability studies in neutral aqueous solutions were as expected: aliphatic substituted thiazolidines yielded no change in the nmr spectrum after a few days; aromatic substituted thiazolidines are not soluble enough in water to obtain a spectrum.

I.6. Protecting Groups for D-Penicillamine

Figure 1(a) shows the reactions involved in the synthesis of the ligand wanted for heart radioimaging. Any organic chemist will recognize the necessity for protection of the reactive thiol and amino groups of D-penicillamine in order to obtain an ether functionality from the carboxylic acid. Formation of the thiazolidine ring is a one-step protection of both the SH and NH_2, although the secondary amine must be further protected. The heterocyclic ring can be opened with release of the original aminoacid coordinating sites in strong base.

The difficulties encountered in the reduction step shown in Fig. 1(a) led to a new approach to the problem. A survey of protecting groups used in blocking cysteine for peptide and protein synthesis was done, and reactions with D-penicillamine were attempted. A large volume of organic chemistry literature is dedicated to the use of protecting groups and some good reviews have been written on the subject (42, 43). Protecting groups are used because the

FIGURE 1
Synthetic pathways for the preparation of a technetium-penicillamine radiopharmaceutical



organic chemist often works with molecules containing several reactive groups, which are to be reacted in a certain sequence, or of which only one is to be reacted. The other reactive groups in the molecule must be deactivated temporarily.

Primary and even secondary amines are very nucleophilic. The bivalent sulfur atom of cysteine and D-penicillamine is also very nucleophilic and can easily be oxidized to disulfides. Some of the most useful amine (and thiol) protecting groups are briefly discussed in the following paragraphs.

Benzyl chloroformate (Cbz) is a convenient protecting agent because it can react with both the amine and thiol groups in one step (44, 45), and it is stable to acids and to mild basic conditions. It is easily removed by HBr in acetic acid or with HCl in ethanol or chloroform.

Carbo-t-butyloxy-amino derivatives of aminoacids have found innumerable applications in aminoacid chemistry (46, 47). The drawback is that even mild acid conditions must be avoided, since the "amide" linkage can easily be cleaved by aqueous acid. Acidic conditions are therefore used to remove this protecting group.

Another class of compounds that has been widely used in aminoacid chemistry are the benzyl, benzhydryl and triphenylmethyl (trityl) chlorides. These compounds react with free aminoacids or with their esters (48, 49). The

nucleophilic character of the benzyl or trityl protected amines is probably very much lower than in the free amine, but the steric effects of these bulky protecting groups also plays an important part. The ease of removal of these protecting groups is as follows: trityl>benzhydryl>benzyl. The first can easily be cleaved by acids in organic solvents, even in dilute acetic acid. S-Benzhydryl-cysteine is more stable than S-trityl-cysteine (49); S-benzyl can only be cleaved by catalytic hydrogenation, which causes fission of other bonds or desulfuration. The trityl group has been used to protect both thiol and amino functionalities in cysteine.

p-Toluene sulfonyl chloride is another amine protecting agent which can be removed by sodium in liquid ammonia (50).

Phthalic anhydride can be fused with alpha aminoacids at high temperature to protect the primary amino group; this sometimes causes racemization. A newer method with N-carboethoxyphthalimide (51) reacting under milder conditions, gives good yields and prevents racemization. The phthaloyl group can be removed by heating with hydrazine in ethanol.

Benzoyl chloride is useful because of its reactivity towards both thiols and amines, but the protecting group is rather difficult to remove (52).

S-Methylacetamide is particularly useful as a

protecting group for cysteine because it is stable to strong acids and to bases such as hydrazine, but it is readily removed by Hg(II) ions and by iodine (53).

I.6.1. Relative Reactivity of D-Penicillamine and L-Cysteine--Biological Significance

Steric hindrance can lower the reactivity of the mercapto group in D-penicillamine (31), where the SH group is attached to a tertiary carbon, while in cysteine the SH is on a more accessible primary carbon atom. The thiol of D-penicillamine is therefore much less reactive than the thiol of other biologically important molecules such as cysteine or glutathione. D-Penicillamine has the lowest reducing power of most biological aminothiols, and so it will be less readily deactivated by oxidation to the disulfide in the body than for example cysteine.

Some reactions have been observed to take place 16 times slower with penicillamine-cysteine disulfide than with cystine (54), and this is ascribed to steric hindrance by the two methyl groups of D-penicillamine.

The biological significance of these reactivities can be summarized very succintly: D-penicillamine has a number of desirable effects in disease treatment because it can, much more efficiently than cysteine, remain stable in the bloodstream long enough to form complexes with metal ions, exchange with disulfides and react with aldehyde groups in

proteins. On the other hand, because D-penicillamine participates in so many interactions, its action in the body is non-specific and can therefore affect a variety of enzymes.

These reactivity differences explain why the protecting group reactions and the reductions occur much more readily with cysteine and its derivatives than with penicillamine.

II. METHODS AND MATERIALS

The preparation of the substituted thiazolidine-4-carboxylic acids was carried out as indicated schematically in Table 1, page 27, and will be outlined in detail below. All the starting materials were reagent grade and were used as received, after checking the nmr spectrum. D-(-)-Penicillamine free base and L-(+)-cysteine hydrochloride monohydrate were supplied by Sigma Chemical Company, St. Louis, Missouri. Formaldehyde, 37% v/v, was supplied by Sargent-Welsh, and acetaldehyde was distilled from paraldehyde (BDH, Toronto, Ontario). Benzaldehyde was obtained from Eastern Chemical, Hauppauge, N. Y., acetone from BDH, Toronto, Ontario, 2-butanone from Aldrich Chemical Company, Milwaukee, Wisconsin and benzoyl chloride from Eastman Kodak Company, Rochester, N.Y..

Mid-range infrared spectra were obtained on a Perkin-Elmer model 283 spectrophotometer. Samples were ground with KBr at a concentration of approximately 1% by weight and then pressed into pellets. Spectra were calibrated with polystyrene. Far infrared spectra were recorded on a Nicolet 7199 FT-IR; samples were suspended in nujol and spread out on a polyethylene plate.

Raman spectra were obtained by exciting the solid

sample in a glass melting point tube with radiation of wavelength of 5145 Å from a Coherent 90 Series argon ion laser. Spectra were recorded on a Spex 14018 double monochromator at room temperature.

Proton nmr spectra were recorded on a Varian EM-390 spectrometer and natural abundance carbon-13 spectra were recorded on a Bruker WP-80 nmr spectrometer (Fourier Transform) at 20.115 MHz, with use of tetramethylsilane as the internal standard, unless otherwise specified. Samples were dissolved in deuterated water, deuterated chloroform, or deuterated dimethyl sulfoxide, depending on sample solubility.

Mass spectra, low resolution, were recorded on a VG Micromass 7070F mass spectrometer by Mr. F. A. Ramelan, with electron impact as the method of ionization.

Melting points were determined on a Gallenkamp capillary melting point apparatus and are not corrected.

Whenever diazomethane was required, the procedure of de Boer and Backer (55), employing "Diazald" (N-methyl-N-nitroso-p-toluenesulfonamide) was used.

Thin layer chromatography (TLC) was performed with silica gel G (E. Merck) as adsorbent in 4:1 benzene:ethyl acetate (v/v). The developed plates were air-dried then exposed to iodine and/or uv light. Column chromatography was performed on Brinkmann silica gel 60 (E. Merck). Solvents were evaporated under reduced pressure, below 50^{o}C.

The pK values of thiazolidines were obtained by titration of an aqueous solution of the thiazolidine against 0.01N NaOH and 0.01N HCl. The pH values were measured with a Corning Model 130 pH meter which was standardized with Scientific Products potassium hydrogen phthalate pH 4.00 buffer, BDH pH 7.00 buffer and Scientific Products boric acid/potassium hydroxide buffer, pH 10.00.

Crystals suitable for X-ray study were obtained by slow evaporation of recrystallizing solutions. Single crystals were selected under the microscope and sealed to glass fibers. Precession photographs were taken to determine the point groups. Crystal structures were determined by Romolo Faggiani of the Institute for Materials Research, with use of methods outlined previously (56-57).

TABLE 1
Synthesis of substituted thiazolidine-4-carboxylic acids

	L-CYSTEINE	D-PENICILLAMINE
Formaldehyde	thiazolidine	5,5-dimethyl-
Acetaldehyde	2-methyl-	2,5,5-trimethyl-
Benzaldehyde	2-phenyl-	5,5-dimethyl-2-phenyl-
Acetone	2,2-dimethyl-	2,2,5,5-tetramethyl-
2-Butanone	2-ethyl-2-methyl-	2-ethyl-2,5,5-trimethyl-

Thiazolidine-4-carboxylic acid (I)

A published procedure (37) was modified as follows: 0.5 g (0.0028 mole) L-cysteine hydrochloride monohydrate was dissolved in 2 mL water, to which 0.4 mL (0.0055 mole) of 40% formaldehyde (v/v) was added and the mixture was allowed to stand overnight. Following addition of 0.5 mL pyridine a white solid started separating slowly 30 min. later. 1 mL ethanol was added to the mixture which was cooled in the refrigerator for two days. Colourless prismatic crystals were separated by filtration and recrystallized from hot water to give 0.35 g (90%) of a white crystalline product, m.p. 185-187^{o}C (dec.), lit. 184-185^{o}C (dec.) (37).

2-Methylthiazolidine-4-carboxylic acid (II)

A published procedure (58) was followed: 2.9 g (0.0165 mole) L-cysteine was dissolved in 14 mL water and 1 mL glacial acetic acid, and 20 mL ethanol were added. Crystals formed slowly and were separated by filtration. The crystals were dissolved in a minimum volume of water and 1 mL acetaldehyde was added. A few days later 0.5 mL pyridine was added to the clear solution. A thick white precipitate formed after allowing the solution to remain in the fridge overnight and was separated by filtration. The yield was 1.5 g of product (61%), m.p. 153-155^{o}C (dec.), lit. 161-163^{o}C (58).

2,2-Dimethylthiazolidine-4-carboxylic acid (III)

3.0 g (0.014 mole) L-cysteine.HCl.H_2O was added to 350 mL of

distilled acetone in a round bottom flask and refluxed for 15 hours. The undissolved solid (0.5 g) was removed by filtration, and the acetone was reduced to a small volume by distillation. The solution was allowed to cool slowly and long prismatic crystals formed. The yield of solid was 2.0 g (89%), m.p. 163-165°C, lit. 163-165°C (59). Crystals suitable for X-ray crystallography were obtained by recrystallization from an aqueous solution.

3-Benzoyl-2,2-dimethylthiazolidine-4-carboxylic acid(IV) A modification of a published method (60) was followed: 3.85 g (0.024 mole) III was added to 175 mL pyridine and stirred until all the solid dissolved. To the cooled stirred solution 3.4 g (0.0245 mole) of benzoyl chloride, was added dropwise. The mixture was placed in an ice bath and stirred for 30 min., then stirred at room temperature overnight. The mixture was evaporated under reduced pressure to leave a yellow oil and some white solid. This was dissolved in 80 mL dichloromethane, then extracted twice with 20 mL water. The combined aqueous layers were extracted once with a small volume of CH_2Cl_2. The combined organic layer was dried with anhydrous sodium sulfate, filtered and evaporated in the rotoevaporator. The yellow solid recovered, which had only a faint pyridine odour at this stage, was dissolved in 20 mL methanol and was acidified to pH 2 to 3 with aqueous HCl. Water was added dropwise until the solution turned slightly cloudy. The

mixture was allowed to stand at room temperature until white crystals formed. These were recrystallized from aqueous methanol to give 4.5 g (70%) of product, m.p. 172-173°C, lit. 180-182°C (60).

3-Benzoyl-2,2-dimethyl-4-methoxycarbonylthiazolidine (V)

A literature procedure (60) was used as follows: 1.0 g (0.0038 mole) IV was dissolved in 10 mL methanol. An excess of ethereal diazomethane solution (20 mL of 0.003 mole/10 mL solution) was added and the mixture was stirred at room temperature overnight. The pale yellow solution was evaporated, yielding a yellow oil which was dissolved in methanol. Water was added dropwise until small white crystals started appearing in the mixture. The mixture was allowed to stand for two hours when 0.7 g of white crystals was separated by filtration (66% yield). White prismatic crystals were obtained by recrystallization from a mixture of methanol and water, which melted at 102-104°C, lit. 105-106.5°C (60).

3-Benzoyl-2,2-dimethyl-4-hydroxymethylthiazolidine (VI)

0.75 g (0.0027 mole) of V was dissolved in 20 mL absolute ethanol and the solution cooled on ice. A large excess of sodium borohydride (1.5 g or 0.038 mole) was added, with fast hydrogen evolution. The resultant mixture was stirred on ice for one hour, then at room temperature overnight. Another 10 mL of ethanol was added to the very gelatinous mixture which was then stirred for a further 6 hours. A

mixture of ethanol and water was added to the cooled reaction mixture to dissolve the unreacted borohydride. The ethanol was removed by evaporation under reduced pressure, and the resultant solution was extracted four times with 15 mL of dichloromethane and once with 15 mL chloroform. The organic extracts were dried with anhydrous Na_2SO_4, filtered, and the organic solvent evaporated to leave a clear oil that crystallized into a wet solid on standing overnight. The wet white solid was dissolved in a 4:1 (v/v) mixture of benzene:ethyl acetate and the components were separated by silica gel chromatography eluting with the same solvent system. Of the two fractions collected the first was the unreacted ester and the second was the reduced product, which was obtained as a pale yellow solid after evaporation of the solvent. The product was recrystallized from aqueous methanol to yield 0.5 g (71%) of white solid, m.p. 117-118.5°C, lit. 114.5-116.5°C (60).

2-Phenylthiazolidine-4-carboxylic acid (VII)

1.2 g (0.01 mole) of L-cysteine was added to a mixture of 1.08 g (0.0105 mole) of benzaldehyde in 30 mL of water at pH 8.0. The mixture was stirred at room temperature and a precipitate started appearing within 30 min.. The mixture was filtered to yield 1.35 g (65%) of white solid, m.p. 154-155°C, lit. 159-160°C (58).

3-Benzoyl-2-phenylthiazolidine-4-carboxylic acid (VIII)

0.42 g (0.002 mole) VII was dissolved in 20 mL of pyridine.

The solution was cooled on ice and it became a light suspension. 0.3 g (0.0025 mole) of benzoyl chloride was added dropwise to the stirred mixture, which slowly turned yellow as the solid gradually dissolved. The reaction was allowed to proceed in the refrigerator overnight. The product was recovered by evaporation under reduced pressure to leave a yellow oil. This was dissolved in dichloromethane and extracted as in the preparation of IV. The crystals obtained were recrystallized from hot methanol to give a pale yellow solid. Yield 0.35 g (60%), m.p. 128-129°C, lit. 153-154°C (61a).

Anal. Calc. C, 65.21; H, 4.78; N, 4.46; S, 10.19; O, 15.29. Found: C, 62.46; H, 5.67; N, 4.10; S, 9.82; O, 17.98. Calc. for VIII.0.7H_2O: C, 62.6; H, 5.1; N, 4.3; S, 9.8; O, 18.2.

Colourless crystals for X-ray diffraction studies were obtained by recrystallization from methanol over a few days at 0°C.

2-Ethyl-2-methylthiazolidine-4-carboxylic acid (IX)

A published procedure (61b) was used as follows: 1.5 g (0.0125 mole) L-cysteine was added to 22 mL of 2-butanone and the mixture was refluxed for 5 hours. The mixture was filtered while hot. Most of the cysteine remained undissolved and unreacted. 0.6 g of white solid was recovered after evaporation of the filtrate, followed by recrystallization from hot 2-butanone. M.p. 130-132°C, lit.

132-133°C (61b).

3-Benzoyl-2-ethyl-2-methylthiazolidine-4-carboxylic acid (X): 1.0 g (0.006 mole) IX, 30 mL of pyridine and 0.8 g of benzoyl chloride were reacted in a flask cooled by an ice bath. 30 min. later a white solid started precipitating out of the pale yellow solution. The work-up procedure was identical to that reported in the preparation of IV. 0.6 g (40%) of a white solid was obtained, m.p. 133-134°C. Nmr spectra are found in Tables 13, 13A and 14. Anal. Calc. C, 60.00; H, 6.07; N, 5.00; S, 11.43; O, 17.14. Found: C, 60.49, H, 6.26; N, 4.81; S, 11.25; O, 17.21.

5,5-Dimethylthiazolidine-4-carboxylic acid (XI) 1.0 g (0.006 mole) D-penicillamine was dissolved in 5 mL acidified water, under nitrogen, and 15 mL ethanol. 0.9 mL 37% formaldehyde (v/v) was added with a pipette, the mixture became clear and within 15 min. a white solid had separated. The mixture was allowed to stand overnight to crystallize and then was filtered to give 0.76 g (79%) of white crystals, m.p. 186-188°C, lit. 193-194°C (61c).

3-Benzoyl-5,5-dimethylthiazolidine-4-carboxylic acid (XII): To 4.6 g (0.029 mole) XI dissolved in 120 mL pyridine was added 4.1 g benzoyl chloride in 80 mL pyridine. The procedure followed was similar to that used in the preparation of IV. The product obtained was recrystallized from aqueous methanol to yield 4.7 g (60%) of product, m.p. 74-76°C.

Anal. Calc. C, 58.65; H, 5.23; N, 5.26; O, 18.05; S, 12.03. Found: C, 58.48; H, 5.69; N, 4.68; O, 18.15; S, 11.91.

3-Benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine (XIII): To a solution of 2.1 g (0.0078 mole) XII in methanol cooled on ice, was added 40 mL of a solution of diazomethane (0.009 mole) in diethyl ether. The colorless solution was stirred overnight in a sealed flask, then it was evaporated on a rotoevaporator to leave a yellow oil which was recrystallized from aqueous methanol. 2.0 g (90%) of a white solid was obtained, m.p. 75-76°C, lit. 63-64°C (61c).

Anal. Calc. C, 60.22; H, 5.71; N, 5.00; O, 17.14; S, 11.43. Found: C, 59.87; H, 6.24; N, 5.06; O, 16.95; S, 11.68.

3-Benzoyl-5,5-dimethyl-4-hydroxymethylthiazolidine(XIV) 0.5 g (0.0018 mole) XIII was dissolved in 25 mL absolute ethanol, and sodium borohydride was added in large excess (0.85 g, 0.022 mole). The mixture was stirred at room temperature overnight, heated to 50°C for 2 hours, and then stirred at room temperature for another 2 hours. Thin layer chromatography of the mixture revealed four to five components. The work-up was done in an identical manner to that used in the preparation of 3-benzoyl-2,2-dimethyl-4-hydroxymethylthiazolidine, VI. The yellow oil contained four components partially separated in a silica gel column

with benzene:ethyl acetate (3.5:1). Each fraction was put through the column again. Three fractions were obtained, the first is the starting ester as shown by ^{1}H nmr spectroscopy, the second appears to be the reduced compound and fraction 3 could not be identified. None of the nmr spectra show clearly a single compound. The thin layer chromatogram of each fraction showed a dark spot at the origin and one higher up on the plate. The yield of fraction 2, the product, was very low, and it was obtained as an oil which could not be crystallized.

2,5,5-Trimethylthiazolidine-4-carboxylic acid (XV)

1.3 g (0.0087 mole) D-penicillamine was dissolved in 12 mL of water, cooled on ice and 0.65 mL acetaldehyde was added. The mixture was allowed to stand on ice for 30 min. during which time a white solid precipitated. The product was separated by filtration and recrystallized from hot ethyl acetate. Yield 1.3 g (84%), m.p. 161-162°C, lit. 165.5-167.5°C (36).

Anal. Calc. C, 48.00; H, 7.43; N, 8.00; O, 18.29; S, 18.29. Found: C, 46.02; H, 7.73; N, 7.52; O, 20.13; S, 20.14.

Crystals suitable for X-ray structure determination were obtained by overnight recrystallization from a solution of XV in D_2O, by slow evaporation, and from an acetone solution by slow cooling followed by evaporation at 4°C.

5,5-Dimethyl-2-phenylthiazolidine-4-carboxylic acid (XVI): A published procedure (61a) was followed: 1.0 g (0.0066 mole) of D-penicillamine was added to 1.0 mL benzaldehyde and 10 mL ethanol, and the mixture was heated for 30 min.. The almost clear mixture was filtered while hot and as the filtrate cooled a white precipitate started separating. The cooled solution was filtered to obtain 1.3 g (80%) of a white solid, m.p. 141-142.5°C, lit. 145-146°C (61a).

3-Benzoyl-5,5-dimethyl-2-phenylthiazolidine-4-carboxylic acid (XVII): 0.24 g (0.001 mole) XVI, 15 mL pyridine and 0.15 g benzoyl chloride were added to a flask, and the pale yellow solution was stirred for 8 hours. The reaction was carried out in the same way as in the preparation of IV. An oil was always recovered in spite of repeated recrystallization attempts.

2,2,5,5-Tetramethylthiazolidine-4-carboxylic acid (XVIII): 1.5 g (0.010 mole) D-penicillamine was dissolved in 20 mL degassed water and 50 mL acetone. The clear mixture was stirred under nitrogen, and allowed to evaporate to dryness. The product was recrystallized from hot acetone to give 1.65 g (87%) of white crystals, m.p. 173-175°C, lit. 172-174°C (62).

3-Benzoyl-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid (XIX): To a solution of 9.5 g (0.0503 mole) XVIII in 350 mL pyridine, cooled on ice, 7.4 g benzoyl chloride was

slowly added while stirring. The reaction mixture was treated in the same way as in the preparation of IV. The yield of white product was 7.6 g (52%), m.p. 158-160°C.

Anal. Calc. C, 61.22; H, 8.33; N, 4.76; O, 16.33; S, 10.88. Found: C, 60.89; H, 6.58; N, 5.02; O, 16.09; S, 10.57.

3-Benzoyl-4-methoxycarbonyl-2,2,5,5-tetramethylthiazolidine (XX): To 1.0 g (0.0034 mole) XIX in methanol was added an excess of diazomethane (0.008 mole) in diethyl ether and the solution stirred for 5 hours. The mixture was evaporated to give a yellow oil which was recrystallized from aqueous methanol to yield 0.85 g (81%) of a crystalline white solid, m.p. 93-95°C, lit. 88-89°C (61d).

2-Ethyl-2,5,5-trimethylthiazolidine-4-carboxylic acid (XXI): To 1.5 g (0.01 mole) D-penicillamine was added 25 mL 2-butanone and the mixture was refluxed for 4 hours. The clear solution was allowed to cool but no crystallization occurred. Evaporation produced 1.5 g (70%) of white solid, recrystallized from 2-butanone, m.p. 117-119°C, lit. 183-183.5°C (61d).

Anal. Calc. C, 52.94; H, 8.33; N, 6.86; O, 15.69; S, 15.68. Found: C, 53.71; H, 8.59; N, 6.69; O, 15.42; S, 15.40.

3-Benzoyl-2-ethyl-2,5,5-trimethylthiazolidine-4-carboxylic acid (XXII): 0.20 g (0.00125 mole) XXI was dissolved in 15 mL pyridine and 0.15 g benzoyl chloride was added.

The mixture was left in the refrigerator overnight. A yellow oil was recovered after evaporation and yielded a yellow crystalline solid after crystallization from methanol/water. The crystals were filtered and washed with ether to give a white solid, 0.15 g (40%), m.p. 182-183°C. See Tables 13, 13A and 14 for nmr spectra.

Bis(5,5-dimethylthiazolidine-4-carboxylic acid)protium chloride hydrate (XXIII): This preparation was carried out using a literature method (53): 0.6 g (0.005 mole) of acetamidomethanol was added to 0.8 g (0.005 mole) D-penicillamine in 5 mL water. Dilute HCl was added to acidify the solution to pH<2. The solution was stirred under nitrogen for 30 min., then the flask was stoppered and allowed to stand at room temperature. Following evaporation of the solution a colourless oil was left. Upon standing overnight some separation of white solid from the oil was observed. Ethanol was added to dissolve the oil and the solid was filtered out. To the ethanol solution anhydrous diethyl ether was added and the mixture was left in the refrigerator. A white precipitate covered by a colourless oil were recovered. The oil dissolved in water readily, and the white precipitate was less soluble. The yield of white solid was 0.6 g (70%), m.p. 181-182°C (dec.).

Long prismatic crystals for X-ray structure determination were obtained by slow crystallization from the reaction mixture over a period of one week.

III. RESULTS AND DISCUSSION

III.1. Summary of the Experimental Approach

This chapter is divided into sections, each covering a different aspect of the experimental work carried out in this project. The first part of the project consisted mainly of synthetic chemistry. A number of thiazolidine-4-carboxylic acids were prepared, and reductions were carried out in order to try to replace the carboxyl group with an alcohol functionality. This was a crucial step in the preparation of the wanted fatty acid-containing ligand for Tc-99m chelation.

One of the wanted alcohols from D-penicillamine was obtained, see Section III.1.2., but not in pure form. It could not be separated from the mixture because there appeared to be many components with similar structure which did not elute from a silica gel column at the appropriate rates for separation. Some of the components were eluted together, because some were fast, and some were very slow and came off the column at a continuous rate over a period of time. High performance liquid chromatography (HPLC) or gas chromatographic (GC) methods would have been more efficient means of separation and identification of components in the reaction mixtures, if time had permitted.

The reductions were carried out with substituted thiazolidines with varying degrees of steric hindrance, both with carboxylic acids and esters. Both types of organic compounds are easily reducible in less hindered aliphatic or aromatic molecules.

Protecting group reactions with D-penicillamine were also attempted because, if instead of a thiazolidine ring there was an open chain, then the reduction step might be a more favoured process. It was expected that the reducing agent would have easier access to a carbonyl center which was not a substituent in a sterically crowded ring system. As explained on p. 14, this thesis became a study of the characterization and spectroscopic properties of thiazolidine-4-carboxylic acids. We have characterized a large number of these compounds by vibrational spectroscopy, nmr and mass spectroscopy. An analysis of the different types of hydrogen bonds observed was undertaken by comparison of X-ray crystallography data with vibrational data.

III.1.1. Synthetic Approach

The approach in the synthesis of a radioimaging agent was to take D-penicillamine and follow one of the two reaction schemes shown in Fig. 1, page 20. The first, Fig. 1(a), consisted of reacting D-penicillamine with a carbonyl compound to form a thiazolidine, and then protecting the

secondary amine with a benzoyl group. The methyl ester was obtained by reaction of the acid with diazomethane in ether. The next step was to reduce the methyl ester to an alcohol followed by reaction of this with a brominated derivative of a fatty acid. The thiazolidine ring could be opened under alkaline conditions, then debenzoylated. The sulfhydryl and amine would then be free for technetium chelation. The second method, Fig. 1(b), was to protect the amino and free thiol groups of the starting aminoacid and then proceed to reduce the carboxyl group. The final step would be to deprotect the S and N containing groups with $NaBH_4$ in methanol and HBr in glacial acetic acid (45), respectively. In theory this appeared to be a relatively simple reaction scheme. It was also expected that once the ligand was available the complex could be made quickly and administered to a patient in a period of time short enough compared to the half-life of the radioactive metal.

Because 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid (TMT) is so easy to prepare and the initial intermediates in any synthetic sequence must be repeatedly made, TMT was synthesized and protected with a benzoyl group. Both the N-benzoyl protected acid and ester were treated with reducing agents under a variety of conditions, as outlined in Appendix A, in efforts to obtain the alcohol derivative without which further reactions would not be possible.

III.1.2. Reduction Attempts

This section should be read in conjunction with Appendix A for details of reaction conditions.

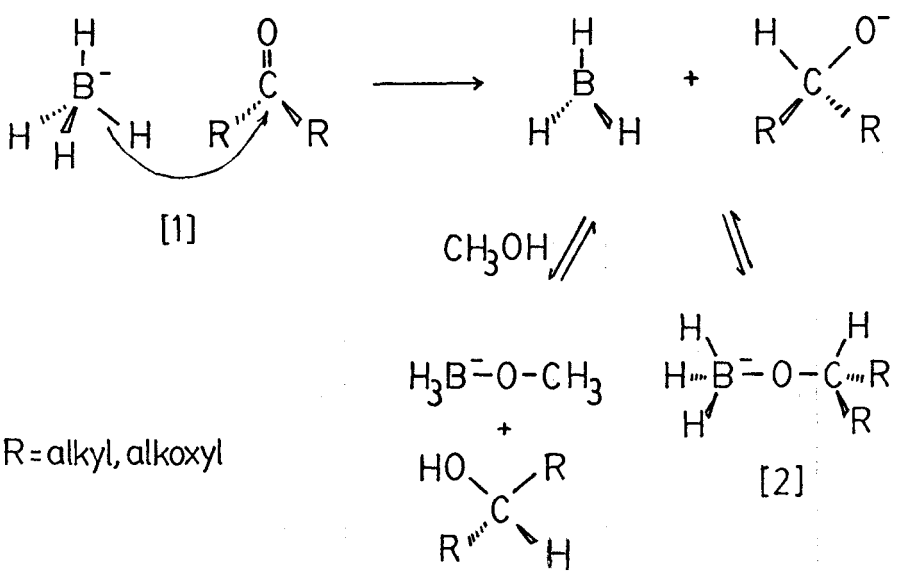
Sodium borohydride, $NaBH_4$, is a good reducing agent and its most important reductions are carried out in methanol and other hydroxylic solvents. Methanol is a good solvent, but it reacts with sodium borohydride, the reducing power of which may be greatly enhanced by using aprotic solvents; even greater reducing power is observed in the presence of the Lewis acids, aluminum chloride and boron trifluoride. Trivalent compounds such as these with only six electrons in the valence shell have the requisite structure for Lewis acids (63). The use of different solvents has a marked effect on the reducing properties of $NaBH_4$.

Most esters are reduced very slowly by sodium borohydride, but in certain instances fast reactions have been observed at room temperature to give the corresponding alcohol, especially with esters like RCOOR', where R' is an electron withdrawing group. There are reports in the literature of esters that have been reduced to varying degrees by a large excess (10 mole) of sodium borohydride in methanol. When reduction of esters under these conditions does not occur, transesterification in methanol can be very fast (64).

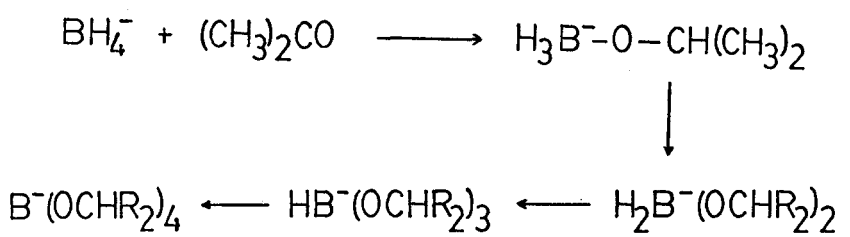
Sodium borohydride-aluminum chloride in diglyme in a 3:1 molar ratio gives a powerful reducing solution, such

that most aliphatic carboxylic acids and esters are rapidly reduced under dry nitrogen at 25°C. The reaction with N-benzoylated esters of TMT and 5,5-dimethylthiazolidine-4-carboxylic acid could not be forced with extreme conditions because of the presence of the disubstituted amide which could also be reduced (to an amine). If the reaction was carried out at high temperature or for long periods of time the solvent used was either isopropanol or diglyme. Esters have been reduced to ethers with sodium borohydride and borane trifluoride (65).

In the reduction of a carbonyl compound with borohydride ion, the hydride ion is transferred to the carbonyl carbon atom as shown below, structure [1]. This step is followed by the formation of an alkoxyborohydride anion [2]. In a hydroxyl containing solvent, exchange with the solvent is possible as illustrated by the reaction with methanol (64):



With lithium aluminum hydride the reaction sequence is essentially the same in a non-protonic solvent. All four hydrogen atoms may be used in the reduction and it has been found both with AlH_4^- and with BH_4^- that each successive hydrogen transfer step occurs more slowly than the preceeding step, see below:



This order of reactivity has allowed the preparation of reduction agents that are less reactive and more selective than lithium aluminum hydride by replacing two or three of the hydrogen atoms with certain primary or tertiary alkoxyl groups. For example $NaBH(OCH_3)_3$ reacts with hydroxylic solvents, so that dimethoxyethane is commonly the solvent of choice. This is a reagent of intermediate strength between sodium and lithium borohydride and it reduces some esters at high temperatures (66). The differing reactivities of the reducing agents may be a result of two opposing factors: the resonance interaction of the alkoxyl group would assist hydride ion transfer and accelerate the reaction and the electron withdrawing effect of that same group would oppose loss of the hydride ion and retard the reaction (64).

An excess of the hydride reagent was always added to the reaction mixture because some of the metal hydride is destroyed by reacting with hydroxyl containing solvents. The isolation of organic products from the sodium borohydride reaction was done by diluting the reaction mixture with slightly acidic water to destroy the excess hydride, and by extracting the organic product from the aqueous solution containing boric acid and its salt. The reaction of the organic boron compound with water probably occurs in the following manner (64):

$$B^{-}(OR)_4 \rightleftharpoons RO^{-} + B(OR)_3 \xrightleftharpoons{H_2O} ROH + HOB^{-}(OR)_3$$

$$\Downarrow$$

$$2\,ROH + O^{-}\!-\!B(OH)_2 \xrightleftharpoons{H_2O} \xrightleftharpoons{H_2O} ROH + O^{-}\!-\!B(OR)_2$$

Reducing agents that have been widely used in ester reduction include a variety of metal hydrides and borohydrides, most of which are more potent than sodium borohydride. The most reactive hydride is lithium aluminum hydride which easily reduces most esters and amides. This side reaction (amide reduction) is undesired in this synthesis (see Fig. 1) because the secondary amine must be blocked for further reactions. The reagent is very sensitive to moisture, so that dry reaction conditions must be used to avoid the danger of explosions.

Lithium borohydride can be made by reacting sodium

borohydride with lithium chloride; it is a reagent of intermediate reducing power between $NaBH_4$ and $LiAlH_4$, but it did not reduce 3-benzoyl-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid. $LiBH_4$ was found useful in the reduction of 3-benzoyl-2,2-dimethylthiazolidine-4-carboxylic acid, possibly with higher yield of product than the sodium borohydride reduction. Both lithium borohydride and lithium aluminum hydride react rapidly with hydroxylic solvents, so that reactions with these reducing agents must be carried out under anhydrous conditions.

Alkylated reducing agents are used for stereochemical and selective reductions, for example if there exists in the molecule more than one functional group that can be reduced. Intermediate strength borohydrides have been used, but the reduction may be complicated by a complex mixture with products of different extent of reduction of the functional groups, the separation of which would require sophisticated separation techniques.

Boranes are efficient in reducing carboxylic acids and a variety of reagents are available that can be used with different solvents and under a variety of conditions. Diborane is the most common of this class of reducing agents; dry organic solvents such as tetrahydrofuran (THF), diethyl ether, toluene can be used in diborane reductions so long as the carboxylic acid is soluble. Boranes also vary in their reducing ability, some are more potent than others,

others react slower and are more selective for certain functional groups.

BH_3 exists as a gaseous dimer, diborane. It can be produced by adding a solution of sodium borohydride in diglyme to boron trifluoride etherate. The carboxyl group can be reduced selectively by diborane in THF in the presence of esters, nitro groups and amides to a primary alcohol. Acyl chlorides and esters are reduced slowly to alcohols and amides react with boranes at higher temperatures to give amines (63).

Borane adds rapidly to carbon carbon multiple bonds with the formation of organoboranes. The mechanism of borane reduction is similar to that of borohydrides in that each successive step is slower than the previous one because of the increasing steric bulk of the partially alkylated boron reagent (64). Trisubstituted olefins normally react with diborane to give dialkylboranes. Similarly with lithium aluminum hydride, this reactivity makes it possible to prepare mono and dialkylboranes which are less reactive and more selective than diborane itself.

Borane methyl sulfide in THF is a stable and safe source of borane and very soluble in many organic solvents. Aliphatic carboxylic acids are readily reduced in THF at room temperature or in refluxing ether to alcohols, but aromatic carboxylic acids must be activated with trimethyl borate before reacting with borane.

Many reactions were carried out as an attempt to reduce 3-benzoyl-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid and its methyl ester, but the wanted product was never recovered or even detected by proton nmr. When a solid or oil was obtained from the reaction mixture, it was either the starting compound or some unidentifiable mixture of starting material and breakdown products. Thin layer chromatography was useful in the determination of the number of components in a solution, but often there were too many components to attempt separation and identification, especially in instances when the starting acid or ester could not be detected in the nmr spectrum. The starting materials were recovered repeatedly from all the reduction reactions attempted using different reducing agents and varying the reaction conditions until the temperature or time of reaction were too excessive for stability of the thiazolidines, at which point only decomposition products were obtained. The proton nmr of the oils recovered consisted of complex patterns of peaks with little or no resemblance to that of the starting acid or ester.

The methyl ester of tetramethylthiazolidine could not be reduced under any of the conditions listed in Appendix A. The neighbouring methyl groups above and below the thiazolidine ring result in a high degree of steric hindrance about the C=O group. Therefore very selective but bulky reducing agents can not be useful with C(5)

disubstituted thiazolidine compounds, since they are not able to get close enough to the carbonyl center for attack of the electrophilic carbon atom.

After having attempted the reduction of the 3-benzoyl-2,2,5,5-tetramethylthiazolidine compounds with all the reducing agents mentioned and repeatedly failing to obtain a reduced product, we tried reducing the less hindered 3-benzoyl-5,5-dimethythiazolidine compounds, also derived from D-penicillamine, which should be easier to reduce. At this point D-penicillamine was reacted also with reagents that had been used successfully as protecting groups of cysteine. It was found that functional groups are much less reactive in D-penicillamine than the corresponding groups in cysteine. This had been pointed out previously by Friedman (31). The protecting group route appeared less direct than the thiazolidine route because it consists of the additional steps of adding and removing the protecting groups, especially if different groups must be used for protection of the amine and the thiol.

Szarek and coworkers (1978) were successful in reducing 3-benzoyl-2,2-dimethyl-4-methoxycarbonylthiazolidine to the corresponding primary alcohol by means of sodium borohydride in methanol at room temperature (60). The same reaction was repeated with the 5,5-dimethylthiazolidine analog prepared from D-penicillamine. We varied the reaction conditions by increasing the amount of the reducing agent, increasing the

time of reaction, heating up the reaction mixture, and using other alcohols as solvents to decrease the rate of reaction of the borohydride reagent with the solvent; none of the modifications made the reduction successful.

The sodium borohydride reaction was repeated several times with 3-benzoyl-2,2-dimethyl-4-methoxycarbonylthiazolidine as we attempted to develop the conditions for highest yield of product. It was observed that a much longer reaction time was required than that reported in the literature (60) to obtain the same yield of product.

When the reaction was repeated with 3-benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine some of the wanted product was obtained in a complex mixture of side (and decomposition) products. Most of the reductions attempted with 3-benzoyl-4-methoxycarbonyl-2,2,5,5-tetramethylthiazolidine were repeated with 3-benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine in an attempt to find an efficient method of obtaining the alcohol. The more harsh conditions of reduction resulted in debenzoylation which was not wanted at this stage.

There are reasons to believe that some 3-benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine was reduced. The proton nmr of the oils recovered from the reaction mixtures showed reduced intensity of the methyl ester peak. It became too time consuming to try to separate the large number of components present in the reaction mixture by

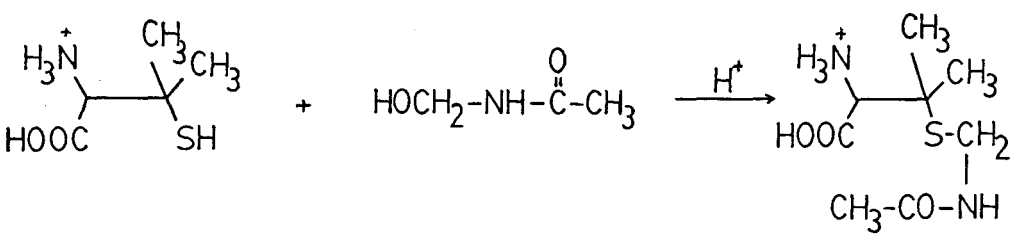
conventional column chromatography. The separation procedure in a silica gel column was repeated twice for one reaction after the initial partial separation, with only slight improvement. Some of the fractions collected from the column still had many components; none of the fractions were pure after pooling and solvent evaporation. There was at least one component adsorbed on the silica in the column that showed up as a bright spot under uv light at the origin of the TLC plate, yet a fluorescent species was present in all the fractions collected. Ethanol appeared to be a better solvent than methanol for sodium borohydride reduction of 3-benzoyl-2,2-dimethyl-4-methoxycarbonyl-thiazolidine because it reacted more slowly with the reducing agent and the yield of reduced 3-benzoyl-2,2-dimethyl-4-hydroxymethylthiazolidine was higher. The same number of reaction components was obtained on the TLC whether the reaction was carried out at room temperature or heated to the boiling point of ethanol for a few hours.

In future work the reaction might be carried out at low temperature for longer time periods, monitoring product formation by TLC and nmr. The separation of the mixture following completion of the reaction should be attempted with HPLC or GC techniques, to establish the conditions for high yield of product.

III.1.3. Reactions of D-Penicillamine with Protecting Groups

Most protecting groups reacted with D-penicillamine to yield oily products which were probably complex mixtures of components. The oils obtained were in most cases soluble in non-polar organic solvents, but if a solvent mixture was used to try to recrystallize the oil it would start separating out of solution, immediately or after a period of standing, as an oil, never as the solid. TLC yielded a complex pattern with streaking spots.

The reaction of D-penicillamine with N-hydroxymethylacetamide, which is a very useful blocking group for the free thiol of cysteine, should give the product shown in Scheme 2 below. Instead of the sulfur-



Scheme 2

protected product, a protonated dimer of 5,5-dimethylthiazolidine-4-carboxylic acid, held together by a very short hydrogen bond, was separated from the reaction mixture. According to Veber et al. (53), only under extremely anhydrous conditions (anhydrous HF at 0°C) is the yield of thiazolidine-4-carboxylic acid minimized. In the acidic

solution, the N-hydroxymethylacetamide reagent must have broken down to generate formaldehyde (and acetamide). The subsequent reaction of this formaldehyde with D-penicillamine gave bis((S)-5,5-dimethylthiazolidine-4-carboxylic acid) protium chloride hydrate. As expected, the dimer decomposes in aqueous solution and the ^{1}H nmr of the dimer is nearly identical to that of 5,5-dimethylthiazolidine-4-carboxylic acid prepared directly from formaldehyde with a downfield shift of only 0.1 ppm for the C(4)-H peak at 3.95 ppm (presumably caused by a pH shift). Similar effects are seen in the carbon-13 spectrum where there is a downfield shift of 0.4 ppm of the C(4) peak and a very small shift of the COOH carbon (67).

III.2. Compound Preparation

Because so many thiazolidine ring compounds were prepared for this study, this discussion will deal mainly with the synthesis and characterization of the substituted thiazolidine-4-carboxylic acids listed in Table 1, page 27, and their derivatives. Their vibrational and nmr spectra will be discussed as well as data obtained from X-ray crystallographic studies of some of the crystals obtained. Some of the compounds prepared during this work had been synthesized from dl-penicillamine shortly after the aminoacid was obtained from penicillin in the 1940s. The melting points of the meso compounds were determined, and

since then very few reports about spectroscopy of thiazolidines have appeared in the literature, except for a high resolution proton nmr spectrum of thiazolidine-4-carboxylic acid (68), and some infrared spectra of only a few thiazolidine compounds, as will be discussed in Section III.3..

A series of C(2), N and C(5) substituted thiazolidine-4-carboxylic acids were prepared by reacting the aldehydes and ketones listed in Table 1 with L-cysteine and D-penicillamine. Almost all of the compounds were purified by recrystallization and their melting points are close to the reported values, except in the cases discussed below. Elemental analyses were obtained for those compounds for which no m.p. was found in the literature and for those submitted for X-ray structure determination. Most of these compounds had been prepared previously but very little is known about their structure and spectroscopic properties. Many of the thiazolidines known today were synthesized before 1949 from dl-penicillamine (61), so that the products obtained consisted of mixtures of stereoisomers. This might explain the melting point disparity between our experimental value and the published value, respectively, of 3-benzoyl-2-phenylthiazolidine-4-carboxylic acid (VIII) (128-129^{o}C vs. 153-154^{o}C), 3-benzoyl-5,5-dimethylthiazolidine-4-carboxylic acid (XII) (74-76^{o}C vs. 63-64^{o}C), 3-benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine (XIII) (75-76^{o}C vs. 63-64^{o}C) and

3-benzoyl-4-methoxycarbonyl-2,2,5,5-tetramethylthiazolidine (XX) (93-95°C vs. 88-89°C). One other compound that deserves special mention in this aspect is 2-ethyl-2,5,5-trimethylthiazolidine-4-carboxylic acid (XXI), a crystalline white solid that was recrystallized from 2-butanone. XXI was observed repeatedly by us to melt at 117-119°C and the published m.p. for the compound is 183-183.5°C (61d). There is every reason to believe that all the compounds above are pure because their m.p. ranges are narrow, and both their proton and carbon-13 spectra were obtained and are consistent with the structure proposed, and the vibrational spectra agree with that of closely related structures, see Section III.3. The elemental analyses of four of the compounds above are close to the calculated values, except for that of compound VIII, suggesting that the material is partly hydrated: the analytical figures are poor for the anhydrous material but agree fairly closely with a 0.7 hydrate.

No literature m.p. values could be found for 3-benzoyl-2-ethyl-2-methylthiazolidine-4-carboxylic acid (X) (m.p. 133-134°C), 3-benzoyl-2-ethyl-2,5,5-trimethylthiazolidine-4-carboxylic acid (XXII) (m.p. 182-183°C) and for bis(5,5-dimethylthiazolidine-4-carboxylic acid)protium chloride hydrate (XXIII) (m.p. 181-182°C) and we believe we are reporting these compounds for the first time. The elemental analyses of all three compounds is nearly the same as the

calculated elemental composition, suggesting that the compounds are pure. These compounds, like all the others reported here, have been characterized by vibrational and nmr spectroscopy.

III.3. Vibrational Spectroscopy

All the compounds prepared and discussed in this work are five-membered heterocyclic molecules with no symmetry elements. There is very little published work related to the vibrational spectra of thiazolidine-4-carboxylic acids. A publication on the vibrational spectra of thiazolidine and N-D thiazolidine was followed by another study of three monomethylthiazolidines, with methyl substitution at C(2), C(4) and C(5) positions, and did not include any C(4)-carboxylic acid molecules (69). The infrared spectra of some chelates of thiazolidine acids, including the spectra of the compounds 2-methyl-, 2,2-dimethyl-, 2,2,5,5-tetramethyl- and 2-benzylthiazolidine-4-carboxylic acid have been reported for the range 4000-400 cm^{-1} (70). Our spectra cover a greater wavenumber range and differ in many details.

Detailed studies of the spectra of D-penicillamine, L-cysteine and some of their methyl substituted derivatives in the solid and solution, including the acid and zwitterion forms, have been reported recently (62, 71-73), based partly on this work.

Tables 2 through 8 list the vibrational spectra of the

compounds prepared for this study. The common features relating to thiazolidine ring deformations and methyl and methylene groups, for example, will be discussed as general characteristics. The mode descriptions in the spectra should be considered approximate since force constant analyses usually show a high degree of vibrational coupling, particularly in the "fingerprint" region (1600-800 cm^{-1}). Spectra-structure correlations will be discussed for infrared spectra unless they are specifically referred to as Raman bands.

III.3.1. Methyl Substituted Thiazolidine-4-carboxylic Acids

The vibrational spectra of the thiazolidine-4-carboxylic acids show many similarities to those of D-penicillamine or of L-cysteine, the main differences being: (i) absence of bands due to vibration and deformation of S-H; (ii) replacement of bands of the NH_3^+ group by those of N-H or NH_2^+ groups, and (iii) presence of the three ring deformations δ CSC, δ CNC, and δ NCS, absent in the aminoacids.

The methyl and methylene group stretching vibrations and deformation vibrations occur in the usual frequency ranges, 3050-2900 and 1465-1365 cm^{-1} respectively, and will not be discussed in detail. Rocking frequencies are in the neighbourhood of 1150 cm^{-1} with a second component of

frequency around 930 cm^{-1}, and a third set of bands at approximately 750 cm^{-1}, similar to assignments made for D-penicillamine (71).

Tables 2 and 3 list the vibrational spectra and assignments for the methyl substituted thiazolidine-4-carboxylic acids prepared. Strong, broad bands in the infrared spectrum at about 2500 and 1950 cm^{-1}, Table 2 (slightly higher in Table 3) are typical of fairly strong O-H...N bonding. These bands appear only in the infrared, and not in the Raman spectra for Table 2. These bands are less consistent in the L-cysteine based compounds, with the unsubstituted thiazolidine showing a single broad band at 2330 cm^{-1} and the 2,2-dimethyl- showing bands at 2530 cm^{-1} (IR and Raman) and 2075 cm^{-1} (IR).

The strong infrared bands at 1744-1715, 1330 and 1190-1215 cm^{-1} are assigned as ν C=O, δOH and ν C-O, respectively, in compounds retaining the aminoacid form. These assignments are consistent with the findings of the X-ray work for (S)-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid, a compound which exists in the solid in the strongly hydrogen-bonded acid form (62). Compounds in the zwitterion form, such as 2,2-dimethyl-, 5,5-dimethyl- and thiazolidine-4-carboxylic acid, are identified by assignments in the regions 1620-1555, and 1425-1393 cm^{-1} for $\nu_a\ CO_2^-$, $\nu_s\ CO_2^-$ and 1585-1550 cm^{-1} for $\delta\ NH_2^+$.

The ring stretching modes can be described only roughly

TABLE 2: Vibrational Spectra of Substituted Thiazolidine-4-carboxylic Acids Related to D-penicillamine.

D-penicillamine Infrared[a]	D-penicillamine Raman[b]	5,5 dimethyl- Infrared	5,5 dimethyl- Raman	2,5,5-trimethyl- Infrared	2,5,5-trimethyl- Raman	2,2,5,5-tetramethyl- Infrared	2,2,5,5-tetramethyl- Raman	Assignment[c]
3445,10,240		3418,25,190		3460,20,220	3464,3	3440,15,200		ν OH
				3245,100,70	3240,20	3270,50	3262,10	ν N-H, associated
					3220,10,25 sh			
3170,55,200								
							3010,10	
	3018,20						2995,35	
	2987,70		3007,10		2990,40	2998,55	2990,35	
2970,85,350	2965,50	2975,85,160	2975,30,20	2973,87	2973,50	2967,75	2980,50	ν_a CH_3,CH_2
							2972,45	
2930,85	2930,80,25	2933,70,200	2938,25,50	2925,80	2942,50,20	2937,55	2935,45,50	ν_s CH_3,CH_2
	2907,40,22		2905,20 sh		2928,100			
2870,80,420	2870,10,25			2870,55,160	2868,20 sh	2880,50,180	2888,15	ν CH
	2780,5						2772,3	
	2742,3							
	2733,5	2692,30,360			2730,5,25			
2600,70,200	2592,10							
2508,65,180	2515,60,20							ν S-H
		2435,40,620		2450,57,500		2470,56,400		O-H...N bonding
			2048,15,140					
2008,15,120				1960,45,360		1940,45,300		O-H...N bonding
				1732,50,110	1700,3,80	1728,68,190	1715,5,25	ν C=O
				1634,20,70			1667,3	
1616,95,80	1630,3							ν_a CO_2^-
1597,100,90		1598,85,120	1582,3,50	1590,15	1580,3	1578 sh		δ_a NH_3^+,NH_2^+
1558,90,100	1556,3,25							
1524,100,80	1518,10,17				1525,3			δ_s NH_3^+,NH_2^+
1476,70	1460,30	1461,70	1460,30	1466,23 sh	1460,25		1468,30	δ_a CH_3
1467,60							1452,5	
1438,65	1440,30,22		1435,20	1448,25,50	1448,25,30	1458,50	1442,10	δ_a CH_3
				1421,25	1420,5 sh	1418,20		
1397,100	1400,30	1385,95,100	1390,8					ν_s CO_2^-
1388,98	1390,20		1375,5	1383,40	1393,5	1392,28	1393,5	δ_s CH_3 out-of-phase
1375,80 sh		1375,95,110	1365,10 sh	1370,42		1375,70	1373,3	δ_s CH_3 in-phase
1337,90	1340,40		1343,20,32	1322,48,70		1329,80,60		δ CH + δ OH

1281,55	1282,5	1305,75 1274,52	1290,15	1280,25 1253,50 1227,50,70	1293,3 1260,3	1290,42 1241,90 1216,45	1298,5 1218,10,20	ν CO
1197,40	1198,15	1216,34 1182,50	1217,10 1180,20	1192,35	1202,5	1195,85		
1163,50	1162,20	1152,30	1153,20 1130,15	1131,50,80	1138,15 1122,15	1137,70	1146,15,30 1123,10	ν_a CCC, τ CH_2 r NH_3^+,NH_2^+
	1122,15	1130,63	1123,15			1111,90	1118,30	ν CCN
1094,55	1097,20	1090,17	1093,3					
1055,50	1058,10	1048,30	1045,10,20	1035,58	1035,10			
1014,30	1015,10					1022,57	1025,5,22	ν C-C
		1002,40	1007,15			1002,53	1000,5	
972,20	963,25 952,20 } 25	950,20	950,15,28	964,60	968,10	972,30	972,20 960,10	r NH_3^+,NH_2^+
				933,55,60	945,10	945,65 sh	945,20	r CH_3, CH_2
922,20	922,30	912,15		914,50		928,100,40	930,5 sh	
888,40	890,10	(884,10)		(886,73,60)	(893,3,20)			δ SH, (r CH_2)
870,50	875,30				(850,3,25)	845,80	848,15	
						825,56		
		830,8	832,30	823,47 db	828,10,20	820,46	820,15	ring breathing
		790,72	787,10	787,30				
			753,50 sh	761,70	765,10			
756,45	758,30	738,10	745,55			757,75	755,10	r CH_3
				700,45	707,10			
673,15	678,30	686,75	686,30		673,25,20	(673,65)	(673,10,18)	δ CO_2^- (hydrogen bonded)
				663,75	622,50	649 sh	650,15	
578,60	580,40					602 w	605,90,20 †	δ COOH
547,85	550,100	607,80	610,100	605,60,40	610,50	578,9	582,100,20	ν CS, FR †2×294
		590,30 sh						
		513,40	512,40	525,30,35	522,5,30			δ CO_2^-
						508,7	506,30	ν CS
468,40	468,5,20			471,32	475,15			
			453,3	456,30		445,16	450,20	δ CCC
		440,30		438,28	437,3			
410,30	407,10,25			408,55	412,10			
				385,40,sh				
		383,65				387,70	388,15	δ NCCO
		375,57	373,60	370,87	372,20		375,10	δ CNC
					360			

358,30	358,30,15				358,35	357,43		δ OC=O
		345,40	345,15		342,15	345,42	345,10 sh	
330,50	332,15,25	335,43		329,64		330,30	338,40 / 332,38	δ $(CH_3)_2CS$
				322,64	321 sh			δ $(CH_3)CS$
300,w	300,w							
	(285,20)		310,20		312,20	300,42	300,35,20	δ CCS ring (skel)
				293,70				
		272,14,35	275,3,50	287,55	297,20,20		294,38,20	δ NCS
256,60	258,15			256,44	255,3	258,20		
				251		234,10	233,3	
200,47	212,10,25	207,45	210,3	209,40	208,10,15			
		193,25	188,10,30	203,42		191,52	188,20	δ CSC
				190				
180,45				165,72	166,3	169,28	170,3	
152,25	155,40	150	143,20			148,44 db		
138,15	138,25	140						
	122,40	120,15	118,30	128,20	125,10			
	102,5		108,20		97,40	102,37	102,30	
					80,20			
	63,20						72,40,30	
	55,10							

[a] Infrared data ν, I, Δ: Band frequency in cm^{-1}, intensity relative to strongest band = 100, half width at half maximum in cm^{-1}.

[b] Raman data Δν, I, Δ: Raman shift in cm^{-1}, intensity relative to strongest band = 100, half width at half maximum in cm^{-1}.

Notations: sh = shoulder, db = doublet, mt = multiplet.

[c] ν = stretch frequency, a = antisymetric, s = symmetric, δ = deformation, τ = twist, r = rock, FR = Fermi Resonance.

TABLE 3: Vibrational Spectra of Substituted Thiazolidine-4-carboxylic Acids Related to L-cysteine

L-cysteine-HCl		Thiazolidine-4-COOH		2-methyl-		2,2-dimethyl-		Assignment[c]
Infrared[a]	Raman[b]	Infrared	Raman	Infrared	Raman	Infrared	Raman	
		3428,7,200		3430,50,300		3450,10,240		ν OH; NH free
3395,95,400	3378,10,60							
						3185,55,160	3170,5,50	ν N-H associated
	3084,8,160	3054,70,120	3045,60	3050,85,210	3095,20			
	2998,60		3015,50		3008,25		2998,50	ν_a CH_3,CH_2
					2985,25	2995 } 75,480		
		2950 } 50				2962		
2950,100,650	2950,100	2935	2940,100,25	2926,85,240	2940,75,25		2967,100,25	ν_s CH_3,CH_2
		2885,40	2882,10,20		2890,10			
			2850,3	2630,85,600	2848,5			
2555,65,400	2568,100							ν S-H
							2553,100	
						2528,65,440	2545,100	O-H...N bonding
		2330,60,700	2320,8,300					
				2035,30		2075,25,140		
1970,25,150								O-H...N bonding
1744,75,95	1743,20			1732,43,65				ν C=O
			1667,3		1697,10			
	1622,5,35	1628,100,100	1630,5,26	1610,100,110	1638,10	1608,97 } 110	1610,11,85	ν_a CO_2^-
					1612,10	1585,100		δ_a NH_3^+,NH_2^+
1580,45,120	1580,5,20		1568,3,35		1583,10			
		1552,66,110		1536,60		1545,80 } 120	1524,10	δ_s NH_3^+,NH_2
1495,65,95	1508,3					1525,sh		
				1485,60				
		1462,70	1460,20	1446,55	1448,17			
	1438,5	1458,70	1438,20	1433,60	1434,15	1426,85	1426,40	δ_a CH_3
1430,45	1430,8	1429,72						
1403,48	1405,20	1380,95,80	1388,10,20	1388,95 } 110		1394,85,50	1396,35	ν_s CO_2^-
					1382,8			
1344,35	1350,12	1340,80,70	1348,5	1365,93	1368,10	1350,85	1342,50	δ_s CH_3,CH_2
							1300,20	

1318,30	1315,10 1272,8	1312,88 1284,70 1261 1255 } 50 1229,55	1310,40 1288,8 1258,10 1232,5	1305,75 1280,60 1240,70	1308,15 1284,10 1244,15	1296,75	1290,20 1265,10	r CH_3
1220,60,120 1198,65,70	1222,15 1208,25			1218,50,80	1215,15			ν CO
		1178,40 1163,50	1168,40		1195,25	1198,30	1200,25,20	
1138,45	1140,25 1122,8	1150,45	1150,25 1123,8	1146,43	1152,15	1142,35	1145,10	ν_a CCC, τ CH_2
1102,40,70	1112,8			1114,25 1085,42	1115,10,20 1089,5	1107,13	1110,10	ν CCN
1059,45,40	1060,10	1055,20	1060,15	1056,40 1027,25	1064,10 1024,50	1064,40	1068,20	
		1014,50	1015,10	1002,25	1010,100		1003,15,25	ν C-C
987,20	992,10	980,40	983,25		982,10		980,10	
933,27	930,10	950,43	953,25	938,20 920,20	942,10,20 920,10	943,30	943,20 937,20	r NH_2 ,NH_2^+,r CH_3 r CH_3
		908,40	908,10					r CH_3,CH_2
866,36	870,30	(885,60) (863,80)	892,25 (862,15)	(874,40,50) (852,36)	(866,20) (856,30)	(868,40,60)	(868,20)	δ SH,(r CH_2)
845,30,50	845,5			838,25,sh				
		801,40	810,40	812,42	817,25 800,22,20	822,20 805,15	820,30 805,15	ring breathing
775,42,90	778,30					769,10	772,30	δ CO_2^-
	755,5 740,30	750,50	752,80	747,50		754,10	750,15	r CH_2, CH_3
					728,30		710	
			705,80		708,40		705,25 sh	
674,26	684,90			675,60	682,70 676,75	692,20	690,70 678,25 sh	ν C-S
					663,40			
		620,80	628,40		640,35	628,40	638,100	ν C-S
598,15	610,15			600,80	609,40			δ COOH
		595,40	595,10	590,sh	583,10			
521,30	527,5	527,70 493	528,28 498,30	(538,80) 496,40	(519,20) 499,35	536,55	535,25 498,10	δ CO_2^-

461,12	458,10	462,50	465,30			460,sh	462,10 sh	
					452	445,40,25	441,25,20	δ CCC
				434,30	433,35,18	434,10		
						411,30,20		
	390,5,30			395,w	397,20,20			
						371,60,60		δ CNC
355,30,50	357,10,25	356,70,25	350,20	356,75,25	357,20	352,15	362,15,20	δ OCO
						336,15		δ $(CH_3)_2CS$
				319,10	319,20,20			δ $(CH_3)CS$
(290,25)	(290,5)		302,10	312,10		304,sh		δ CCS ring (skel)
		297,46,27		300,w 280,w	282,10	295,47 287,55 } 45	298,10,20	δ NSC ring
						276,sh	270,7	
247,10				254,15 252,15 } db	254,15		258,7	
		217,38				215,28 205 } 50 db	209,15,25	
192,25	197,20,25		208,15			200,15		
		191,45	188,35	191,30		191,10		δ CSC
				184,50	182,20			
		173,sh		174,25	173,15	175		
	160,5			169,10				
153,35					158,15	156 147 } 28,40 mt		
	140,w	144						
			130,50	136,130,db		137,131,db		
125,15		123	120,50			124	120,20	
110,15		108	117,60 sh	108		115,110		
		103	103,60	103		102		
			95,80					
			67,70					
			53,40					

a,b,c Footnotes as for Table 2.

as two ν C-S, two ν C-N and ν C-C, with asymmetric stretches being more intense in the infrared, and symmetric (such as "ring-breathing"), more intense in the Raman spectra. Absorptions around 820 cm^{-1} have been assigned to the thiazolidine ring breathing; these bands are present in all the thiazolidine compounds but not in the starting aminoacids.

We assigned the strong Raman bands at 610-582 cm^{-1}, in Table 2, and 705-690 cm^{-1} in Table 3, to ν C-S. Some of these bands show a splitting which is attributed to Fermi resonance with the overtones of bending modes at 294 or at around 340 cm^{-1}. The medium intensity band at 512-506 cm^{-1} in Table 2, and 628-640 cm^{-1} in Table 3, is assigned to the asymmetric ν C-S. The values of C-S frequency bands are determined by two opposing factors: ring strain increases the frequencies and steric hindrance effectively reduces them. The two factors are not independent for (S)-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid (62). The substitution at the C(5) and C(2) centres with bulky methyl groups affects the conformation of the molecule in a way that seems to be a combination of the following effects: (1) the C-S bonds are lengthened as compared to both thiazolidine-4-carboxylic acid and D-penicillamine, (2) the C-S-C angle is increased compared to unsubstituted thiazolidine-4-carboxylic acid, (3) the C(2) and C(5) atoms rotate in opposite directions to minimize the C-S-C angle,

for which 90^{o} is the preferred equilibrium value. Our series shows that dimethyl substitution at C(5) has a greater lowering effect on ν C-S than at C(2). Dimethyl substituted thiazolidine-4-carboxylic acids and long C-S bonds suggest that ν C-S should be lower than the normal range in cyclic sulfides (720-670 cm^{-1}) (74). The observed absorption frequencies are lower for one band but not as low as expected. For 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid the C-S absorption is higher than in D-penicillamine (580 vs. 548 cm^{-1}) (71), close to the value observed in di(t-butyl)sulfide. The assignment of the asymmetric ν C-S is supported by the appearance of a weak side band of position and intensity as expected for ^{34}S, which occurs at 506 cm^{-1} for the tetramethyl compounds.

The ring deformations are δ CNC at 375-370 cm^{-1}, δ NCS at around 290 cm^{-1} and δ CSC at 190 cm^{-1}. The deformations involving the sulfur atom are intense in the Raman spectrum. The strong Raman bands at 338 and 332 cm^{-1} are not observed in unsubstituted thiazolidine-4-carboxylic acid, and are therefore assigned as δ CCS, a deformation of the $(CH_3)_2$-C-S moiety. Assignment of bands at 320 cm^{-1} to δ CCS for the moiety CH_3-C-S of C(2) is consistent. The δ CNC band appears to increase with increasing numbers of methyl groups, especially at C(5). In both the unsubstituted and the 2-methyl- compounds there is no 370 cm^{-1} band but there is a band at 356 cm^{-1} of sufficient intensity and breadth in

the infrared to be assigned to δ CNC possibly overlapping with another band.

III.3.2. Aromatic Substitution in Thiazolidine-4-carboxylic acids

Tables 4 and 5 list the vibrational spectra of the thiazolidine-4-carboxylic acids prepared by condensation of D-penicillamine and cysteine with benzaldehyde and 2-butanone. There are a large number of bands in the fingerprint region of all infrared and Raman spectra of the thiazolidine compounds under study and vibrational bands for the more significant groups in these molecules are assigned with confidence.

In the 3-benzoyl compounds and in the thiazolidine compounds derived from benzaldehyde there are peaks which result from aromatic ring stretches and from aromatic C-H bonds. These give rise to multiple absorption peaks in the 3100-3000 cm^{-1} region of the spectrum, while aliphatic C-H bonds stretch at 3000 cm^{-1} or lower. For a monosubstituted aromatic ring, carbon-carbon stretching frequencies have been assigned to bands in the regions 1608-1600, 1589-1580, 1495-1490 and 1452-1446 cm^{-1}. Bands at 1240±8, 1177±6, 1156±5, 1073±4 and 1027±3 cm^{-1} have contributions from the bending vibrations of aromatic C-H bonds (75). These bands are present in our spectra and they are slightly sharper than neighbouring bands in the infrared spectra. The reason

TABLE 4: Vibrational Spectra of Substituted Thiazolidine-4-carboxylic Acids Related to D-penicillamine.

2-phenyl-5,5-dimethyl-		2-ethyl-2,5,5-trimethyl-		3-benzoyl-2-ethyl-2,5,5-trimethyl-		Assignments[c]
Infrared[a]	Raman[b]	Infrared	Raman	Infrared	Raman	
3440,14,200		3440,18,300		3470,19,350		ν O-H
3298,56	3285,11	3285,32 }db, 3266,37 shp	3270,10 }db 3250,11			ν N-H
				3200,w,br		overtone
3085,36	3080,13					
3030,44	3033,22				3055,45	ν =C-H
	2978,18	2975,93	2980,92	2986,64		
2965,66	2965,20		2970,100	2974,68 broad wing,	2982,17,db	ν_a CH_3,CH_2
2950,65	2946,12		2960,sh	tailing to 2200 cm^{-1}	2962,32	
2925,64	2930,16	2930,79	2935 }210,db 2926		2932,32	ν_s CH_3,CH_2
2870,58	2880,9	2895,63	2882,64	2887,55	2895,16	
	2853,3		2852,56		2855,9	
	2725,3		2730,11,25			
		2680,52		2680,36		O-H...O bonding
				2565,34		
2490,70,200		2480,68,200		end of wing		O-H...N bonding
				1976,8,br }		phenyl ring overtone
				1900,10		
1900,54,200		1930,57,160				O-H...N bonding
1727,94,50		1720,95,70		1744,87	1740,5	ν C=O
	1700,3		1705,14,45			
1642,w				1656,48		ν N-C=O
	1596,26		1593,5	1608,90 } 60	1600,19	
1580,w	1580,6			1593,48	1588,13	ν C=C
1500,40				1496,40	1572,18	

1455,87	1460,5 1448,4	1455,81	1460,57	1458,sh 1448,65	1460,13,db 1438,19	δ_a CH_3 ν C=C, δ C-H
1426,66	1428,6	1432,36	1410,88	1405,14		
1390,30		1382,68	1380,7,db	1394,sh } 60		δ_s CH_3 (out-of-phase)
1370,60		1371,74	1366,6	1376,73		δ_s CH_3 (in-phase)
1355,95						
1328,100		1324,99,50 1295,70	1325,6,db	1318,50,30 1287,31	1310,6	δ OH
1268,95		1283,100,shp	1280,15	1268,20	1262,9	ν CCN
1240,87			1240,7			
1222,70	1232,11	1232,91,40		1213,69,sh	1210,12	ν C-O
1205,sh	1198,4		1198,17			
1192,56	1183,29	1193,83		1184,89 }70	1200,6 1175,sh	} δ_s CH_3, ν CNC
1162,w	1170,15 1150,19	1177,76	1148,15	1156,sh	1165,18 1140,7	ν_a CCC, τ CH_2
1128,81	1123,6 1115,6	1138,84 1110,100	1135,24 1110,23	1126,76	1118,11 1108,5	ν CCN
1075,55	1076,3			1077,49		
		1038,66	1048,17	1042,42	1040,5	} ν C=C + δ C-H
1025,30	1020,23	1012,w	1032,11	1020,w 1002,w	1025,12	ν C-C, phenyl
	997,100		1000,19,db	998,w	997,100	ring breathing
		987,55		982,w	980,9	
970,30		972,sh		970,30		
958,30	966,8 950,9	962,w 946,sh	968,15 958,21		965,11	
	938,3	938,80	940,21	930,30		} r CH_3,CH_2
922,sh	918,3	920,89 } 50	917,11	918,30		
910,96	908,7			902,35	897,6	ω =C-H
		902,84		885,39	880,5 862,6	

848,40	845,6	847,67 830,w,sh	847,21		845,3	
822,20	824,4	822,w,sh	820,21	806,30	805,5	thiaz. ring breathing
765,82	763,5 752,4	788,10 752,65	785,7 750,13	787,35 755,25	780,12 760,5	r CH_3
727,10	720,27			728,25	738,12	
698,80	698,3		687,4	700,75	690,4	δ phenyl ring
670,sh		670,65	668,15			
660,40	658,5	642,27	640,13	650,50	654,12	δ COOH
627,43	625,5 608,29 596,30 }		630,14 605,98,db	622,50	620,14 600,14 }	ν_s C-S-C
588,52	580,13	583,13	574,79	584,10		δ COOH
564,41	555,11					
		545,24	535,77	538,5	525,10	ν_a C-S-C
490,11		490,30		508,12	500,9	
472,40,db	480,9	479,16 } br 460,16	485,15 472,15	488,10,br	483,5	
447,45	442,3	448,20,db 435,10	452,15,20	442,50 435,35 408,30	435,10 400,6	δ CCC
388,35 382,43 } mt		388,100	383,16	389,45	380,6	δ NCCO
374,43	368,17	368,w 360,18 347,30	370,15	376,47 356,sh	370,6 345,sh	δ CNC

338,55,br	335,3 315,7	333,18 325,12	322,52,25	341,15	335,7	δ $(CH_3)_2CS$ or δ CCS (substituents)
296,45 } db	290,5	300,60		300,w	312,15	δ CCS
288,40		282,sh	285,77			δ NCS
264,20	260,45				260,9,db	
250,w		250,w		254,38		
	240,7	238,20	238,6		232,9	
209,22 }	205,10	201,50		218,15,mt	218,4	
201,50				202,10,mt		
		195,30				
193,52	186,23	189,30	180,22,20	180,5 170,5	178,26	δ CSC
157,55 }	155,23	150,10 140,w	135,20		140,16,db	
148,50		129,10				
	118,32	123,w		121,20		

[a] Infrared data ν, I, Δ: Band frequency in cm^{-1}, intensity relative to strongest band = 100, half width at half maximum in cm^{-1}.

[b] Raman data Δν, I, Δ: Raman shift in cm^{-1}, intensity relative to strongest band = 100, half width at half maximum in cm^{-1}.

Notations: sh = shoulder, db = doublet, mt = multiplet.

[c] ν = stretch frequency, a = antisymetric, s = symmetric, δ = deformation, τ = twist, r = rock, ω = wag.

TABLE 5: Vibrational Spectra of Substituted Thiazolidine-4-carboxylic Acids Related to L-cysteine.

2-phenyl-		3-benzoyl-2-phenyl-		2-ethyl-2-methyl-		3-benzoyl-2-ethyl-2-methyl-		Assignment[c]
Infrared[a]	Raman[b]	Infrared	Raman	Infrared	Raman	Infrared	Raman	
3440,10,200		3420,23,300		3420,12,200		3440,14,180		ν OH
						3220,37,100		overtone
	3060,47	3060,57,520	3067,54			3070,sh,br	3068,sh	
	3042,25		3058,sh					ν =C-H
			3035,10				3055,37	
	3020,13	3030,65	3000,20		3014,37		3015,10	
			2980,13		2990,49	2980,70	2998,10	ν_a CH_3,CH_2
2970,61 } 200	2970,28			2970,85 } 200	2970,38		2983,16	
							2948,37	
2930,59	2960,65	2940,50	2948,23	2940,83	2945,100	2930,63	2933,22,35	ν_s CH_3,CH_2
			2912,14		2900,36			
broad wing					2863,15	2870,61	2875,7	
tailing to			2835,5		2850,13		2853,7	
2200 cm^{-1}					2760,7			
2740,69					2750,7			
2665,65 } 600		2670,28,100		2650,w,br		2570,48		O-H...O
2600,68		2560,25,150		2550,w,br		2505,50,200		bonding
2470,66				2350,55,450				O-H...N bonding
1920,17				1990,43				O-H...N bonding
						1956,14,100		phenyl ring overtone
						1910,13		phenyl ring overtone
1825,4								
		1747,92,shp	1725,5			1733,95,shp	1727,5	ν C=O
1702,sh		1708,sh				1700,70,shp		
		1690,sh						
	1621,15			1625,100,90	1630,7			ν_a COO^-

		1611,98,shp	1620,24			1645,51	1640,3	ν N-C=O
	1596,42		1600,42		1603,7	1607,sh		
							1600,70	δ NH_2^+
		1596,86				1589,100	1582,12	
1572,100	1580,12	1583,78	1583,13			1575,92	1572,14	ν C=C
		1533,43						
1494,60		1492,54	1495,3			1495,47	1490,4	ν C=C
1475,62					1475,12			
					1460,24			
1452,sh	1450,5	1450,59	1452,4	(1447,80)	(1442,33)	(1446,70)	(1455,13)	(δ_a CH_3)
1432,74	1435,12	1435,100,shp	1435,10		1435,35		1438,17	ν C=C, δ C-H
	1428,7							
			1418,11,160			1415,95	1412,13	
1376,77	1380,11			1388,93	1388,25	1375,87	1370,6	ν_s COO^-
				1350,93				
	1330,4	1338,15		1322,98	1330,7	1326,70	1332,4	δ CH + δ OH
							1315,6	
1304,65	1297,10	(1300,20)		1296,sh	1300,15	(1295,39)		δ N-H
	1280,11	1278,15	1277,7	1282,88	1287,16	1270,35	1285,6	
	1257,6	1263,10		1260,sh	1263,7		1260,9	
						1250,sh		
1233,50	1235,10	1240,35	1250,18	1224,53		1233,sh	1222,7,35	
		1212,35	1215,8			1215,86		ν C-O
1207,36	1206,3		1192,26					
1185,sh	1190,36	1175,95,shp	1182,13	1175,64	1178,13	1175,50	1176,7	
			1176,12					
		}Δ=60						
			1168,10	1162,58	1160,13			
1158,10	1157,35	1153,97,shp	1156,22,db			1160,59	1150,10	ν C—C
1135,31	1138,9		1128,3		1130,33		1118,7	} ν CCN
				1112,55	1120,26	1106,33	1108,5	

1072,19	1075,4	1078,50	1075,3	1070,5	1070,28			
1058,22	1060,31			1048,60	1050,14		1040,6 }	ν C=C-H
	1035,26	1030,20	1030,25			1028,37	1025,9	
					1017,18			
1010,60				1018,20	1010,18			
	1000,100	1000,64	1000,100				997,100	ν C--C, phenyl
			990,9			990,28		ring breathing
				975,15	974,27		970,4	
965,15	968,11		963,18		(956,9)	954,28	953,4	r CH_3, CH_2
	930,9	(938,15,br)		949,15	947,10			r NH_2
916,28,db	912,5	920,20	917,3	906,15	906,6		915,3	
882,16	883,4	880,54,shp	887,8		895,11	895,47	890,7	r CH_2, ω =C-H
							880,5	
852,60		861,15		865,44	867,11		860,sh	
				850,sh	852,13		848,3	
			843,7	838,62	839,15	828,29	825,3	
805,40	812,9	820,25,db	816,7	804,57	810,40	806,14		thiaz. ring breathing
	790,34	789,sh	790,34		787,5	790,12		δ =C-H (out-of-plane)
		771,79 }	778,5					
760,70	763,10	759,71 }	758,10			765,46	765,10	r CH_3, CH_2
			740,15			732,54		
		730,45	728,13				723,6	
710,35	712,30	713,78	710,15		718,72	710,33	708,15	δ C--C-H
		702,89 }						
		695,96						
688,75	700,33		700,11			688,68	662,8	ν_s C-S-C
		666,sh	660,3		660,35			
		655,30						
640,38	647,6					656,53		δ C=O
		636,50	630,8	628,73 }	630,sh	636,33		
610,39	612,31		616,27	615,72	620,37	616,45	620,13	ν_a C-S-C
		606,45	598,7		600,18	607,37	608,12	δ COOH
583,31	580,13			580,30		565,12		

				542,68	540,11	550,13	546,9
528,30	520,10	528,16	532,5	525,67	522,11	538,12	δ COO^-
		512,15	510,7	507,50	502,13		
500,34	497,10	495,20	490,10		497,11		
456,50	450,7	455,40		467,45 }db	462,10 }db	460,55	452,6 δ CCC
				445,55	448,8		
			413,18		420,w	420,20	
406,sh }	404,3	406,20			405,w	406,13	405,5,db δ C--C-H
388,575	390,3	387,20	373,5	388,45	384,25	384,52	387,3 δ CNC
		356,25	360,5	354,58	355,23	367,sh	
325,25	324,10	320,20	330,5		337,19	337,5	333,5 δ CCS
					323,19	329,w	
304,10	300,8						
			278,18	275,55	277,10,br	277,16,br	δ NCS
264,25	257,14	264,15					
			240,25			240,w	248,8
			222,28			224,25,db	
201,30		201,18	200,16		200,8		218,8
199,10 }db	190,14	192,12,db		181 }20,db			180,22,db δ CSC
189				175			
172,33		172,22	172,53				
157,w							
149,23	145,sh	149,14	140,sh	150,30			140,15
131,18		131,10				137,12	
	120,5				121,62		
					103,90		

a,b,c Footnotes as for Table 4.

for the wider frequency ranges than in benzene alone is that in these molecules there are both phenyl and benzoyl groups contributing to the bands. Bands around 1600 cm^{-1} have been observed in some cases to be a doublet of 1620-1585 cm^{-1} with a weaker band at 1590-1565 cm^{-1}, which is not always detected. In the compounds discussed here the second band is not observed except in the Raman spectrum of a few compounds. Medium-strong bands at 751±15 and 697±11 cm^{-1} are also characteristic of monosubstituted rings. The frequencies of these bands are variable because of the interaction with out-of-plane ring bending. Raman bands expected for monosubstituted benzene rings are 1620-1565, 1005-990 (very strong), 625-605 and 415-400 (very weak) cm^{-1} (75), all of which are observed and listed in Tables 4 and 5.

All of the compounds in Table 5, including the two 3-benzoyl derivatives, are carboxylic acids having C=O stretching frequencies around 1725 cm^{-1}.

2-Phenylthiazolidine-4-carboxylic acid and 2-ethyl-2-methylthiazolidine-4-carboxylic acid are zwitterions; there are no bands in the C=O region of 1740-1725 cm^{-1} or in the C-O region (1215-1190 cm^{-1}). However, ν COO^- stretching bands are very intense in the infrared at 1625 cm^{-1}, although weaker in the Raman at 1630 and 1603 cm^{-1}, for 2-ethyl-2-methylthiazolidine-4-carboxylic acid. 2-Phenyl-thiazolidine-4-carboxylic acid has carboxylate stretching

bands at 1572 cm^{-1} in the infrared spectrum. This is an unusually low frequency, probably caused by the proximity of the phenyl group; there are three Raman bands between 1621 and 1580 cm^{-1}. The symmetric vibrations of COO^- in both zwitterions are assigned to the bands at 1388-1376 cm^{-1}.

The amide C=O band was assigned to 1660-1620 cm^{-1}, typical for disubstituted amides.

The C-S stretching frequency has been assigned in D-penicillamine and D-dimethylcysteic acid to 548 cm^{-1}, a very strong Raman band. In L-cysteine it has been assigned to 678 cm^{-1} (71) and it has been concluded that substituents on carbon atoms adjacent to sulfur cause a decrease in the stretching frequency of the C-S bond (71), as previously discussed. Bands in the region of 680 and 600 cm^{-1}, Table 4, 630 and 540 cm^{-1}, Table 5, are so assigned.

Thiazolidine ring modes have been assigned as follows: 1150-1140 cm^{-1} arise from CCN stretches; 380, 330 cm^{-1} and 191 cm^{-1} bands result from CNS, NCS and CSC deformations, respectively. Deformations involving sulfur usually have been found to be intense in the Raman, and showed isotopic shifts caused by the adjacent CD_3 groups in tetramethylthiazolidine-4-carboxylic acid prepared from deuterated acetone (62).

III.3.3. Other Thiazolidine Ring Compounds: Esters and Alcohols

Table 6 summarizes the vibrational spectra of

TABLE 6: Vibrational Spectra of Derivatives of 2,2-Dimethylthiazolidine-4-Carboxylic acid.

3-benzoyl-4-carboxy-		3-benzoyl-4-methoxy-carbonyl		3-benzoyl-4-hydroxymethyl		Assignment[c]
Infrared[a]	Raman[b]	Infrared	Raman	Infrared	Raman	
		3480,10				
		(3270,20)		3320,db,69,280		ν O-H (overtone)
	3064,43	3063,21	3065,39	3064,26	3070,18	ν =C-H
		3042,25	3036,14		3057,38	
3000,74,550	3013,18	3010,35,300	3004,12			
	2988,21	2982,46	2990,15	2980,48	2987,58	ν_a CH_3,CH_2
wing,	2968,22	2960,42	2980,24		2975,30	
3500-2200cm^{-1}	2950,sh		2954,46			ν_s CH_3,CH_2
	2938,29	2938,40	2933,34	2930,54	2932,18	
	2882,7	2880,sh	2882,8	2885,47	2868,20	ν C-H
		2850,sh				
2780,51						
2695,45						
2580,43						
2510,36						
1976,6,db		1976,w,db				phenyl overtone
1908,6						
1740,100	1735,6	1750,100,30	1745,6			ν C=O
		1710,10				
1650,75		1640,100,100	1637,22			ν N-C=O
1595,99,db	1602,68	1604,30	1600,33,shp	1600,100,110	1606,42	ν C=C
					1595,72	
1588,94		1580,33	1576,11		1576,28	ν C=C
1535,sh						
1492,30	1490,5	1495,35		1492,30		ν C=C
				1479,39		
1464,20		1465,52	1462,10	1458,57	1460,22	δ_a CH_3
1446,40	1447,12	1446,67	1438,20	1442,40	1443,23	ν C=C
1432,30	1432,14	1440,72				
1395,91 } 60	1400,15,35	1388,100,60	1385,9,db	1386,100,60	1395,21	δ_s CH_3 (out-of-phase)
1380,88		1375,sh		1370,94		δ_s CH_3 (gem, in-phase)
1363,50	1365,5	1360,70				

1320,20		1333,71	1332,6			δ_s CH_3,CH_2
1312,30	1313,7	1285,40	1286,6	1285,40	1304,10	ν C-N
1268,w	1270,6			1260,49		
		1225,95,40	1223,25			ν C-O, ester
1202,90	1215,21			1202,60	1220,45	ν C-O, acid
1174,74	1182,16	1180,53	1183,14		1173,22	ν C=C + δ CH
1156,77	1157,23	1163,78	1160,14	1166,68	1160,20	ν_a CCC, τ CH_2
	1135,3					
1125,30	1120,8	1130,40	1120,11	1125,44	1122,17	
	1112,6		1115,7	1115,43	1115,13	ν CCN
1074,20		1067,10		(1053,80,br)	(1060,17)	(ν C-O, alcohol)
					1035,sh	ν C=C + δ C-H
1025,20	1026,16	1023,20	1027,14	1028,52	1026,35	
1016,47	1015,11					
1002,37	1000,100	1002,59	1008,sh	1000,sh	1000,100	ν C=C
	995,sh	997,64	998,100		987,sh	
948,20	942,12,br		943,8,db		927,17	r CH_3
933,32		920,27	919,13	910,55	910,15,db	
891,58	890,12	888,65	888,20	878,38	880,14	r CH_3,CH_2
				852,15	853,10	
835,43,br	830,6,db	843,26	847,5,db			
822,33		812,51	813,6,db			
			811,6,db			
799,48	802,7				793,18	
772,57	773,16	773,64	777,13	777,49	787,sh	
					755,9	
733,62	738,7	753,10		735,68	737,8	δ =C-H, in phase, out-of-plane
711,20	718,54	715,10	715,45		717,50	ν C-S
702,30	700,sh	698,73,shp	700,8	697,71	702,13	phenyl ring bend
690,65,shp				678,43,sh	680,15	
660,30	665,18	670,20	672,14			
	628,23	624,49	628,35	622,52	629,48	ν_s C-S-C
620,40	615,28,shp	612,49	615,29,shp	608,30,sh	615,46	phenyl ring
608,34						δ COOH
600,34			586,5			
572,28	585,11	570,13	570,5	582,30	578,6	
530,10	532,5	545,36	540,6	550,20	548,15	
512,sh	513,7			516,27	514,16	
		502,6	500,9			
458,15	460,8	463,10	463,5	463,30	465,6	δ CCC
440,19				460,28		

430,30	430,10,db					
	418,6			420,30	418,39	δ C-O-H, alcohol
405,20	404,10	413,27	410,25	405,18	404,18,shp	
377,50		380,32	380,3	386,15,db	385,16	δ NCCO
372 367 } 23	363,8,30	364,55,db	363,5	369,50,br	364,18,16	δ CNC
348,21,db	350,7	350,40	348,9	353,15,db	353,14	δ OCO
330,23 }						δ $(CH_3)_2$ CS
325,sh						
315,sh	316,4,20	322,w,sh		313,sh	312,18	δ CCS ring
302,10		306,8	305,9	306,23		δ CCS ring
273,17						δ NCS
267,15		282,15		275,11	273,16	
257,15,db	250,13		248,18	251,17	255,21	
				242,sh		
218,30						
205,sh	200,21	209,51	207,23	214,sh	214,35	
188,10 }		189,15 }	202,21	190,15		δ CSC
184,10		184,15				
160,sh		179,sh				
156,50	150,25	124,21		140,24		
150,50		118,16	114,vs			
124,20						
117,20						

[a] Infrared data ν, I, Δ: Band frequency in cm^{-1}, intensity relative to strongest band = 100, half width at half maximum in cm^{-1}.

[b] Raman data Δν, I, Δ: Raman shift in cm^{-1}, intensity relative to strongest band = 100, half width at half maximum in cm^{-1}.

Notations: sh = shoulder, db = doublet, mt = multiplet.

[c] ν = stretch frequency, a = antisymetric, s = symmetric, δ = deformation, τ = twist, r = rock, FR = Fermi Resonance.

substituted derivatives of 2,2-dimethylthiazolidine-4-carboxylic acid. Many of the spectral characteristics common to thiazolidines have already been discussed. Special features in the spectra shown in Table 6 are a result of the presence of three different functional groups bound to C(4) of the thiazolidine ring: a carboxyl group, a methyl ester and a primary alcohol. The carboxylic acid has a very strong absorption band at 1740 cm^{-1}. Carboxylic acid monomers absorb at 1760 cm^{-1} and hydrogen bonding causes a decrease in the stretching force constant of C=O weakening the bond, causing a decrease in the stretching frequency.

The carboxyl group of esters absorbs at higher frequencies than carboxylic acids, compare 1750 with 1740 cm^{-1}, because the singly bonded oxygen is electronegative and draws electron density from the oxygen atom of the carbonyl to the double bond, strengthening it. Amide carbonyls absorb at wavenumbers below 1700 cm^{-1} because the nonbonding electron pairs in the nitrogen atom can conjugate with the carbonyl, resulting in increased single bond character of the C=O bond and lowering its stretching frequency. The amide ν C=O was assigned to 1650-1640 cm^{-1} but it is only about 1600 cm^{-1} in 3-benzoyl-2,2-dimethyl-4-hydroxymethylthiazolidine, probably because of the absence of stabilizing resonance and the inductive effects of the neighbouring CH_2OH group. The intense absorption band at 1360 cm^{-1} was assigned to the bending frequency of the

methoxy group of the ester.

Alcohols are hydrogen bonded structures which absorb strongly near 3300 cm^{-1} because of the stretching of O-H...O bonds. The C-O stretches of alcohols are fairly intense bands at 1075-1000 cm^{-1}, caused by asymmetric CCO vibrations.

Out-of-plane C-O(H) deformations in the bonded state absorb near 650 cm^{-1} with a broad band. The in-plane C-O(H) deformation is too complex to identify because of interaction with hydrogen wagging vibrations in primary alcohols. There are in these compounds associated bands near 1420 and 1330 cm^{-1} caused by δ O-H and by δ C-H deformations, respectively.

Aromatic carbon-carbon bond stretches and C-H bends have been assigned to frequencies similar to those discussed in Tables 4 and 5. C-S bands have been assigned to frequencies of approximately 570 cm^{-1}.

Table 7 lists the vibrational spectra of N-benzoylated acids derived from D-penicillamine. The carboxylic acids have C=O stretching bands at 1745 cm^{-1} and the esters at 1745 and 1732 cm^{-1}, only slightly lower, perhaps because of inductive effects by the methyl group. The carboxylic acids listed in Table 7 have strong hydrogen bonds as indicated by the broad bands around 3000 cm^{-1} rather than at the higher frequency of 3400 cm^{-1} as previously observed for weaker hydrogen bonds. There is evidence also of some degree of

TABLE 7: Vibrational Spectra of Derivatives of Thiazolidine-4-carboxylic Acid Prepared from D-penicillamine

3-benzoyl-5,5,-dimethyl-		3-benzoyl-4-methoxy-carbonyl-5,5-dimethyl-		3-benzoyl-2,2,5,5-tetramethyl-		3-benzoyl-4-methoxy-carbonyl-2,2,5,5-tetramethyl-		Assignment[c]
Infrared[a]	Raman[b]	Infrared	Raman	Infrared	Raman	Infrared	Raman	
		3595,14						
3490,25 } 200		3450,14		3480,w		3490,13,200		
3420,25 }		3405,15						
		3270,12				3300,11		ν OH overtone
3060,46	3066,40	3060,26	3070,51	3065,75	3067,30	3090,w,sh	3068,36	ν =C-H
	3035,16		3060,sh	3040,74,550			3045,sh	
wing, 3600-2200 cm^{-1}			3030,8	wing 3500-2300 cm^{-1}	3052,sh		3010,sh	wing, OH...O bonding
	3003,16	2995,36	2993,12		2990,15	2990,51	2996,26,db	ν_a CH_3,CH_2
	2975,22	2970,71	2968,39	2980,75	2980,15	2978,48	2970,28	
(2960,45,400)	2965,22					2954,44,db	2953,35	ν_s CH_3,CH_2
	2945,38		2942,19,db				2945,34 }	
	2928,32	2920,38	2925,18,db		2933,13	2925,44	2915,sh	(O-H...O)
		2908,37	2907,24					
		2870,27	2878,9					
			2862,sh					
2600,38,br				2690,38,br		2860,sh		O-H...O bonding
		2015,4		2560,34	2675,7			
		1975,6		1975,11				
		1905,5		1915,10,db				
		1828,13		1825,10				
				1790,sh				
1745,62		1732,100,30	1730,7	1745,100,30		1745,100,25	1743,14	ν C=O
1715,68	1705,6			1702,sh		1703,10		
1695,66		1690,38						
1640,70	1630,40	1635,100,80	1635,34			1657,97,30	1650,32	ν N-C=O
1605,68		1603,75	1600,51	1612,95	1605,25	1615,sh	1600,33	ν C=C
						1603,30		
1590,sh	1597,32	1580,70,shp	1578,19,shp	1596,97	1578,13	1580,16	1578,15	ν C=C doublet
1578,56	1572,10			1570,85,sh				
1538,sh								
1530,40		1520,10		1520,10				

1498,40 1488,45		1495,60,shp	1495,6	1498,15		1490,39	ν C=C
	1463,11	1465,sh	1467,13	1470,20		1465,55	1460,16 1450,sh	δ CH_2
					1458,10		
1450,66	1444,8,db	1450,80	1452,12	1448,80		1440,72	1442,19	δ_a CH_3
1430,70	1438,8	1430,60	1438,11	1438,20	1438,10			
1418,78				1410,94				
1390,80	1385,12	1385,96	1384,17	1390,92 1380,92	1390,10	1389,78		δ_s CH_3 (gem)
							1375,9	
		1368,86				1368,97,db		δ CH_3 ester
1370,sh				1360,81,shp	1360,20			δ_s CH_3 (gem)
				1340,10		1357,sh	1340,13	
1328,66		1324,70	1323,6	1325,75		1338,90		δ OH
1290,70		1302,65	1295,4	1308,20				r CH_3, ν C-N
		1268,94	1280,6	1278,54		1272,52	1274,13	r CH_3
1242,30								δ C--C-H
		1220,55	1220,9			1218,82	1230,9	ν C-O ester
1214,40,br	1210,10			1216,60,db	1215,20			ν C-O acid
		1204,80	1203,16			1204,80		ν_a C-C $(CH_3)_2$
		1182,30	1180,10		1188,7	1184,77		
1175,70				1173,100	1175,8			δ C=C-H
		1162,20	1162,16		1160,10	1166,76	1165,19	
							1155,12	
1140,50		1134,83	1140,13	1143,sh		1143,sh	1142,12	ν_a CCC
1126,sh	1122,7		1122,10	1125,60,db		1132,61		ν CCN
						1114,51	1118,9,db	r CH_3
		1088,49						
1074,30				1073,20		1072,20		
1028,35	1029,10	1025,79	1028,14	1030,20	1030,8	1028,sh	1028,17	δ C=C-H, δ C-H
		1017,89	1012,sh	1019,sh		1020,52	1018,9	
1002,48	1007,22	1010,79	1000,100	1000,100	1000,69		1000,100	ν C--C, phenyl
	998,100			988,49	990,sh	992,58		ring breathing
	966,7		976,4	970,38	960,37	960,12		
			946,9					
934,40		934,35	933,6	935,42,db		930,sh	932,32	r CH_3
920,40	924,6	924,35	923,4	926,30	917,5	922,15		r CH_3,CH_2
				915,30				
						907,45	910,10	
						902,sh		
	872,17 867,6	880,40 868,sh	878,11 862,3	892,30 858,30	857,11	855,14	860,10	r CH_2

848,30	846,16 817,12	832,20	833,10	820,47			830,10	ring breathing (thiazolidine)
795,60	797,18	794,60,shp	795,10	792,70				
782,50	778,30	782,sh 775,50	783,45 776,28			780,52 765,50	788,11 766,13	δ =C-H (out-of-plane) r CH_3,CH_2
750,68	748,14,br	757,52 722,85,shp	758,19 723,3	750,70 720,47				
708,100		695,85,shp	700,3	698,80		698,75		δ phenyl ring
680,70,db		675,34	677,4			682,45,shp	687,12	
664,78	668,4							
648,84	648,10	650,70,shp	653,13	648,70 623,60,shp	652,14 628,15	620,55,shp	626,48	
	617,28	610,51	615,71		615,22		617,55,db	ν_s C-S-C
605,64	606,22,br			602,20	608,sh	605,25		phenyl ring bend
558,34				573,20		569,5	575,9	
524,18		522,20	519,9	515,sh 500,33	512,11	505,28	510,34	ν_a C-S-C
454,26		460,38	460,4			470,9	470,17	
436,16,db	442,8	438,50	435,18	427,11	430,11			δ CCC
							412,34	
409,48	404,8	404,22	404,13	401,13		402,24	405,26	δ C=C-H (out-of-plane)
		396,10	393,4				390,10	δ NCCO
386,50		379,54,db				385,16		δ CNC
363,32	361,19	363,30		356,50	358,6	361,30		δ OCO
347,12		355,sh	353,27	346,38		346,70	347,13	
332,20,db	320,8			332,30	322,9	331,35	330,15	δ $(CH_3)_2CS$
		311,20	308,14	312,20			320,21,db	δ CCS
293,sh								
289,64		280,10	282,6	295,w		285,20,db		δ NCS
276,sh				274,8		278,sh		
		265,10	264,9					
			253,14	254,sh		256,22	260,13	
	253,8	255,21		251,22		250,sh		
235,sh				243,23	243,15	241,10	243,12,db	
212,50	214,8	216,30	218,9	216,36	220,7	218,12		
204,53						206,30	204,6	
200,sh	195,6	182,35,db	185,26,db	182,20,db	184,30	189,25	192,27	δ CSC
191,10								
183,10								
175,10								
		178,sh		172,sh				
168,s	167,9			152,12				
	143,50		142,sh	143,12			132,sh	
	120,12							
	115,22		114,sh	116,34,db				

a,b,c Footnotes as for Table 6.

hydrogen bonding in the 2,2,5,5-tetramethylthiazolidine methyl ester, which has a broad band at 3490 cm^{-1}, typical of weak hydrogen bonds.

The carboxylic acids in Table 7 have unusually high frequency C=O stretching bands of 1745 cm^{-1} instead of within the usual frequency range of 1730-1700 cm^{-1}. Ring strain and steric hindrance by the thiazolidine ring substituents may be responsible for this effect, an effect also observed for cyclic ketones.

Amide carbonyl stretches were identified at 1650-1635 cm^{-1}; these frequencies are within the normal values for amide C=O stretches. C-O stretching frequencies at 1230-1214 cm^{-1} are present in all four compounds in Table 7. Out-of-plane bending vibrations of the O-H group of the carboxylic acids are normally low to medium intensity bands at approximately 930 cm^{-1}, and may overlap in these compounds with bands of the methyl group rocking vibrations.

The abundance of geminal methyl groups in these compounds gives multiplets of absorption bands in the infrared and Raman spectra, especially in the thiazolidine esters. In the carboxylic acids many of these bands can not be seen because of strong and broad hydrogen bonding bands in the same frequency range. There is a large number of methyl group deformation bands in the frequency region of 1390-1200 cm^{-1}, some of which are caused by the geminal methyl groups while others result from the methyls vibrating

in-phase and out-of-phase, and from methyl rock motions.

Thiazolidine ring deformations, and absorption bands caused by aromatic group vibrations, were assigned as in the tables of thiazolidine compounds of similar structure previously discussed.

III.3.4. Special Case of a Protonated Dimer

The infrared and Raman spectral bands of bis((S)-5,5-dimethylthiazolidine-4-carboxylic acid) protium chloride hydrate (XXIII) are listed in Table 8, see Fig. 3, p. 132. Many of the bands are assigned by comparison with the spectra of methyl-substituted thiazolidine-4-carboxylic acids, discussed above. A broad band at 3360 cm^{-1} (infrared) is typical of a weak hydrogen bond (O...O = 2.77 Å) and is assigned to hydrogen-bonded lattice water. The broad wing at 3100-2600 cm^{-1}, with multiple peaks on the low frequency side, is typical of these secondary aminoacid compounds having zwitterion form, and includes absorption from symmetric and asymmetric stretching vibrations of the NH_2^+ group which is hydrogen bonded to the lattice water molecule. There are also ν_a and ν_s bands of the CH_2 and CH_3 groups superimposed on the broad absorption wing. The 2700-2300 cm^{-1} bands are combination bands. The N-H...O bond lengths of 2.89 and 2.82 Å correlate with absorption frequencies of about 3100 cm^{-1}. The carboxylate bands of the hemi-protonated groups are intermediate between those of

Table 8: Vibrational spectra of bis((S)-5,5-dimethylthiazolidine-4-carboxylic acid) protium chloride hydrate

Infrared[a]	Raman[b]	Assignments[c]
3360,70,200		OH...O bonding, lattice water
3017,95	3012,40	maximum of wing (3100-2700)
	2992,50	ν_a CH_3
	2980,100	
2973,100	2950,40	ν_a CH_3, CH_2
	2940,50	ν_s CH_3, CH_2
2920,90	2910,40	ν CH
	2868, sh	
2840,80, br		NH...O bonding
	2735,10	
2700,80		
2605, sh		
2568,80	2570, w, br	combination bands
2530, sh		
2490,70		
2400, 45		
2320,20		
1727,90,55		ν_a CO_2^-
1692,100,60	1690,w,br	
1454,35	1468,40	δ_a CH_3
	1440,25	
1385,45	1395,6	δ_s CH_3, out-of-phase
1368,50	1372, w	δ_s CH_3, in-phase
	1335,10	
1305,35,60	1295, w	ν_s CO_2^-
1250,20		τ NH_2^+
	1216,6	
	1201,20	
1152,20	1155,15	r NH_2^+, ν CCN
1125,25	1130,18	ν CCN
1030*	1040,8	* very broad band, 1100-500, max. intensity 70 at 800 cm^{-1}, other peaks superimposed

Infrared[a]	Raman[b]	Assignments[c]
1000, br	1005,18	
	982,15	
	951,16	
	942, sh	
	930,15	
910,70,br	918,w	ν_a OH...O, strong hydrogen bond
	825,12	
	808,10	
	771,20	r CH_3, CH_2
765	760,10	
	738,27	
658	670,15, br	
	612,55	ν C-S
	598,40,35	ν C-S
	505,22	ν C-S
470,20		
	443, w	
	385,10	
373,s	369,20	δ CNC
337,m	337,10	δ $(CH_3)_2CS$
320,m		δ CCS
306,m	305,18,db	ν_s O...H...O
296,m		
273,m,br	275,w	δ NCS
240,w		
	230,19	
207,s		δ CSC
189		
175		
168		
165	150,br,w	

[a,b,c] Footnotes as for Table 2
Notations: s = strong, m = medium, w = weak, br = broad, sh = shoulder.

carboxylate and carboxylic acid structures.

The most unusual feature of the spectra in Table 8 occurs in the infrared in the region below 1100 cm^{-1}: there is a very broad band, 1100-500 cm^{-1}, centered at around 800 cm^{-1}, with other peaks superimposed on it. This broad band was not present in the 5,5-dimethylthiazolidine-4-carboxylic acid made with formaldehyde, nor indeed with our other substituted thiazolidines. This band is assigned to the antisymmetric stretching frequency of the very strong hydrogen bond, O(1)...O(2)', 2.450(5) Å long, which links the dimer through the carboxylate groups. The Raman band at 305 cm^{-1} is assigned to the symmetric stretching frequency of this hydrogen bond.

III.3.5. Hydrogen Bonds in Thiazolidine Compounds

Characteristic O-H stretching bands are present in the infrared at 3460-3400 cm^{-1} for all compounds containing COOH functional groups. There are also fairly intense broad bands at about 3000 cm^{-1} for some of the compounds as well as distinct bands between 2500 and 1940 cm^{-1}. These broad absorptions at lower frequency are a result of moderately strong hydrogen bonds in some of these compounds. In L-cysteine and D-penicillamine the hydrogen bond absorptions are so strong that they mask the CH_2 and CH_3 absorptions almost completely (71).

Three types of hydrogen bonds can occur in

thiazolidine-4-carboxylic acid derivatives: O-H...O, O-H...N and N-H...O bonds. The first type can be much shorter than the other two; therefore it absorbs at lower frequency, normally in the region of 3400-3100 cm^{-1}. Hamilton and Ibers (76) have discussed correlations between the frequency of anti-symmetric stretching modes and the O...O or N...O distance in such bonds. A lowering of OH frequency correlates with a lower force constant and a longer OH bond. The O-H bond length actually increases as the O...O bond length decreases. Thus lower O-H stretching frequencies correlate with formation of stronger O-H...O hydrogen bonds. Increase of band width and intensity enhancement occur simultaneously. Similar effects are observed for both O-H...N and N-H...O bonds.

Hydrogen bonds of the type O-H...O are expected to have infrared bands between 3500 and 2600 cm^{-1} for O...O distances of 2.90 to 2.60 Å, as it was observed with bis(5,5-dimethylthiazolidine-4-carboxylic acid)protium chloride (XXIII), 2,2-dimethyl- (III) and 3-benzoyl-2-phenylthiazolidine-4-carboxylic acid (VIII). Hydrogen bonds between nitrogen and oxygen atoms have lower stretching frequency bands of 2600-1900 cm^{-1}, see Tables 2 and 5. All compounds in Tables 4 and 5 show hydrogen bonding bands in the range 3450-3000 cm^{-1}. Some compounds show splitting of bands and others have additional absorption bands at lower wavenumbers. These observations imply that there are

moderate O...O hydrogen bonds, in the range of 2.88 to 2.60 Å (76), for example compound VIII, see Section III.5. Hydrogen bonds of the O-H...N or the N-H...O type only exist for the non N-benzoylated compounds, and are characterized by two bands in the regions 2500-2350 cm^{-1} and 1990-1900 cm^{-1}, as observed previously for tetramethylthiazolidine-4-carboxylic acid (71).

In general, ν OH frequencies are more difficult to assign for very strong O-H...O bonds than for weak or medium ones, because as the O...O distance becomes shorter, the ν OH band in the infrared spectrum becomes less prominent--lower in frequency, weaker in intensity and ill-defined in shape. However, plots of ν OH vs. O...O distance show good correlation for weak hydrogen bonds and a reasonably good one for stronger hydrogen bonds. For a number of compounds containing strong hydrogen bonds, ν OH is in the range 1800-700 cm^{-1}. In particular, the centred hydrogen bonds of acid salts of carboxylic acids have ν OH below 1000 cm^{-1} (77). Thus there are precedents for the unusual assignment of the Raman band at 305 cm^{-1} to ν_s O-H of XXIII.

Moreover, our data for XXIII show a parallel with data for sodium dihydrogen diacetate and its deuterated derivatives discussed by Novak (77) as an example of the special case of a symmetric, single-minimum potential for a short hydrogen bond. For that compound, the frequencies 720 (510), 1540 (1150), and 1285 (960) cm^{-1} were assigned to

ν OH (OD), δ OH(OD) and γOH(OD). In addition, the ν_s O...O band was observed in the Raman spectrum at 320 cm^{-1}.

For further discussion of hydrogen bonds refer to the section on crystal structures of hydrogen bonded thiazolidine compounds, Sections III.6. and III.7..

III.4. Nuclear Magnetic Resonance Spectroscopy

"Proton nmr has been the most powerful method for the study of conformational analysis in the past twenty years" (Levy and Nelson) (78). It is a very popular technique because of the relevance of the information it provides. The proton nucleus is perhaps the best suited for this purpose because of its high natural abundance (99.98%), high sensitivity and spin of 1/2, which gives simple spectra. Besides all these obvious advantages there is one more of great importance: hydrogen is ubiquitous in nature and therefore it makes the technique extremely useful in organic compound analyses.

The proton nmr spectra and assignments of the methyl substituted thiazolidine-4-carboxylic acids are given in Table 9. The non-methylated compound has the simplest spectrum with the C(2) hydrogens giving rise to a singlet which indicated both protons have the same average chemical environment. The downfield signal is the hydrogen at C(4), which is next to an electron withdrawing carboxyl group having a deshielding effect; the signal is split into a

TABLE 9
^{1}H nmr spectra of methyl substituted thiazolidine-4-carboxylic acids[a,b,c]

Compound	H(C-2)	H(C-4)	H(C-5)	CH_3(C-2)	CH_3(C-5)
Thiazolidine	4.35,s,10	4.40,dd,5	3.32,m,10	-	-
2-Methyl-	4.60,q,6	5.05,t,6	3.50,m,12	1.73,d 18 1.76,d	-
2,2-Dimethyl-	-	4.77,dd,3	3.45,d 8 3.50,d	1.70,s,18	-
5,5-Dimethyl-	4.45,s 12 4,50,s	3.95,s,7	-	-	1.42,s,21 1.68,s,21
2,5,5-Trimethyl-	4.90,q,5	3.94,s 5 4.02,s	-	1.58,d,14	1.37,s 28 1.63,s
2,2,5,5-Tetramethyl-	-	4.2,s,44	-	1.76,s,16 1.84,s,18	1.43,s,18 1.68,s,17

[a]Solutions in D_2O with TSP as the internal standard
[b]The chemical shift in ppm is followed by the peak multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and by the integrated peak area
[c]For coupling constants see Table 9A

TABLE 9A
Coupling constants of methyl substituted thiazolidine-4-carboxylic acids[a]

Compound	$^{2}J_{H\text{-}C5,H\text{-}C5}$	$^{3}J_{H\text{-}C5,H\text{-}C4}$	$^{3}J_{H\text{-}CH_3,H\text{-}C2}$
Thiazolidine	5.2	2.6	--
2-Methyl-	5.6	2.6	6.0
2,2-Dimethyl-	7.9	4.0	--
5,5-Dimethyl-	--	--	--
2,5,5-Trimethyl-	--	--	7.8
2,2,5,5-Tetramethyl-	--	--	--

[a] J values are in Hz; ^{1}H nmr spectra recorded at 25°C

doublet of doublets by the two neighbouring protons on C(5). The signal of the C(5) proton is upfield; the two C(5) protons have slightly different chemical environments because of their proximity to the carboxyl group; each proton gives rise to a doublet as a result of splitting by the vicinal proton on C(4).

2-Methylthiazolidine-4-carboxylic acid is a mixture of two diastereoisomers in the ratio of 4:5; C(4) is a fixed chiral center, derived from L-cysteine in this case and with the same R conformation, but there is a new chiral carbon, C(2) which can be R or S. The lowest field triplet is the C(4) hydrogen. C(2)-H is split into a quartet by the methyl group attached to the same carbon. The C(5)-H signal, of chemical shift 3.5 ppm, is a multiplet because it results from two overlapping doublets of doublets, which arise from splitting by the C(4) proton and by the geminal proton. The methyl group on C(2) gives a doublet and there are two such signals because the methyl group can be on the same side of the ring as the carboxyl group or on the opposite side.

The two methyl groups of the 2,2-dimethyl compound give only one singlet in the spectrum, therefore they have equivalent chemical environments. They are situated far enough away not to be affected by the carboxyl group, but the two C(5) protons, both doublets of doublets, give rise to two distinct signals, split by the C(4) proton and this is in turn split by the other C(5) proton, resulting in a

quartet of peaks of equal intensity. For the C(4) proton a triplet is observed instead of a doublet of doublets.

It is not surprising that the two protons on C(2) of the 5,5-dimethyl compound are two different signals in the spectrum. The two methyl groups should and do appear as two singlets because there is no plane of symmetry in the molecule, and the chemical shifts are very distinct.

2,5,5-Trimethylthiazolidine-4-carboxylic acid has two chiral centers, and can exist as two diastereomers (S,R or S,S) in any proportion. Two sets of resonance signals for each type of proton in the molecule are expected; however, only one signal was observed for the C(2) proton and another one for the methyl group.

The nmr spectrum of 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid is as expected. It consists of five singlets, one for each methyl group and one for the single proton bonded to C(4). The methyls on C(2) are the downfield singlets because they are more deshielded by the S and N, the first of which is electron withdrawing. This assignment was confirmed previously by deuteration of the C(2) methyl groups (62).

All the C(5) methyl groups in Table 9 have very consistent chemical shifts, generally to high field of the C(2) methyl groups.

NOE experiments have been carried out with derivatives of penicillin to study thiazolidine ring conformation (79),

and have shown that the pro-R methyl hydrogens are always at higher field than the hydrogens of pro-S methyl groups. By analogy the 1.68 ppm peak in the spectrum of 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid is assigned to the pro-S methyl of C(5) and the 1.43 ppm singlet to the pro-R methyl protons. A study of erythro and threo stereochemistry of five membered rings by proton nmr lists also the spectra of the 2,2,5,5-tetramethylthiazolidine compound and their assignments agree with those above (80).

Carbon-13 nmr spectroscopy is also very useful in structure determination because ^{13}C chemical shifts reflect not only the electronic environment at a carbon nucleus but also steric and conformational effects in a molecule. Generally proton decoupled carbon-13 spectra are obtained. Otherwise large carbon-hydrogen coupling makes the spectra of all but the simplest organic compounds very difficult to interpret, because of a high degree of peak overlap. Proton decoupling enhances carbon signals because of the nuclear Overhauser effect and it gives simplified spectral patterns. Table 10 shows the carbon-13 shifts observed for the same set of compounds listed in Table 9. In all the compounds listed in Table 10, C(4) is the most deshielded carbon, next to the carbonyl carbon to which it is directly bonded. The oxygens on the carboxyl group have a strong deshielding effect not only on the carbon to which they are attached but also to a lesser degree on neighbouring carbon atoms. C(2)

TABLE 10

^{13}C chemical shifts of methyl substituted thiazolidine-4-carboxylic acids[a,b]

Compound	C-2	C-4	C-5	C(OOH)	CH_3(C-2)	CH_3(C-5)
Thiazolidine	50.00	65.30	34.29	173.14	-	-
2-Methyl-	62.04 62.57	64.84 65.60	33.99 34.20	172.89	19.80 18.85	-
2,2-Dimethyl-	63.52	55.63	32.81	171.36	25.04 27.85	-
5,5-Dimethyl-	53.84	73.08	46.87	170.16	-	26.45 28.26
2,5,5-Trimethyl-	58.38 58.83	73.29 74.51	54.18 54.84	170.86	28.49 30.94	26.79 28.14
2,2,5,5-Tetramethyl-	73.46	73.46	61.62	171.31	32.24 34.36	28.52 29.61

[a]Solutions in D_2O

[b]Chemical shifts in ppm downfield from TMS

is expected to be deshielded by the neighbouring sulfur atom. The methyl groups on C(5) have chemical shifts upfield of those of C(2) in almost every case.

It is interesting to note that C(2) is shifted further downfield as it becomes methylated--the deshielding effect of methyl group substitution. The same trend is noted with C(5) less consistently, and the C(5) methyl groups also affect C(4) shifts.

The carboxyl carbon is highly deshielded by the two oxygens, and the signal is well downfield, always 174-170 ppm. C(4) is expected to be the next most deshielded carbon, its signals range from 75 to 55 ppm. As previously discussed with respect to the proton nmr spectra, the proton on C(4) is also the most deshielded because of the proximity to the carboxyl group. C(2) is more deshielded than C(5) as illustrated by thiazolidine-4-carboxylic acid, with C(2) and C(5) assigned chemical shifts of 50 and 34.29 ppm, respectively. This trend continues down the table, although some signals are quite close.

The carbon-13 chemical shifts of 2-methylthiazolidine-4-carboxylic acid and of thiazolidine-4-carboxylic acid are very similar. C(4) and C(5) are deshielded to nearly the same extent by the γ-effect from an additional methyl group on C(2). The greatest change was observed with C(2), with the methyl group on C(2) causing a downfield shift of 12 ppm, as expected.

In the 2,2-dimethylthiazolidine compound the chemical shift of C(2) increased only slightly, compared to the same carbon in the 2-methylthiazolidine compound. The shift of C(4) has decreased, which can be explained by the upfield shift normally caused by a methyl group. The carboxyl carbon has its chemical shift lowered by more than 1 ppm. The signal of the C(2) methyl carbon was shifted downfield considerably, compared with 2-methylthiazolidine-4-carboxylic acid.

The chemical shifts of C(4) and C(5) in 5,5-dimethylthiazolidine-4-carboxylic acid were shifted downfield by about 12 ppm, compared to the values in the non-methylated thiazolidine compounds; these are α and γ effects of adding two methyl groups to the molecule. The chemical shift of C(2) has reverted to nearly the same value as in the nonmethylated thiazolidines. The C(5) methyl groups always occur to lower chemical shifts than the C(2) methyl groups, presumably because of γ-shielding of the carboxyl group. This is a general tendency which becomes more apparent as more methyl groups are introduced into the molecule.

With the 2,5,5-trimethylthiazolidine compound, C(2) again showed an increase in chemical shift relative to the 5,5-dimethyl- compound. This molecule, like 2-methylthiazolidine-4-carboxylic acid, contains two chiral centers, the one at C(4) being always S. The compounds are probably

50:50 mixtures of the two diastereomers, judging from the heights of the duplicated proton nmr signals. The increased chemical shifts of C(2) and C(5) peaks relative to non-methylated compounds reflects the presence of methyl groups on both these carbons. The chemical shift of C(5) has increased by almost 10 ppm; the presence of one more methyl group on another carbon in the molecule is not a sufficient reason to explain such a large effect, unless the stereochemistry of the ring has changed in such a way as to bring the new methyl spacially close to the C(5) atom so that the nuclear shielding is altered.

The α-effect is observed also in the spectrum of 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid, in the downfield shift of the C(2) peak compared to the previous compound which only had one C(2) methyl group. It should be noted that because there is peak overlap in this compound, either of the peaks at 61.62 or 76.46 ppm could be assigned to C(2) and it can be argued which of the assignments is correct. The chemical shift of C(2) is more likely to be 73.46 ppm, since it is expected to be higher than that of C(5), because of the higher deshielding effects of the N and S atoms around C(2) in the ring. For this compound, the methyl group chemical shifts have been assigned previously (62) to C(2) and C(5) methyl carbons by deuteration of the C(2) methyls. The 61.62 ppm peak assigned to C(5) is of higher chemical shift than expected from the values assigned

to C(5) of the other thiazolidine molecules listed in Table 10. Previously published spectra of N-formyl-2,2,5,5-tetramethylthiazolidine compounds (68) helped in the assignment of peaks, as well as the recording of "spin-sort" spectra in which the peaks arising from carbons with an odd number of protons attached show up below the baseline while carbons with an even number of protons give rise to peaks above the baseline. The methyl group carbons deserve a comment. In thiazolidine-4-carboxylic acids that have both C(2) and C(5) methyl substituents, the methyls on C(2) have higher chemical shifts than C(5) methyls, probably because of the proximity to the electronegative N and S. In substituted penicillins the relative shifts were C(2) > C(5) and pro-S CH_3(C(5)) > pro-R. If 2,2,5,5-tetramethyl-thiazolidine-4-carboxylic acid can be considered analogous, the assignments have the same order.

The proton nmr spectra of 2,2-dimethylthiazolidine-4-carboxylic acid and the two benzoylated derivatives are listed in Table 11. The 3-benzoyl derivative gave a rather identical spectrum to that of the parent thiazolidine compound. A new peak is observed at 7.37 ppm, which is the resonance of the aromatic protons; a multiplet was expected because protons on a monosubstituted benzene ring are not all equivalent. The two protons ortho to the carbonyl should show a deshielding effect. The slightly broadened singlet observed in the spectrum must in reality be a

TABLE 11
^{1}H nmr spectra of 2,2-dimethylthiazolidine-4-carboxylic acids and derivatives[a,b,c]

Compound	C_6H_5	H(C-4)	CH_3(COO)	H(C-5)	CH_3(C-2)	CH_2(OH)
2,2-Dimethyl-	-	4.72, dd, 10	-	3.46, dd, 10 3.12, dd, 10	1.90, s 60 1.86, s	-
3-Benzoyl-2,2-dimethyl-	7.37, s, 15	4.68, dd, 3	-	3.08, dd 7 3.38, dd	1.83, s 18 1.87, s	-
3-Benzoyl-2,2-dimethyl- 4-methoxycarbonyl-	7.36, m, 19	4.75, dd, 4	3.52, s, 10	3.13, m 8 3.35, m	1.84, s 24 1.87, s	-
3-Benzoyl-2,2-dimethyl- 4-hydroxymethyl-	7.35, s, 56	4.23, q, 12	-	3.55, dd 24 3.53, dd	1.83, s 68 1.84, s	3.22, t, 23 4.85, t, 11 (OH)

[a]Solutions in DMSO-D_6
[b]Footnote as for Table 9
[c]For coupling constants see Table 11A

TABLE 11A
Coupling constants of 2,2-dimethylthiazolidine-4-carboxylic acids and derivatives[a]

Compound	$^{2}J_{H\text{-}C5,H\text{-}C5}$	$^{3}J_{H\text{-}C5,H\text{-}C4}$	$^{3}J_{H\text{-}C4,H\text{-}COH}$
2,2-Dimethyl-	7.5	3.8	--
3-Benzoyl-2,2-dimethyl-	10.0	3.6	--
3-Benzoyl-2,2-dimethyl-4-methoxycarbonyl-	12.0	2.2	--
3-Benzoyl-2,2-dimethyl-4-hydroxymethyl-	6.3	2.2	3.0

[a] J values in Hz; ^{1}H nmr recorded at 25°C

multiplet. The two C(5) protons give a doublet, being nonequivalent because of the presence of the carboxyl group on a neighbouring carbon. A similar effect was observed with 2-methylthiazolidine-4-carboxylic acid. The two methyl groups of C(2) also have distinct resonances. The C(4) proton is a doublet of doublets because it is split in turn by each of the protons on C(5), which are in nonequivalent chemical environments, as explained above.

There are some differences in the spectrum of the methyl ester derivative, besides the obvious singlet of the methyl ester group. Its resonance is at 3.52 ppm, downfield relative to that of the methyl groups at C(2), because of the strong deshielding effect of the oxygen to which the methyl ester is directly attached. The protons at C(5) give rise to resonance peaks of unclear splitting. This is an ABX system and eight lines should be present in a high resolution spectrum. The aromatic protons gave a multiplet of peaks of varying height, with some peak overlap.

The reduced compound, 3-benzoyl-4-hydroxymethyl-2,2-dimethylthiazolidine yielded a good spectrum with no change in the chemical shifts of the two methyl groups relative to the other thiazolidines in Table 11. The C(5) proton peaks are at lower field: doublets of doublets are observed again but the coupling constants ($J_{4,5ab}$) are very small, and the chemical environments are very similar. The C(4) hydrogen

in the previous compounds was a doublet of doublets, in this compound it is a quintet, which can be explained in terms of the C(5) protons having given signals that differ so little in value that their splitting of the proton at C(4) is combined with the two protons of the adjacent CH_2OH group. A broadening of the aromatic signal has taken place, so that a singlet instead of a multiplet is observed. The methylene group of the alcohol functionality is a triplet and the hydroxyl proton is a slightly broadened triplet. OH groups do not exchange very rapidly in DMSO, although they do exchange if the solution is heated in the presence of a catalyst such as the hydroxide ion.

The proton nmr spectra of benzoyl derivatives of 5,5-dimethylthiazolidine and 2,2,5,5-tetramethylthiazolidine compounds are listed in Table 12. The spectrum of 3-benzoyl-5,5-dimethylthiazolidine-4-carboxylic acid is exactly as expected, with the two C(2) protons and the two methyl groups each giving a singlet. In the methyl ester derivative the C(2) protons are slightly more deshielded. 3-Benzoyl-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid and its methyl ester have very similar chemical shifts for corresponding protons, like the 2,2-dimethyl compounds discussed above.

The proton nmr spectra of thiazolidine-4-carboxylic acids derived by condensation of D-penicillamine and L-cysteine with benzaldehyde and 2-butanone and their 3-

TABLE 12
^{1}H nmr spectra of derivatives of thiazolidines obtained from D-penicillamine[a,b]

Compound	C_6H_5	H(C-4)	CH_3(COO)	H(C-2)	CH_3(C-2)	CH_3 (C-5)
3-Benzoyl-5,5-dimethyl-	7.55, s, 20	4.48, s, 4	-	4.63, s 8 4.80, s	-	1.47, s 24 1.60, s
3-Benzoyl-5,5-dimethyl-4-methoxycarbonyl-	7.56, s, 53	4.56, s, 10	3.70, s, 10	4.90, d 20[c] 4.77, d	-	1.40, s 65 1.60, s
3-Benzoyl-2,2,5,5-tetra-methyl-	7.35, m, 15	4.30, s, 3	-	-	2.00, s, 16	1.30, s, 8 1.67, s, 8
3-Benzoyl-2,2,5,5-tetra-methyl-4-methoxycarbonyl-	7.35, m, 28	4.40, s, 5	3.60, s, 15	-	2.00, s, 27	1.30, s, 14 1.67, s, 14

[a]Solutions in DMSO-D_6
[b]Footnote as for Table 9
[c] $^2J_{H\text{-}C2,H\text{-}C2}$ = 14.4 Hz

TABLE 13
^{1}H nmr spectra of substituted thiazolidine-4-carboxylic acids[a,b,c]

Compound	C_6H_5	H(C-4)	H(C-5)	H(C-2)	CH_3(C-5)	CH_3(C-2)	CH(C-2)
2-Phenyl-	7.42,m,50	3.92,t 10 4.22,t	3.26,m,50	5.50,s 10 5.68,s	-	-	-
3-Benzoyl-2-phenyl-	7.30,m,60	4.90,t,7	3.45,m,12	6.28,s,6	-	-	-
5,5-Dimethyl-2-phenyl-	7.45,m,25	3.56,s 6 3.67,s	-	5.62,s 6 5.83,s	1.63,s 15 1.51,s 1.32,s 15 1.29,s	-	-
2-Ethyl-2-methyl-	-	4.46,t,7	3.36,m,14	-	-	1.62,s,20	1.92,dq 35 0.90,t
3-Benzoyl-2-ethyl-2-methyl-	7.35,m,50	4.72,dd,9	3.15,m,25	-	-	1.83,s,31	2.45,m,20 0.90,t,30
2-Ethyl-2,5,5-trimethyl-	-	3.80,s 16 3.70,s	-	-	1.45,s 48 1.50,s 1.20,s 46 1.25,s	1.60,s 48 1.57,s	1.80,q,30 1.00,t,46
3-Benzoyl-2-ethyl-2,5,5-trimethyl-	7.40,m,30	4.30,s 6 4.38,s	-	-	1.30,s 20 1.27,s 1.60,s 20 1.64,s	1.95,s,20	0.93,q 30 1.00,t

[a]Solutions in DMSO-D_6
[b]Footnote as for Table 9
[c]For coupling constants see Table 13A

TABLE 13A
Coupling constants of the thiazolidine-4-carboxylic acids of Table 13[a]

Compound	$^{2}J_{H\text{-}C5,H\text{-}C5}$	$^{3}J_{H\text{-}C4,H\text{-}C5}$	$^{2}J_{H\text{-}CC2,H\text{-}CC2}$
2-Phenyl-	6.4	1.6	--
3-Benzoyl-2-phenyl-	7.8	--	--
5,5-Dimethyl-2-phenyl-	--	--	--
2-Ethyl-2-methyl-	6.4	1.2	6.0
3-Benzoyl-2-ethyl-2-methyl-	6.6	2.2	7.2
2-Ethyl-2,5,5-trimethyl-	--	--	4.4
3-Benzoyl-2-ethyl-2,5,5-trimethyl-	--	--	4.4

[a] J values in Hz; ^{1}H nmr spectra recorded at 25°C

benzoyl derivatives are in Table 13. Peaks at 7.42 ppm are assigned to the aromatic protons, a multiplet being observed because the protons are not all equivalent. The hydrogens on C(4) have chemical shifts between 3.56 and 4.90 ppm depending on the overall structure of the molecule. The lowest chemical shift is the C(4) hydrogen in 5,5-dimethyl-2-phenylthiazolidine-4-carboxylic acid and the greatest deshielding of a C(4) proton is in 3-benzoyl-2-phenylthiazolidine-4-carboxylic acid. In general the chemical shift of the C(4) proton is higher in the the N-benzoyl derivatives than in the other thiazolidine compounds. C(5) hydrogens are mostly unaffected by the presence of the benzoyl group, since they are spatially removed from the nitrogen atom, although some deshielding is noticed if there is a phenyl group on C(2). Hydrogens on C(2) are markedly deshielded compared to hydrogens on other ring carbons, probably because of the presence of the phenyl ring on the same carbon. Deshielding is especially pronounced in 3-benzoyl-2-phenylthiazolidine-4-carboxylic acid because of the proximity of the carbonyl of the amide, which attracts electron density from neighbouring atoms.

The spectra of 2-phenylthiazolidine and 2-methylthiazolidine compounds are similar in that both are mixtures of stereoisomers and each proton type in the molecule gives rise to two signals, both observable if the splitting is relatively simple. The C(5) protons are different, but the

chemical shift difference is probably very small, so that only one signal is detected. The three-line signal of the hydrogen at C(4) was expected to be a four-line signal.

The benzoyl derivative of 2-phenylthiazolidine-4-carboxylic acid has some new aromatic peaks in a multiplet at 7.30 ppm, and the downfield shift of the proton at C(2) was increased significantly, probably because of the proximity of the amide carbonyl group which attracts electron density from neighbouring atoms. Even though the molecule is still a mixture of diastereomers, only one signal is observed for each type of proton, because there is negligible difference in the deshielding of the protons, whether they point up or down relative to the ring.

The two methyl groups of 2-phenyl-5,5-dimethylthiazolidine-4-carboxylic acid, each of which gives one singlet, but there are four different methyl groups in the two diastereomers. Otherwise the spectrum is identical to that of the L-cysteine analog.

The C(4) proton of 2-ethyl-2-methylthiazolidine-4-carboxylic acid gives a triplet at low field and the C(5) protons cause overlapping doublets of doublets. A singlet at 1.62 ppm results from the resonance of the methyl protons on C(2). The ethyl group shows two sets of peaks: the methyl group is a triplet and the methylene gives two quartets, or what really should be a quartet of quartets if there were no overlap, because the two different protons

split each other into a doublet and the methyl splits each peak further into a quartet (ABC_3 system). The splitting pattern is incomplete, and even the methyl group attached to the methylene should show splitting derived from the nonequivalent protons. Fast rotation about carbon carbon bonds must account for the simple spectrum observed.

The spectrum of 3-benzoyl-2-ethyl-2-methylthiazolidine-4-carboxylic acid is essentially the same as the previous one with additional aromatic peaks. Both nmr spectra show two closely spaced signals for each type of proton, like all the other compounds in Table 13, because of the presence of a new asymmetric center at C(2).

The carbon-13 chemical shifts of the compounds just discussed are shown in Table 14. Some of the peak assignments, especially those of the carbons in the ring, were very difficult to make. Spin sorted spectra of nearly all of the compounds were obtained and compared, and it is believed the peaks are assigned correctly. Only general trends of the data listed in Table 14 will be noted here.

The carboxyl carbons have very consistent chemical shifts, near 170 ppm, and thus this group is very little affected by other ring substituents. The next most deshielded carbon is the carbonyl of the amide in the benzoylated compounds, the signal occuring at 138.7-145.1 ppm. The aromatic carbons all have peaks between 125 and 137 ppm, with the two carbons nearest the C=O being the most

TABLE 14
^{13}C chemical shifts of substituted thiazolidine-4-carboxylic acids[a]

Compound	COOH	CO(N)	C_6H_5	C-5	C-4	C-2	CH_3(C-5)	CH_3(C-2)	CH_3CH_2(C-2)
2-Phenyl-	173.24 172.58	-	128.76 128.50 127.84 127.53 127.19	38.30 37.20	71.11 71.38	65.83 65.23	-	-	-
3-Benzoyl- 2-phenyl-	171.21	145.07 143.89	136.99 132.95 129.86 129.36 128.22 127.32 126.96 126.68 125.41	40.02	40.02	64.69 64.28	-	-	-
5,5-Dimethyl- 2-phenyl-	170.79 170.48	-	128.95 128.56 128.26 127.42 126.95 126.34	61.53 60.83	74.19 73.32	69.12 67.81	29.15 28.26 27.83 26.82	-	-
2-Ethyl-2-methyl-	172.77	-	-	37.72	64.34 64.18	80.51	-	38.17 36.29	29.44 26.59
3-Benzoyl-2-ethyl- 2-methyl-	171.84 171.60	138.80	132.91 129.20 128.46 125.88	32.90	67.41	76.72	-	32.90	27.22 26.00
2-Ethyl-2,5,5- trimethyl-	170.64	-	-	77.22	60.20 59.71	72.69 72.15	30.77	37.70 36.09	28.69 27.66
3-Benzoyl-2-ethyl- 2,5,5-trimethyl-	170.73 169.64	138.94 138.69	129.86 129.22 129.05 128.69 125.70 125.22	78.09 77.91	77.24 77.01	78.09 77.01	27.99	33.09 32.78	33.76 26.61 25.81

[a]Concentrated solutions in DMSO-D_6
[b]Footnote as for Table 10

deshielded.

The carbon in the thiazolidine ring with the highest chemical shift in general is C(4), except when C(2) or C(5) is doubly substituted. The highest field ring carbon is C(5), which has low chemical shift values unless there are methyl or ethyl substituents directly bonded to it. Methyl groups on C(5) give peaks around 30 ppm and those on C(2) are believed to have higher chemical shifts of 33-38 ppm. Ethyl group carbons are not assigned specifically in Tables 13 and 14, but the terminal methyl carbon gives a peak of higher field than the methylene carbon.

III.5. Mass Spectrometry

The mass spectra of some of the thiazolidines discussed in this thesis are shown in Table 15.

All compounds listed in Table 15 show molecular ion peaks with intensities ranging from 4 to 27%. Most (M+1) peaks are of higher intensity than that predicted from isotopic composition, suggesting there is hydrogen transfer before the molecule undergoes fragmentation. The benzoylated thiazolidine compounds have a base peak of m/e=105, the benzoyl ion. This is a fairly stable fragment, but it is further cleaved into benzyne (m/e=76) or phenyl cation (m/e=77) and a stable molecule of C=O. Most spectra with an (M-105) peak also show an (M-104) peak which arises from hydrogen transfer. Loss of the carboxyl group gives

TABLE 15

Fragmentation patterns of 3-benzoyl-2,2-dimethyl-4-hydroxymethylthiazolidine(I) 3-benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine (II), bis(5,5-dimethylthiazolidine-4-carboxylic acid)protium chloride hydrate (III) 3-benzoyl-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid (IV) and 3-benzoyl-4-methoxycarbonyl-2,2,5,5-tetramethylthiazolidine (V)

m/e	Relative Intensities					m/e	Relative Intensities				
	(I)	(II)	(III)	(IV)	(V)		(I)	(II)	(III)	(IV)	(V)
42	-	-	-	8	-	75	8	8	86	2	10
50	-	-	-	2	-	76	10	10	17	-	9
51	22	22	-	4	20	77	52	50	17	34	50
52	-	7	-	-	5	78	16	15	-	2	12
55	8	13	-	2	9	81	-	-	12	-	12
58	16	-	-	2	8	82	-	8	23	-	-
59	15	13	-	5	20	83	8	20	20	-	7
60	-	-	17	-	-	84	10	-	18	-	6
61	-	-	35	-	-	85	-	-	15	-	7
62	-	-	52	-	-	86	-	-	12	-	-
68	10	8	17	2	12	87	-	8	100	2	10
69	-	-	88	6	13	88	15	-	28	2	8
70	-	-	32	2	5	89	-	-	12	-	-
71	8	-	20	-	5	96	-	-	7	1	7
72	8	-	14	-	-	97	-	-	8	5	8
73	15	7	21	-	9	98	-	-	8	-	-
74	8	6	20	2	9	99	8	-	10	-	-

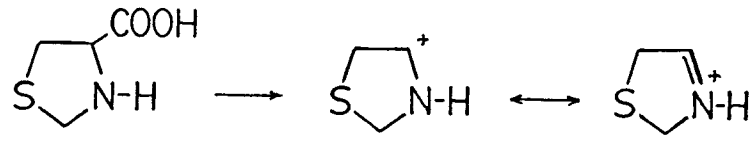
m/e	Relative Intensities				
	(I)	(II)	(III)	(IV)	(V)
100	28	10	25	-	-
101	-	-	23	-	-
102	-	-	13	-	-
105	100	100	-	100	100
106	30	28	-	7	28
107	8	7	-	-	7
109	-	-	5	-	9
110	-	-	6	2	8
112	-	-	6	2	-
113	20	-	8	-	7
114	22	13	20	4	6
115	-	35	12	2	10
116	9	10	85	-	-
117	-	-	20	-	-
118	-	-	18	-	-
126	-	-	8	-	-
127	-	-	8	-	8
128	-	-	8	8	35
129	-	-	18	-	11
130	18	-	8	-	-

m/e	Relative Intensities				
	(I)	(II)	(III)	(IV)	(V)
140	-	-	6	2	-
141	-	-	6	-	-
142	-	7	-	-	-
143	-	-	8	2	-
146	18	-	8	-	-
149	-	-	8	-	-
154	-	-	10	-	10
155	-	-	-	27	15
156	-	-	-	10	10
159	-	-	-	-	12
160	-	-	12	3	-
161	-	-	53	-	7
162	30	-	15	-	-
163	13	-	12	-	-
164	-	10	-	-	-
165	-	50	-	-	-
166	-	20	-	-	-
167	-	12	8	-	-
169	-	-	-	-	45
170	-	-	-	-	30

m/e	Relative Intensities				
	(I)	(II)	(III)	(IV)	(V)
171	-	-	-	-	10
174	-	35	-	-	-
175	-	10	-	2	-
176	-	8	-	-	-
181	-	-	8	-	-
188	-	-	-	12	10
189	-	-	-	1	-
192	-	-	6	-	-
193	-	-	-	1	10
195	-	-	7	-	-
202	-	-	-	-	35
203	-	-	-	-	12
204	-	-	-	-	8
209	-	-	8	-	-
220	48	15	-	-	-
221	20	7	-	-	-
222	12	-	-	-	-
223	-	-	8	-	-
233	8	-	-	-	8
234	-	-	-	-	7

m/e	Relative Intensities				
	(I)	(II)	(III)	(IV)	(V)
236	24	-	-	-	-
237	8	-	8	-	-
248	-	8	-	2	18
249	-	-	-	-	8
250	-	-	-	-	6
251	27	-	8	-	-
252	13	-	-	-	-
265	-	-	8	-	-
278	-	-	-	10	10
279	-	30	-	2	-
280	-	20	-	-	-
281	-	10	-	-	-
292	-	-	-	-	35
293	-	-	-	4	15
294	-	-	-	1	10
307	-	-	-	-	10
308	-	-	-	-	15
309	-	-	-	-	8
375	-	-	12	-	-
376	-	-	5	-	-

the (M-45) peak in the spectrum of carboxylic acids; this peak is expected in compounds containing the acid group, because the resulting charge is stabilized by the unshared electrons on the nitrogen atom in the ring:

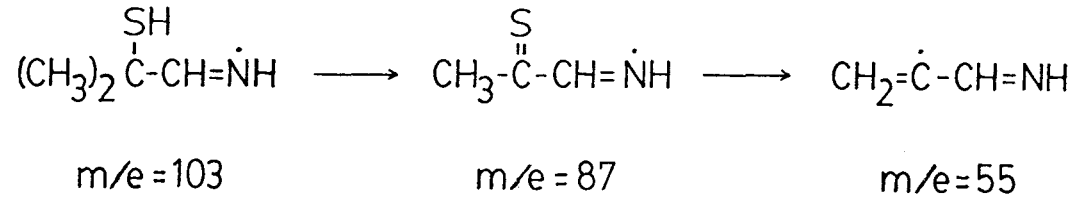


Loss of the methyl ester group gives a peak of (M-59) and occurs readily for the same reason as above, and it can take place in two stages. First the methoxy group may be lost through cleavage of the C-O bond to give an (M-31) peak of m/e=248 in II, to be followed by loss of carbon monoxide. Some (M-15) peaks can be detected resulting from the loss of methyl groups. It has been determined in a study by Howard-Lock *et al*. (62) that methyl group loss occurs more commonly from C(2) of the thiazolidine ring than from C(5) in 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid, when the fragmentation pattern of a C(2) methyl deuterated analog was obtained and only (M-18) peaks could be detected through loss of CD_3.

Fragmentation patterns of several thiazolidine-4-carboxylic acids have been obtained in this work and it was observed that the ring is preferentially cleaved through 1,4- and 2,5-ring cleavages; both types of cleavages are established pathways of thiazolidine ring fragmentation

(81). The 1,4-ring cleavage occurs coupled to a proton transfer from N-H or COOH to the sulfur containing radical to give $(CH_3)_2\dot{C}SH$ of m/e=75, a fragment observed in the mass spectra of all compounds of Table 15. In general radicals containing sulfur have high intensities and because of proton transfer the (M-74) peak is accompanied by an (M-75) peak. Both 1,4 and 2,5-cleavages give fragments of the same m/e value in 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid derivatives so that one can not distinguish the two types of fragmentation from peak intensities. Neither type of ring cleavage was very prominent in the other compounds in Table 15.

The ions resulting from ring cleavage of the type $(CH_3)_2C=\overset{+}{N}H-\dot{C}H-COOR$ (with m/e=115 for R=H and m/e=127 for $R=CH_3$) can be further fragmented first by losing a molecule of water or methanol in an acid or a methyl ester respectively, to give $(CH_3)_2C=N^+=CH-\dot{C}\equiv O$ of m/e=97. This ion-radical rapidly loses a molecule of $C\equiv O$ to give $(CH_3)_2\dot{C}-N^+=CH$ (m/e=69), observed in three of the five compounds, and even further decomposition could be predicted but it is somewhat hypothetical. No (M-42) peaks were detected from loss of $(CH_3)_2C^+$, m/e=42, but there are peaks of mass 87 and 55 in the 5,5-dimethyl- and 2,2,5,5-tetramethylthiazolidine compounds, which means that the fragment of mass 42 is generated but is too unstable, and other likely rearrangements may occur as follows:



Some (M-33) and (M-138) peaks have been observed indicating loss of SH from the original molecule or from the fragment after debenzoylation.

In the spectrum of bis(5,5-dimethylthiazolidine-4-carboxylic acid)protium chloride hydrate, the molecular ion, M^+, is at m/e=376. Normally in chlorine containing compounds if there is a molecular ion there is also an (M+2) peak of 32.5% the intensity of the M^+ peak; there is a peak in the spectrum at (M+1) but not at (M+2). There is an intense m/e=161 peak caused by the cleavage of the molecule into two 5,5-dimethylthiazolidine-4-carboxylic acid units of mass 161, and there is also the corresponding hydrogen transfer peak at m/e=162. The low intensity peak at m/e=265 resulted from (M-35) followed by 1,4-ring cleavage and loss of a methyl group. The remaining five peaks at regular intervals of 14 mass units suggest that the methylene groups and the nitrogen atom in the molecule were lost one at a time and the methyl groups were cleaved with simultaneous hydrogen transfer. The peak at m/e=128 is caused by loss of H_2O and CH_3, and the intense peak at m/e=116 results from loss of COOH. Other peaks in the spectra could be assigned tentatively as fragments of ions derived from further decomposition of 2,5- or 1,4-ring fragments, which give

peaks of low m/e values and characterize the individual compounds. Some peak assignments can only be made unquestionable through fragmentation studies of isotopically labeled molecules.

III.6. Degree of Ionization in Thiazolidines

We tried to obtain as much structural information as possible on the series of thiazolidine compounds with various degrees of substitution in an attempt to determine the factors which cause ionization of these compounds. It was found that there is a small energy difference between the aminoacid and the zwitterion form, and that the free energy of conversion between the two forms appears to be near zero in some cases. Perhaps some conclusions can be drawn as to the stabilizing factors favouring the aminoacid form in thiazolidines while most other compounds with a carboxyl and an amino groups are more stable as zwitterions.

Values of pK represent the extent of protonation of ionizable groups and are presented in Table 16. The pKs of the carboxyl and aminogroups of aminoacids are typically near 1.5 and 8, respectively, while the corresponding values for thiazolidine-4-carboxylic acid have been reported as 1.6 and 6.24 (37), and in tetramethylthiazolidine-4-carboxylic acid the pKs have been found at 2.8 and 5.5. There is a downward shift in amino group pK with increasing methyl group substitution, especially on C(2). This is attributed

TABLE 16
pK values of L-cysteine, D-penicillamine and some thiazolidine-4-carboxylic acids

Compound	pK_1[a]	pK_2[b]	ΔG(Kcal.mol-1)	Isoelectric Point[c]
L-Cysteine	1.96[d]	8.18[d]	-4.23	5.07
D-Penicillamine	1.8	7.9	-4.14	4.9
Thiazolidine-4-carboxylic acid	1.51[d]	6.21[d]	-3.19	3.86
2-Methyl-	2.8	6.0	-2.17	4.4
2,2-Dimethyl-	2.7	5.7	-2.04	4.2
5,5-Dimethyl-	2.7	5.8	-2.11	4.3
2,5,5-Trimethyl-	2.6	5.6	-2.04	4.1
2,2,5,5-Tetramethyl-	2.8	5.5	-1.83	4.4
2-Ethyl-2-methyl-	2.7	7.8	-3.50	5.3
2-Ethyl-2,5,5-trimethyl-	2.9	7.4	-3.07	5.2

[a]pK of the carboxylic group
[b]pK of the amino group
[c]calculated from the pK values
[d]obtained from ref. 37

to ring strain, which is believed to inhibit the sp^3 nitrogen hybridization necessary for tetrahedral bonding (62). The increase in the pK of the COOH group from aminoacids to methyl substituted thiazolidines is probably caused by inductive effects of the methyl group. There is a small energy difference for the conversion of the aminoacid to the zwitterion form, ΔG, which varies between -4.2 and -1.8 kcal/mol for L-cysteine and 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid. 2,2-Dimethylthiazolidine-4-carboxylic acid has a lower conversion energy than 5,5-dimethylthiazolidine-4-carboxylic acid.

Thiazolidines with less than four methyl groups were expected to have pK values between those of thiazolidine-4-carboxylic acid and 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid.

We have shown that methyl substitution at the C(2) and C(5) positions of the thiazolidine ring indeed affects the aminoacid zwitterion equilibrium. It was originally thought that the acidity might be proportional to the number of methyl groups in the molecules. The shift in equilibrium did not follow this simple relationship, however, since from the infrared spectra the 5,5-dimethyl- compound showed no aminoacid form in the solid, while the 2-methyl- and the 2,2-dimethylthiazolidine-4-carboxylic acids showed evidence for both aminoacid and zwitterion forms in the solid. It seems likely that the methyl substitution has affected the

ring conformation and the hydrogen bonding patterns in ways which would make either the aminoacid or the zwitterion more stable. Crystal structure data support these observations, see Tables 17-21, and discussion to follow.

Compounds which exist in the aminoacid form in the solid include 2,5,5-trimethyl- and 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid, derived from D-penicillamine, and 2-methylthiazolidine-4-carboxylic acid, derived from L-cysteine. When the 2,5,5-trimethylthiazolidine-4-carboxylic acid is crystallized from D_2O, however, it occurs as the zwitterion. In D_2O solutions, zwitterion forms are present for all three compounds, although the 2,2,5,5-tetramethyl compound still has a detectable concentration in the aminoacid form, as shown in the infrared spectra.

Values of pK were obtained for 2-ethyl-2-methyl- and 2-ethyl-2,5,5-trimethylthiazolidine-4-carboxylic acids, Table 16, and not for the phenyl substituted compounds because of their poor solubility in water. The amino group pKs for the two compounds above are 7.8 and 7.4. These are the highest values for amino group ionization in this series of compounds. The carboxyl group pKs of 2.7 and 2.9 are within the experimental range for substituted thiazolidine-4-carboxylic acids, but the pKs of aminogroups were expected to be more closely related to that of tetramethyl-thiazolidine-4-carboxylic acid than to that of thiazolidine-4-carboxylic acid. Steric effects on the thiazolidine ring

and especially near the aminogroup were observed to lower its pK value.

While pKs for all the compounds could not be obtained, it is possible to assign their form in the solid state as either aminoacid or zwitterion from the vibrational spectra. The N-benzoyl derivatives were all carboxylic acids. The 2-phenyl- and 2-ethyl-2-methylthiazolidine-4-carboxylic acids are zwitterions in the solid. The 2-ethyl-2,5,5-trimethyl-thiazolidine compound has pK values typical of a zwitterion in solution but shows the characteristic C=O and C-O stretching bands of an aminoacid in the solid. The only correlation in the nmr spectra related to these equilibria was found in the ^{13}C spectra, where the shift of a carboxylate group carbon was slightly greater for 2-phenyl- and 2-ethyl-2-methylthiazolidine-4-carboxylic acid, close to the value of the unsubstituted thiazolidine-4-carboxylic acid, all of which were zwitterions in the solid.

III.7. Crystallography Data and Hydrogen Bonding

X-Ray structures of thiazolidine-4-carboxylic acid have been published (82) showing the compound as a zwitterion with nearly equivalent C-O bond lengths of 1.240(8) and 1.248(8) A. The vibrational spectra and X-ray data of 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid have been published and show that this compound is a carboxylic acid in the solid state and vibrational studies show that there

are significant amounts of the acid present in solution (62).

The measured pK values for 2,2-dimethylthiazolidine-4-carboxylic acid are 2.7 and 5.7. The crystal structure of this compound is unique in that the acid form and the zwitterion coexist in equal amounts in the crystal (Table 17). The unit cell is composed of dimers, see Fig. 2, each containing both an aminoacid, of C-(OH) and C=O bond lengths of 1.325(6) and 1.205(6) A respectively and C(4)-C-O bond angles of 110.8(4) and 123.4(5)^{o}, and a zwitterion of C-O bond distances of 1.227(5) and 1.271(5) A and C(4)-C-O bond angles of 114.9(4) and 119.0(4)^{o}. These distances and angles are in agreement with the limits for both carboxyl and carboxylate groups, set by Borthwick (83) who reported a statistical study of crystal structures of compounds with COOH, COO^{-} and methyl ester groups. In the aminoacids the C=O and C-O bond distances are characteristic of the acid form, differing by 0.12 A with a carbon-oxygen double bond and a single bond, while the amino group is neutral with only one hydrogen atom. In the carboxylate group the C-O bonds are not equivalent but they only differ by roughly 0.045 A. This implies that the two oxygens would be interchangeable in a carboxylate salt but because of strong hydrogen bonding between the two molecules in the dimer, one of the C-O bonds is slightly longer and is hydrogen bonded. Hydrogen bonding is very strong as the O...O distance is

TABLE 17
Selected interatomic distances (Å) and angles (deg) for hydrogen bonded 2,2-dimethylthiazolidine-4-carboxylic acid

	A	B		A	B
S-C(2)	1.825(5)	1.867(5)	C(2)-N	1.508(6)	1.437(6)
N-C(4)	1.498(5)	1.450(6)	C(4)-C(5)	1.532(6)	1.564(7)
C(5)-S	1.809(5)	1.790(5)	C(4)-C(1)	1.540(6)	1.528(6)
C(1)-O(1)	1.271(5)	1.325(6)	C(1)-O(2)	1.227(5)	1.205(6)
C(2)-C(21)	1.515(6)	1.532(8)	C(2)-C(22)	1.522(6)	1.527(7)
Hydrogen bonds					
O(1)...O(1)'	2.586(4)	O(1)...H	1.490(3)	O(1)'-H	1.192(3)
C(5)-S-C(2)	90.3(2)	90.8(2)	S-C(2)-N	101.7(3)	105.4(3)
C(2)-N-C(4)	112.9(3)	109.5(4)	N-C(4)-C(5)	108.1(3)	110.8(4)
C(4)-C(5)-S	106.6(3)	107.4(4)	N-C(4)-C(1)	108.4(3)	111.6(4)
C(4)-C(1)-O(1)	114.9(4)	110.8(4)	C(4)-C(1)-O(2)	119.0(4)	123.4(5)
C(5)-C(4)-C(1)	112.1(4)	107.5(4)	O(1)-C(1)-O(2)	126.1(4)	125.8(5)
S-C(2)-C(21)	112.6(3)	109.5(4)	S-C(2)-C(22)	111.1(3)	109.3(4)
N-C(2)-C(22)	110.0(4)	110.9(4)	C(21)-C(2)-C(22)	111.1(4)	110.5(4)

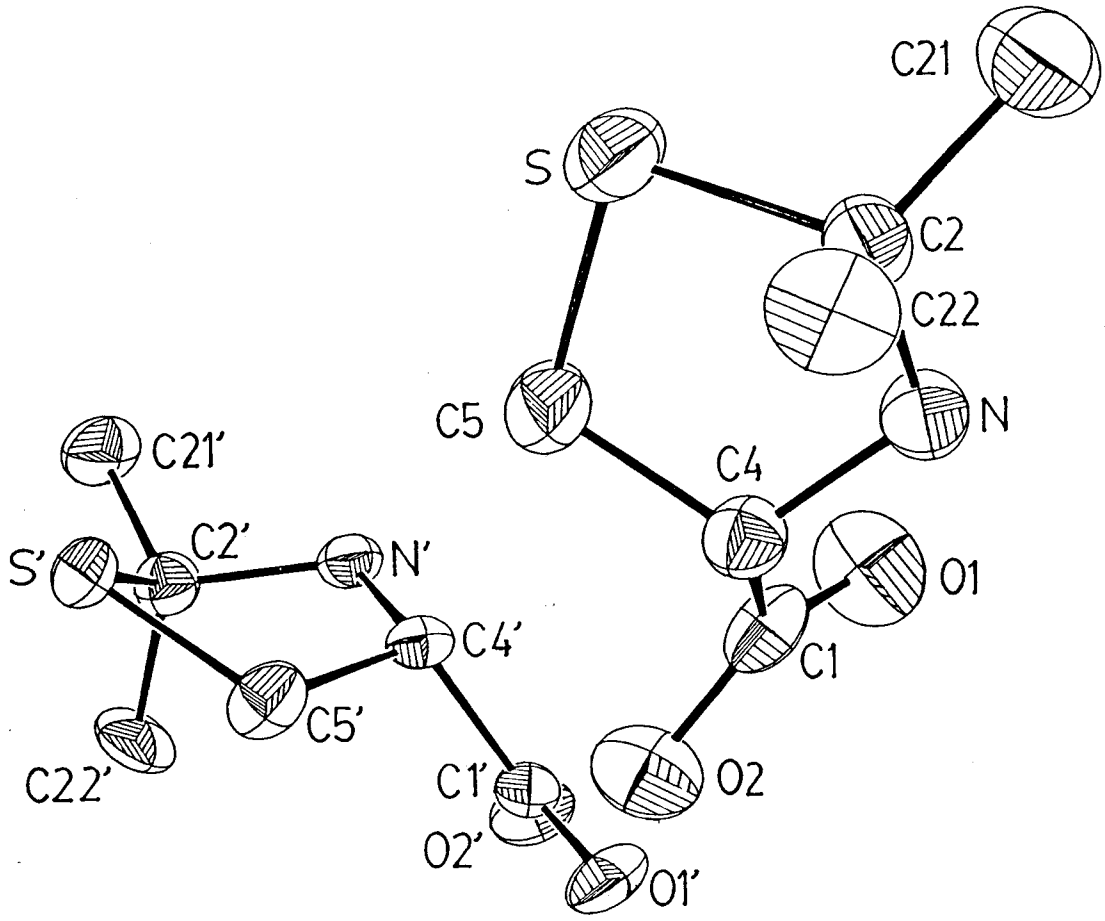


FIGURE 2
Hydrogen bonded molecules of 2,2-dimethylthiazolidine-4-carboxylic acid

only 2.586(4) Å. This is an example of an asymmetric hydrogen bond, with a long and a short O...H, the shorter of the two can be considered covalent. The C(2)-S and C(2)'-S' distances (1.825(5) and 1.867(5) Å) are longer than C(5)-S and C(5)'-S' distances (1.809(5) and 1.790(5) Å) because of the presence of two methyl groups at C(2), lengthening the C(2)-S bond.

Another thiazolidine-4-carboxylic acid dimer with strong hydrogen bonding is the hemiprotonated dimer of 5,5-dimethylthiazolidine-4-carboxylic acid chloride. Selected bond lengths and angles are shown in Table 18, and the molecule is shown in Fig. 3. There are significant, but minor, differences in comparable bond lengths and angles associated with the S-C(2)-N-C(4) portion of the two rings, although others, particularly those in exocyclic fragments, do not differ significantly. The C(5)-S, C(5)'-S' distances (1.828(5), 1.847(5) Å) are longer than the S-C(2), S'-C(2)' distances (1.784(5), 1.816(5) Å) presumably because of the greater repulsive forces of the methyl groups. This is exactly the same effect discussed above for the 2,2-dimethyl- compound. In general distances and angles are similar to those found in 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid and other substituted thiazolidine-4-carboxylic acids discussed in this section. Associated with the differences noted above there is a distinct difference in the conformation of the rings, as discussed in a paper

TABLE 18
Selected interatomic distances (Å) and angles (deg) for
bis(5,5-dimethylthiazolidine-4-carboxylic acid)protium chloride hydrate

	A	B		A	B
S-C(2)	1.784(5)	1.816(5)	C(2)-N	1.514(6)	1.465(6)
N-C(4)	1.500(6)	1.467(6)	C(4)-C(5)	1.537(6)	1.555(6)
C(5)-S	1.828(5)	1.847(5)	C(4)-C(1)	1.536(7)	1.526(6)
C(1)-O(1)	1.223(6)	1.222(5)	C(1)-O(2)	1.272(6)	1.270(6)
C(5)-C(51)	1.537(7)	1.548(7)	C(5)-C(52)	1.542(5)	1.536(7)
Hydrogen bonds					
N'...O	2.818(5)	N'...Cl	3.062(4)	N...O	2.886(5)
N...Cl	3.291(4)	O...Cl	3.133(4)	O...O(1)	2.766(5)
O...O(2)	2.450(5)				
C(5)-S-C(2)	92.4(2)	94.8(2)	S-C(2)-N	107.0(3)	104.9(3)
C(2)-N-C(4)	112.2(3)	109.7(3)	N-C(4)-C(5)	107.3(4)	106.9(3)
C(4)-C(5)-S	102.3(3)	103.5(3)	N-C(4)-C(1)	109.0(4)	110.7(4)
C(5)-C(4)-C(1)	115.2(4)	113.8(4)	C(4)-C(1)-O(1)	119.4(5)	119.0(4)
C(4)-C(1)-O(2)	112.5(4)	113.7(4)	O(1)-C(1)-O(2)	128.0(5)	127.2(5)
C(4)-C(5)-C(51)	111.1(4)	111.7(4)	C(4)-C(5)-C(52)	111.6(4)	112.2(4)
S-C(5)-C(51)	107.0(4)	110.6(3)	S-C(5)-C(52)	111.0(3)	108.0(4)
C(51)-C(5)-C(52)	113.2(5)	110.5(4)			

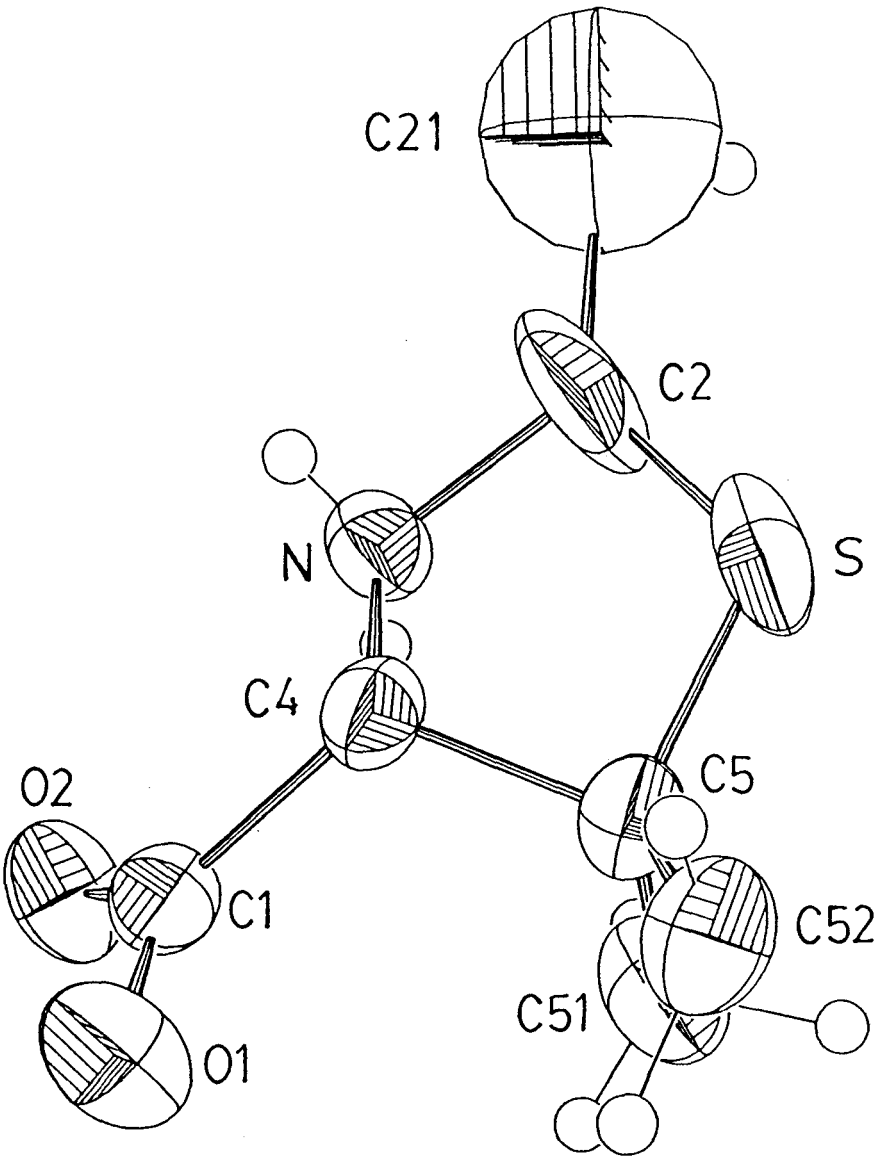


FIGURE 3
The molecular diagram of 2,5,5-trimethylthiazolidine-4-carboxylic acid recrystallized from acetone, showing the atoms numbered

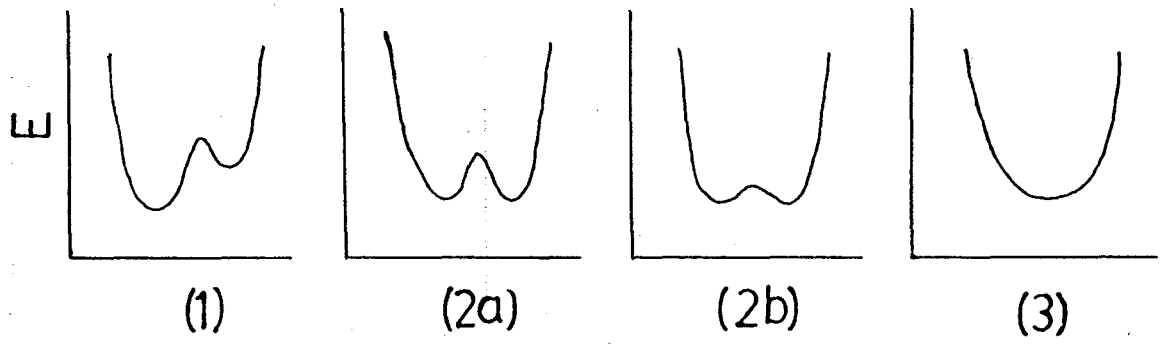
already submitted (84). One of the rings has an envelope structure with C(4) out of the plane, whereas the primed ring has a pseudo-C_2 structure.

The two parts of the cation are joined by a very strong hydrogen bond (O(2)...O(2)', 2.450(5) Å). This is in the range expected for symmetrical hydrogen bonds, although close to the upper limit. The hydrogen atom, H1, lies close to half-way between the two oxygen atoms, O(2) and O(2)', but the errors in bond lengths and bond angles are too large to decide on the degree of symmetry of the bond. The similarity of the C(1)-O(1), C(1)-O(2) and C(1)'-O(1)' and C(1)'-O(2)' distances, however, is consistent with a symmetric hydrogen bond. A similar strong (2.586(4) Å) but definitely asymmetric bond, found in (S)-2,2-dimethylthiazolidine-4-carboxylic acid caused considerable differences in the C-O bond lengths in the two carboxylate groups. The cation described here is noteworthy, in that it is one of the extremely rare cases where the hydrogen atom in a very short hydrogen bond is not on, or disordered about, a crystallographic symmetry element, and thus the similarities in the two halves, noted above, are not artifacts of the space group.

In symmetric hydrogen bonds the proton is generally required to lie on a crystallographic element of symmetry, or it may be a result of a disordered structure. The ranges of symmetric hydrogen bond distances were defined by

Hamilton and Ibers in 1968 as 2.40-2.55 Å, and have been shortened to 2.40-2.47 Å by 1974. Catti and Ferraris (85) discussed symmetry restricted short hydrogen bonds in organic compounds and concluded that it is difficult to determine the disorder of a hydrogen atom because its two extreme positions are too close. The first truly symmetric short O...H...O bond was found in potassium hydrogen chloromaleate by Ellison and Levy (86). The hydrogen atom was found to be at equal distances from the chemically non equivalent oxygens within experimental error, by neutron diffraction techniques.

Strong hydrogen bonds can be explained by means of potential energy diagrams, see below: (1) most hydrogen bonds are asymmetric, with the proton in the first potential minimum; (2) as the hydrogen bond becomes stronger the two minima approach the same energy level and the barrier decreases. The energy well becomes very broad and diffuse making it impossible to find the proton by X-ray crystallography; (3) the hydrogen atom is in a symmetric position in a single minimum potential function with a well defined energy level (87).



Crystals of 2,5,5-trimethylthiazolidine-4-carboxylic acid were obtained from solutions in D_2O and in acetone, see Tables 19 and 20, and Fig. 4. From the crystal structure of the compound that crystallized from acetone, an aminoacid is present in the solid state. The C-O bond lengths of the carboxyl group reveal a short double bond of 1.195(9) Å and a longer C-(OH) bond of 1.312(8) Å. The bond angles are $121.9(6)^{\circ}$ for C(4)-C=O and $113.0(6)^{\circ}$ for the corresponding angle. These values are typical bond angles of carboxylic acids according to Borthwick, 123(2) and $112(2)^{\circ}$, respectively (83). The crystal structure of the same compound obtained from D_2O, however, is a zwitterion, of C-O bond lengths 1.246(7) and 1.236(7) Å, with two essentially equivalent oxygens, the difference in the bond distances being insignificant when the degree of uncertainty is considered. There is hydrogen bonding of the type N-H...O in the compound crystallized from D_2O. The fact that the same compound crystallized from two different solvents in different ionization forms confirms the observation that the energy of conversion between the two forms is very low. Solvent interactions are enough to stabilize one structure over the other, depending on the ability of the solvent to accommodate charged groups.

Interconversion is more difficult with bulky substituents and ionization is not favoured over the acid form. An example of such an acid with C(2) and N aromatic

TABLE 19
Selected interatomic distances (Å) and angles (deg) for hydrogen bonded 2,5,5-trimethylthiazolidine-4-carboxylic acid recrystallized from D_2O

	A	B		A	B
S-C(2)	1.770(10)	1.806[a]	C(2)-N	1.490(10)	1.474(4)
N-C(4)	1.484(8)	1.484[a]	C(4)-C(5)	1.545(8)	1.557(9)
C(5)-S	1.839(7)	1.850[a]	C(4)-C(1)	1.533(8)	1.555(10)
C(1)-O(1)	1.246(7)	1.249(14)	C(1)-O(2)	1.236(7)	1.231(8)
C(2)-C(21)	1.330(14)	1.266(3)	C(5)-C(51)	1.544(10)	1.552(9)
C(5)-C(52)	1.516(10)	1.491(10)			
Hydrogen	bonds				
N...O(1)'	2.733(7)	O(2)...N'	2.852[a]	O...N'	2.680[a]
N...O(2)'	2.852[a]	O...O(2)'	2.655[a]		
C(5)-S-C(2)	95.2(4)	a	S-C(2)-N	107.6(6)	a
C(2)-N-C(4)	107.3(6)	a	N-C(4)-C(5)	106.9(5)	a
C(4)-C(5)-S	102.2(4)	a	N-C(4)-C(1)	111.0(5)	a
C(4)-C(1)-O(1)	115.6(5)	118.4(6)	C(4)-C(1)-O(2)	118.9(6)	113.5(10)
C(5)-C(4)-C(1)	115.2(5)	113.3(6)	O(1)-C(1)-O(2)	125.5(6)	128.0(11)
C(4)-C(5)-C(51)	113.1(6)	118.2(6)	C(4)-C(5)-C(52)	111.3(6)	112.8(6)
C(51)-C(5)-C(52)	111.4(6)	110.7(6)	S-C(2)-C(21)	126.6(11)	a
N-C(2)-C(21)	120.9(11)	a			

[a]Data is incomplete; some more calculations must be done to refine and complete the solution of this crystal structure.

TABLE 20
Selected interatomic distances (Å) and angles (deg) for
2,5,5-trimethylthiazolidine-4-carboxylic acid recrystallized from acetone

Bond	Length	Bond	Length
S-C(2)	1.834(7)	C(2)-N	1.479(8)
N-C(4)	1.461(8)	C(4)-C(5)	1.578(8)
C(5)-S	1.846(6)	C(4)-C(1)	1.525(7)
C(1)-O(1)	1.195(9)	C(1)-O(2)	1.312(8)
C(2)-C(21)	1.487(12)	C(5)-C(51)	1.498(11)
C(5)-C(52)	1.505(11)		
Bond	Angle	Bond	Angle
C(5)-S-C(2)	94.8(3)	S-C(2)-N	105.9(4)
C(2)-N-C(4)	105.9(4)	N-C(4)-C(5)	109.6(4)
C(4)-C(5)-S	101.6(4)	N-C(4)-C(1)	110.4(5)
C(4)-C(1)-O(1)	121.9(6)	C(4)-C(1)-O(2)	113.0(6)
C(5)-C(4)-C(1)	112.0(5)	O(1)-C(1)-O(2)	125.0(5)
C(4)-C(5)-C(51)	112.1(6)	C(4)-C(5)-C(52)	111.4(5)
C(51)-C(5)-C(52)	111.1(6)	S-C(2)-C(21)	113.5(7)
N-C(2)-C(21)	112.1(6)		

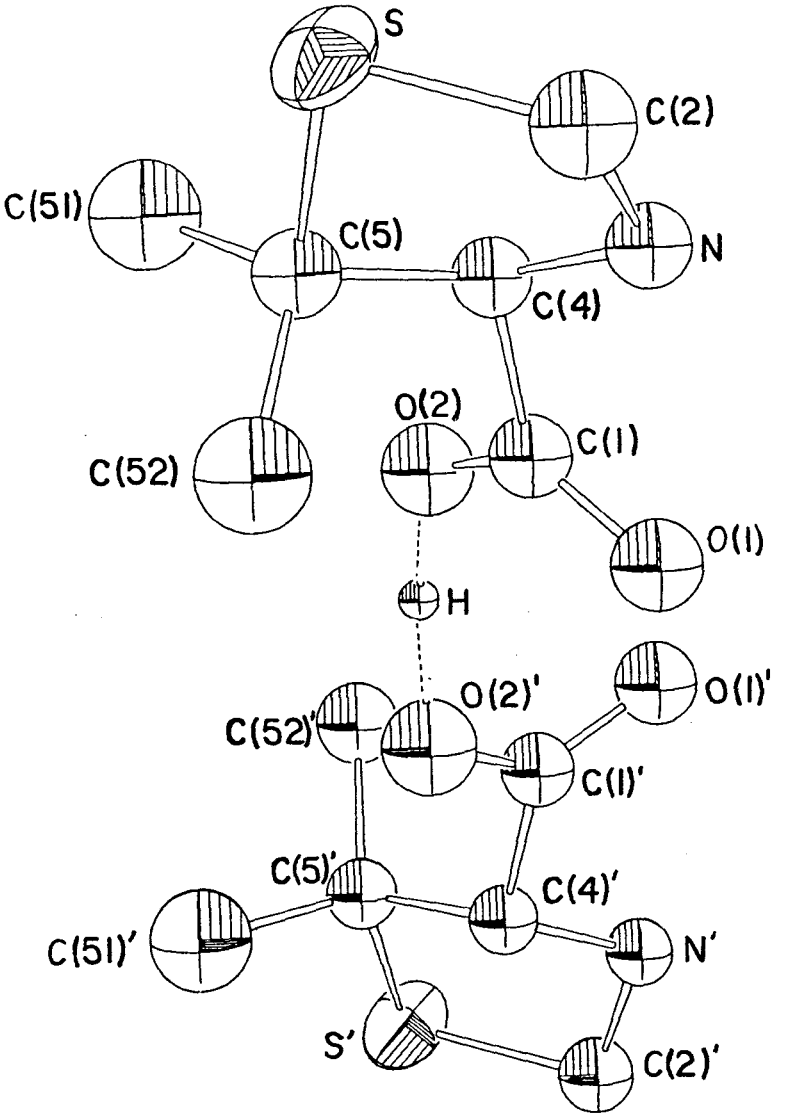


FIGURE 4
The molecular cation bis(5,5-dimethylthiazolidine-4-carboxylic acid) protium showing the atom numbering

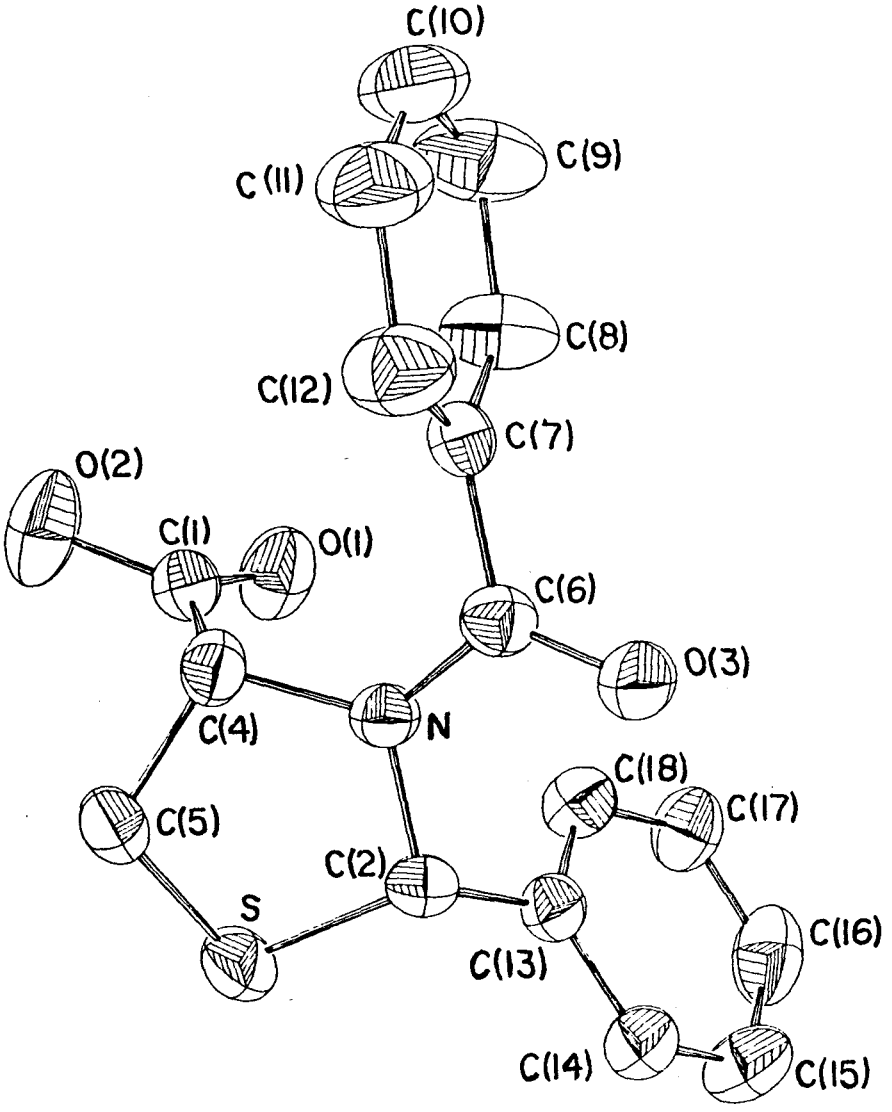


FIGURE 5
The molecular diagram of 3-benzyl-2-phenylthiazolidine-4-carboxylic acid showing the atom numbering

TABLE 21
Selected interatomic distances (Å) and angles (deg) for
3-benzoyl-2-phenylthiazolidine-4-carboxylic acid

Bond	Length	Bond	Length	Bond	Length
S-C(2)	1.818(3)	C(2)-N	1.474(4)	N-C(4)	1.463(4)
C(4)-C(5)	1.522(5)	C(5)-S	1.808(3)	C(4)-C(1)	1.511(5)
C(1)-O(1)	1.205(4)	C(1)-O(2)	1.318(4)	N-C(6)	1.347(4)
C(6)-O(3)	1.232(4)	C(6)-C(7)	1.493(5)	C(7)-C(8)	1.368(5)
C(8)-C(9)	1.386(6)	C(9)-C(10)	1.357(7)	C(10)-C(11)	1.362(7)
C(11)-C(12)	1.386(6)	C(12)-C(7)	1.374(5)	C(2)-C(13)	1.512(4)
C(13)-C(14)	1.379(5)	C(14)-C(15)	1.386(6)	C(15)-C(16)	1.376(6)
C(16)-C(17)	1.372(6)	C(17)-C(18)	1.389(5)	C(18)-C(13)	1.380(5)
C(19)-O(4)	1.394(6)				
Hydrogen	bonds				
O(2)...O(4)	2.593(4)	O(2)-H	1.063(3)	O(4)...H	1.561(3)
O...O(4)	2.686(4)	O(4)-H	1.034(3)	O...H	1.660(4)
Bond	Angle	Bond	Angle	Bond	Angle
C(5)-S-C(2)	90.9(1)	S-C(2)-N	104.5(2)	C(2)-N-C(4)	116.5(3)
N-C(4)-C(5)	105.9(3)	C(4)-C(5)-S	104.2(2)	N-C(4)-C(1)	113.2(2)
C(5)-C(4)-C(1)	111.8(3)	C(4)-C(1)-O(1)	126.5(3)	C(4)-C(1)-O(2)	110.3(3)
O(1)-C(1)-O(2)	123.3(3)	C(2)-N-C(6)	117.9(3)	C(4)-N-C(6)	123.0(3)
N-C(6)-C(7)	118.4(3)	N-C(6)-O(3)	121.0(3)	O(3)-C(6)-C(7)	120.6(3)
C(6)-C(7)-C(14)	119.5(3)	C(6)-C(7)-C(8)	121.1(3)	C(7)-C(8)-C(9)	120.3(4)
C(8)-C(9)-C(10)	120.5(4)	C(9)-C(10)-C(11)	119.6(4)	C(10)-C(11)-C(12)	120.6(4)
C(11)-C(12)-C(7)	119.9(4)	C(12)-C(7)-C(8)	89.8(3)	N-C(2)-C(13)	114.6(3)
S-C(2)-C(13)	109.6(2)	C(2)-C(13)-C(18)	121.5(3)	C(2)-C(13)-C(14)	118.9(3)
C(13)-C(14)-C(15)	119.9(3)	C(14)-C(15)-C(16)	120.5(4)	C(15)-C(16)-C(17)	119.8(4)
C(16)-C(17)-C(18)	120.0(3)	C(17)-C(18)-C(13)	120.2(3)	C(18)-C(13)-C(14)	119.6(3)

substituents was obtained as a crystal, and its structure was determined by X-ray diffraction. The molecule is shown in Fig. 5 and selected bond lengths and angles are listed in Table 21. The C-O bond lengths of the carboxyl group are 1.205(4) and 1.318(4) Å and the bond angles of interest are 126.5(3) and 110.3(3)°, which are again within the limits specified by Borthwick for protonated carboxylic acids. The C(2)-S bond is longer than the C(5)-S, which is in agreement with the earlier discussion of elongated C-S bonds by substituents on a carbon adjacent to sulfur.

The pKs of this compound could not be determined because of its insolubility in water, but one can assume that ionization is not favoured under normal conditions.

IV. CONCLUDING REMARKS

The spectroscopic properties of a series of related compounds which have not been studied in the past were investigated. Some of the thiazolidine compounds obtained in this work are believed to have been prepared for the first time.

There are good reasons to continue research in the area of synthetic and structural studies of thiazolidine ring compounds, as well as in the synthesis of radiopharmaceuticals.

The synthesis of the radiopharmaceutical proposed initially in this project involved a crucial reduction step. It is likely that the least hindered thiazolidine compound could be reduced if the following conditions are met: (i) careful control of the humidity in the reaction atmosphere, (ii) use of the appropriate reducing agent, (iii) following of the reaction by TLC and nmr and (iv) replacement of the benzoyl group with a less bulky amine protecting group. Easy access of the nucleophile to the reaction center is extremely important in this type of reaction. A better way would be to approach the problem of the reducing step with an open chain carboxylic acid or ester. This would involve finding the appropriate

protecting groups for D-penicillamine, groups which must withstand reduction conditions and be easily cleaved by hydrolysis or by another mild reaction. The protecting groups that were used in this project worked well with cysteine, but did not react sufficiently with D-penicillamine, which is much less reactive than the natural aminoacid. This is, of course, why penicillamine, and not cysteine, is prescribed--because of its higher, but as yet rather obscure, selectivity. In future work other D-penicillamine analogs could be used as precursors for radioimaging agents, providing they can form complexes with technetium.

The study of compounds derived from D-penicillamine, such as the thiazolidines studied in this work, is relevant medically because penicillamine is a prescribed drug against several serious illnesses. The side effects of this drug could be better understood if the mechanism by which the drug interacts with enzymes and other proteins in the body, as well as the decomposition products of the compounds formed, were known. The biological activity of thiazolidine derivatives, such as possible antibacterial or antibiotic activity, should be evaluated.

The hydrogen bonding capability of these compounds merits emphasis in future work. Most of the thiazolidine-4-carboxylic acids studied exist as dimers in

the solid state; the two molecules in a dimer are held together by O...O or N...O hydrogen bonds. Some of these hydrogen bonds are very short, such as those observed in bis(5,5-dimethylthiazolidine-4-carboxylic acid) protium chloride hydrate and in 2,2-dimethylthiazolidine-4-carboxylic acid, the first of which is a rare case of a short symmetric hydrogen bond not on a symmetry element, and the second is a non-symmetric strong hydrogen bond. Thiazolidine-4-carboxylic acids are aminoacid-like compounds, and generally the more substituents that are present on the ring atoms, the greater the tendency of the molecule to behave like an aminoacid rather than a zwitterion. This is not strictly true in all cases and sometimes the interconversion energy between the two forms is very low. An example of this is the 2,5,5-trimethylthiazolidine-4-carboxylic acid structure which was found to our surprise to crystallize both as the acid and the zwitterion form depending solely on solvent interactions. When recrystallized from a highly polar solvent, D_2O, the compound obtained was clearly a hydrogen bonded zwitterion, but in the crystals obtained from acetone, less polar and incapable of solvating charged groups, both the carboxylic and aminogroups were uncharged. This shows that there are suble effects which determine the ionization state of these molecules, in addition to the degree of ring substitution.

APPENDIX A

Reductions of benzoylated thiazolidine compounds were repeatedly attempted using procedures which have been successful in reducing carboxylic acids and esters. These procedures have employed such reducing agents as sodium borohydride, alone or in combination with anhydrous $AlCl_3$ or LiCl (88, 89), lithium aluminum hydride (90) or the intermediate strength reducing agents lithium borohydride and sodium trimethoxyborohydride (66, 91, 92). Other reducing agents that generally are efficient in reducing carboxylic acids to alcohols are the boranes which are available in a variety of solvents or combined with other reagents for enhanced reactivity or selectivity (93-98).

Below are examples of some of the reactions attempted. A procedure is given for each type of reaction and in cases where the reaction was repeated under varying conditions, a summary of these is presented in table form. The reactions with the different thiazolidine compounds are shown roughly in chronological order, that is, reductions of 3-benzoyl-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid and its methyl ester were attempted before 3-benzoyl-5,5-dimethyl-thiazolidine-4-carboxylic acid or its methyl ester were reduced; reactions with 3-benzoyl-2,2-dimethyl-4-methoxy-

carbonylthiazolidine were carried out with the purpose of optimizing conditions for reduction of the thiazolidine compound derived from D-penicillamine.

The amounts of reagents shown in the Tables in this Appendix are in mmoles.

3-Benzoyl-4-methoxycarbonyl-2,2,5,5-tetramethylthiazolidine (XX) + $NaBH_4$: 0.3 g (0.001 mole) XX was dissolved in 5 mL of anhydrous methanol, the solution was cooled on ice and stirred. To this 0.4 g (0.01 mole) $NaBH_4$ was added in small portions with fast gas evolution. The mixture was allowed to stand on the bench overnight, and it was worked up by pouring it into ice-cold water. A white precipitate (0.2 g) formed in the refrigerator and it was shown by ^1H nmr to be the starting material. The reaction was repeated varying the conditions as shown in the table below:

Solvent	XX	$NaBH_4$	Reaction Conditions
MeOH	1.0	5.0	50°C, 3 hrs; stir 16 hrs
MeOH	0.5	2.5	50°C, 8 hrs
MeOH	0.5	2.5	65-70°C, 4.5 hrs; stir r. t. 2 days; 60°C, 2 hrs
i-PrOH	0.8	1.2	r. t. 2 days
i-PrOH	1.0	10.0	40°C, 5 hrs; r. t. 20 hrs
i-PrOH	1.0	10.0	60-70°C, 5 hrs; r. t. 15 hrs Dec.

3-Benzoyl-4-methoxycarbonyl-2,2,5,5-tetramethylthiazolidine (XX) + $NaBH_4$ + LiCl: 0.3 g (0.001 mole) XX was added to an ice cooled solution of 0.2 g (0.005 mole) $NaBH_4$ and 0.2 g (0.005 mole) LiCl in 5 mL of diglyme. There was fast hydrogen evolution initially, then the mixture was left in the refrigerator for two days. To the cold mixture dilute HCl was added until the bubbling stopped. The mixture was extracted three times with a total of 60 mL of chloroform. The aqueous layer was evaporated to leave a white solid which when left on the bench overnight turned into a white oily material. No peaks were observed in the ^1H nmr spectrum. The organic layer was evaporated under reduced pressure to leave a white solid which was shown by nmr to be identical to the starting ester.

This reaction was repeated three times with varying amounts of reagents and conditions as shown in the table below:

XX	$NaBH_4$	LiCl	Reaction Conditions
0.4	2.0	2.0	r. t. 3 days
1.0	2.5	1.0	50-60°C, 3 hrs; r. t. 2 days
0.4	2.5	1.5	r. t. 15 min.; 80°C, 90 min.; r. t. 15 hrs; 60°C, 90 min.

3-Benzoyl-4-methoxycarbonyl-2,2,5,5-tetramethylthiazolidine (XX) + $NaBH_4$ + $AlCl_3$: 0.3 g (0.008 mole) of sodium borohydride was added to 3 mL of diglyme. To the mixture

0.3 g (0.001 mole) of XX was added and all the solid rapidly dissolved. 0.45 mL ($4.5.10^{-5}$ mole) of 0.1M solution of aluminum chloride in diglyme was added dropwise to the stirred mixture with gas evolution. The reaction mixture stirred for three hours at r. t. then was heated at 50°C for 30 min. and was left stirring overnight. The mixture was added to crushed ice to which a few drops of dilute HCl had been added. A white foam formed which upon filtration yielded 0.2 g of white solid. This was shown by ^1H nmr to be the starting material.

The reaction was carried out repeatedly with amounts of reagents and conditions as follows:

XX	$NaBH_4$	$AlCl_3$	Reaction Conditions
1.0	0.06	0.05	r. t. 3 hrs; 50°C, 30 min.; r. t. overnight
1.8	3.0	1.00	r. t. 2 hrs; 50°C, 2 hrs; r. t. 3 days
0.7	1.0	0.04	50°C, 16 hrs
0.5	1.0	0.25	55°C, 8 hrs; 80°C, 2 hrs
0.5	1.0	0.15	r. t. 30 min.; 80°C, 16 hrs
0.5	1.0	0.25	100-110°C, 2 hrs
0.5	2.5	2.00	r. t. 16 hrs; 90-100°C, 2 hrs; 55°C, 20 hrs

3-Benzoyl-4-methoxycarbonyl-2,2,5,5-tetramethylthiazolidine (XX) + $NaBH(OMe)_3$: 0.25 g XX (<0.001 mole) was dissolved in 20 mL dimethoxyethane and 0.4 g (0.0015 mole)

$NaBH(OMe)_3$ was added to the mixture, which was stirred under nitrogen at r. t. with no apparent gas release. The reaction mixture was refluxed for 4 hours, then the bright yellow solution was stirred overnight. The reaction was worked up by adding water followed by a few drops of dilute HCl. Long thin crystals were separated by filtration (0.15 g) and were soluble in chloroform. The ^1H nmr spectrum revealed that the starting material had been recovered. When the reaction mixture was extracted with ether or chloroform the ester was recovered in the organic layer and the inorganic borates which are biproducts are water soluble and could be isolated by evaporation. This reaction was repeated as follows:

XX	$NaBH(OMe)_3$	Reaction Conditions
0.8	0.8	50-60°C, 5 hrs; 40°C, 15 hrs; stir r. t. 24 hrs
1.0	3.0	85°C, 4 hrs
0.3	0.5	85°C, 14 hrs
0.3	0.5	80-90°C, 20 hrs

3-Benzoyl-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid (XIX) + $LiAlH_4$: 0.15 g (0.0005 mole) XIX was dissolved in 2 mL dry THF and the solution cooled to -15°C. 2 equiv. $LiAlH_4$ were slowly added to the stirred solution. Fast gas production was observed for a few min., and the white suspension quickly became a light yellow solution.

This was stirred on ice for 1 hour, then it was left stirring overnight. Some of the THF had evaporated and the mixture turned into a gel. 2 mL THF was added and the mixture was treated with cold saturated NH_4Cl. The mixture was filtered and the small amount of solid was washed with dichloromethane. The filtrate was evaporated under a nitrogen stream to leave a dry yellow residue soluble in MeOH, but the solution did not turn cloudy on addition of water. The solution was left in the refrigerator and a white solid was filtered out the next day; the solid was insoluble in all the solvents tested (dichloromethane, chloroform, acetone, THF, DMSO). Some yellow solid was recovered from the MeOH solution which dissolved in DMSO but not in $CHCl_3$. The proton nmr indicated the solid was impure starting material.

Two other reactions with $LiAlH_4$ were attempted, one reacted in the refrigerator overnight and the other was stirred at r. t. for 10 min. then left in the refrigerator for 5 hours. In either case the solid obtained was only partly soluble in DMSO and it could not be identified by nmr.

3-Benzoyl-4-methoxycarbonyl-2,2,5,5-tetramethylthiazolidine (XX) + Na/EtOH: 0.3 g (0.001 mole) XX was dissolved in 32 mL absolute EtOH in a round bottom flask equipped with a condenser and a $CaCl_2$ drying tube. The temperature of the mixture was raised by addition of 0.5 g Na(s). The mixture

was allowed to stand for 20 min. in a water bath at r. t. and all the sodium dissolved causing the solution to turn yellow. About 10 mL of water was added to the cooled solution, which was warmed slightly for 10 min. to remove the ethanol, and the yellow colour intensified. The solution was partly evaporated in the rotoevaporator, then extracted with ether, and only a very small amount of residue was obtained from the organic layer on evaporation. The aqueous layer was evaporated to leave a yellow oil sticking to the walls of the round bottom flask. Methanol was added to the flask and it partially dissolved the thick oil. The supernatant was transferred to a beaker; upon standing in the refrigerator for several days, the solution crystallized into long yellow needles. The proton nmr spectrum in D_2O had no proton peaks.

The proton nmr of the oil from the organic layer in $CDCl_3$ indicated that the thiazolidine ring was no longer intact.

3-Benzoyl-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid (XIX) + Borane-methyl sulfide (BMS): 0.3 g (0.001 mole) XIX was added to 3 mL of anhydrous ether in a round bottom flask equipped with a condenser and a nitrogen gas bubbler. To the stirred mixture 0.6 mL (0.0012 mole) BMS was added dropwise with gas evolution. The acid dissolved rapidly. The mixture was refluxed for 50 min., gas evolution was fast initially, but in the last 15-20 min. it

could not be detected. The cooled solution was poured into cold methanol and it remained clear, contrary to what was expected (97). The solution was evaporated to leave an oil, and when a few drops of water were added the oil turned into a white solid. This was recrystallized from aqueous methanol. The ^{1}H nmr spectrum showed that this oil was the starting acid. The reaction was repeated under the following conditions:

XIX	BMS	Solvent	Reaction Conditions
1.0	1.2	ether	35°C, 1 hr; stir r. t. 1 hr
1.0	1.5	ether	35°C, 1.5 hrs; r. t. 15 hrs
1.3	2.0	ether	35°C, 4 hrs
1.0	2.0	THF	66°C, 2 hrs
0.8	1.0	ether	35°C, 15 hrs

3-Benzoyl-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid (XIX) + $NaBH_4$-Boron trifluoride etherate: 0.039 g (0.001 mole) $NaBH_4$ was added to 5 mL of predistilled diglyme. 0.30 g (0.001 mole) XIX was added slowly with fast gas production. 0.16 mL (0.0011 mole) of 2M boron trifluoride etherate solution in diglyme was added dropwise to the stirred mixture on ice. The mixture was left in the refrigerator over the weekend. It was then stirred at r. t. for 5 hours, then filtered into crushed ice and the resultant white suspension was placed in the refrigerator overnight. A small amount of precipitate was removed by

filtration and the proton nmr showed that the starting acid was recovered. This reaction was repeated as shown in the table below:

XIX	$NaBH_4$	BF_3	Solvent	Reaction Conditions
1.0	2.0	0.8	diglyme	stir r. t. overnight
1.0	4.0	0.6	THF	55°C, 8 hrs
1.0	2.5	0.8	diglyme	r. t. 1 day; 50-60°C, 7 hrs
1.0	2.0	0.8	diglyme	r. t. 1 day; 70°C, 40 min. Dec.
0.5	2.0	0.3	THF	stir r. t. 2 days; 50-65°C, 8 hrs; 45°C, 15 hrs

3-Benzoyl-2,2,5,5-tetramethylthiazolidine-4-carboxylic acid (XIX) + Borane-THF complex: 0.18 g (0.0006 mole) XIX was dissolved in 2 mL cold THF. 2 mL (0.002 mole) 1M BH_3.THF was added slowly to the stirred solution at 0°C, and continued stirring for 30 min. on ice, then at r. t. for 7 hours. To the solution on ice 4 mL of 1.5M NaOH was added. The white suspension turned yellow within a few minutes. A few drops of dilute HCl were added to obtain a pH of approx. 11, and the mixture became colorless. The THF in the mixture was removed by evaporation to leave a white suspension which was extracted three times with 45 mL of $CHCl_3$. The organic layer was evaporated under nitrogen stream to leave a thick orange oil soluble in $CHCl_3$ and

DMSO. The ^{1}H nmr did not help in identifying the species present, because of the large number of peaks, some of which were broad.

At this point it was decided to try to reduce the less sterically hindered thiazolidine also derived from D-penicillamine, 5,5-dimethylthiazolidine-4-carboxylic acid. In order to optimize conditions for the reduction of 3-benzoyl-2,2-dimethyl-4-methoxycarbonylthiazolidine (2,2-DMT), for which a procedure using sodium boroydride had been published (61) and the extent of reaction could be monitored by TLC, the reaction was carried out a number of times in an attempt to increase the yield of the wanted alcohol (see the following table). The procedure for this reduction has been given in Section II.. Generally the yield was better with longer reaction times and when a large excess of $NaBH_4$ was used. Ethanol appeared to be a better solvent than methanol.

XIX	$NaBH_4$	Solvent	Reaction Conditions
1.0	22.0	MeOH	r. t. 3.5 hrs
1.0	10.0	MeOH	r. t. overnight
1.3	20.0	MeOH	r. t. 30 hrs
1.0	8.0	MeOH	r. t. 6 days
1.0	10.0	MeOH	r. t. 30 min.; 65^{o}C, 2 hrs
2.8	30.0	EtOH	r. t. 24 hrs
0.8	2.2	EtOH	r. t. 3 days
0.5	10.0	EtOH	r. t. 15 hrs; 78^{o}C, 1 hr

3-Benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine (XIII) + $NaBH_4$: The procedure for this reaction has already been given in the Methods and Materials section. The table below summarizes the conditions under which the reaction was attempted. Most reaction products show partial reduction to a greater or lesser extent depending on the conditions of reaction and the reaction mixtures treated to high temperatures show partial debenzoylation in the nmr.

XIII	$NaBH_4$	Solvent	Reaction Conditions
1.0	22	MeOH	r. t. 5.5 hrs
0.8	10	MeOH	r. t. overnight
0.8	10	MeOH	r. t. 16 hrs; 50°C, 27 hrs. Dec.
0.5	12	MeOH	r. t. 35 hrs
0.5	12	MeOH	r. t. 5 days
0.8	3.5	EtOH	r. t. overnight
1.0	10	EtOH	r. t. 2 hrs; 50°C, 1 hr
0.8	12	EtOH	r. t. 16 hrs; 78°C, 2 hrs
0.8	12	EtOH	r. t. 24 hrs; 78°C, 1 hr
1.8	20	EtOH	r. t. 15 hrs; 50°C, 2 hrs
1.2	5	EtOH	50°C, 16 hrs
1.0	12	i-PrOH	40°C, 16 hrs

3-Benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine (XIII) + $LiBH_4$: To 0.16 g (0.0006 mole) XIII dissolved in 5 mL THF an excess of $LiBH_4$ (0.008 mole) was added, with

fast gas production. The reaction was followed by TLC. 30 min. after mixing the reagents a new spot of Rf lower than that of the starting ester could be seen on the TLC plate, as expected. There were also two unexpected spots of Rf > Rf of the starting ester. The reaction mixture was worked up by slow addition of dilute HCl followed by extraction of the aqueous solution with dichloromethane. A colorless oil was recovered after evaporation of the organic layer. The TLC, developed in a 4:1 Benzene:Ethyl Acetate mixture, showed a streaking spot below the spot of the starting ester, which was very weak. The nmr shows that there was some reduction, indicating that possibly this is a more efficient method of reducing the thiazolidine esters than sodium borohydride.

3-Benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine (XIII) + LiCl: 0.07 g (0.0018 mole) $NaBH_4$ was added to 2 mL diglyme. To this mixture 0.1 g (0.0004 mole) XIII and 0.07 g (0.0017 mole) LiCl were added and the mixture was stirred at r. t. for 5 days. The reaction mixture was worked up by slowly adding cold water until a precipitate formed and disappeared. The solution was extracted three times with 60 mL $CHCl_3$. The dried organic layer was evaporated to yield an oil. The proton nmr showed that the thiazolidine compound was no longer methylated or benzoylated, and the TLC showed the presence of three components. Other reactions were attempted:

XIII	LiCl	$NaBH_4$	Reaction Conditions
1.0	3.0	5.0	r. t. 1 hr
0.8	3.0	3.0	r. t. 6 hrs; 50°C, 3 hrs
0.4	2.0	3.0	r. t. 16 hrs
0.4	2.0	2.0	67°C, 3 hrs; r. t. 16 hrs. Dec.

3-Benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine (XIII) + $AlCl_3$: 0.04 g (0.001 mole) $NaBH_4$ in 3 mL diglyme was added to a cooled mixture of 0.2 g (0.0008 mole) XIII and 0.02 g (0.0002 mole) $AlCl_3$ in 1 mL diglyme. The reaction mixture was stirred overnight then heated to 65-70°C for 5 hours, and again stirred at r. t. overnight. A small fraction of the reaction mixture was removed and worked up in the same way as the LiCl reaction previously described. The nmr spectrum showed that the recovered solid was the starting ester. The remainder of the reaction mixture was heated further for 2 hours at 50°C, then worked up to recover a white solid which had an identical nmr spectrum with that of the first fraction.

3-Benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine (XIII) + $NaBH(OMe)_3$: 0.15 g (0.001 mole) XIII was dissolved in 7 mL dimethoxyethane and to this solution 0.2 g (0.0013 mole) $NaBH(OMe)_3$ was added slowly to the stirred solution, with gas being evolved. The mixture was stirred for 30 min., then heated at 60°C for 1 hour and allowed to react at 50°C overnight. To the suspension about 5 mL of water was

added and then it was extracted four times with a total of 60 mL of $CHCl_3$. The organic layer was evaporated to leave an oil which crystallized as long thin crystals. These were filtered to give 0.09 g of solid the ^1H nmr spectrum of which was identical with that of the starting material. Three other reactions were carried out:

XIII	$NaBH(OMe)_3$	Reaction Conditions
0.5	1.3	50°C overnight; r. t. 2 days
0.5	1.3	50°C, 24 hrs; stir r. t. 3 days
0.5	1.6	85°C, 16 hrs. Dec.

3-Benzoyl-5,5-dimethyl-4-methoxycarbonylthiazolidine (XIII) + $LiAlH_4$: To 0.15 g (0.0005 mole) XIII and 2 mL of anhydrous ether 0.005 mole $LiAlH_4$ was added. The mixture was made up on ice then it was left in the refrigerator for 4 hours. The mixture was extracted three times with a total volume of 50 mL $CHCl_3$. The organic layer was separated, dried and evaporated. A small amount of orange oil was obtained which gave a TLC with four spots of closely related Rf values. The ^1H nmr of this complex mixture was not obtained.

Another reaction was carried out with the same amounts of reagents and allowed to react in the cold overnight. An oil was recovered following treatment of the reaction mixture as before. The ^1H nmr of the oil suggested the ester was still present and that the benzoyl group had been

removed.

3-Benzoyl-5,5-dimethylthiazolidine-4-carboxylic acid (XII) + $NaBH_4/(COCl)_2$: 0.5 mL (0.004 mole) of oxalyl chloride was added to 0.002 mole DMF in 3 mL CH_2Cl_2 at 0°C. The mixture was stirred for an hour then it was evaporated in the rotoevaporator to leave a white residue. To this 3 mL of CH_3CN and 5 mL THF and a solution of 0.002 mole XII in 3 mL THF were added while the reaction was kept at -50°C. The mixture was stirred for one hour and 15 min. at -50 to -25°C. To the mixture at -60°C, 0.002 mole $NaBH_4$ in 5 mL DMF was added. The mixture was stirred for two hours then the temperature was allowed to rise slowly to 0°C. 4 mL of 2M HCl was added to the mixture with fast gas release. 10 mL of water was added, and the mixture was extracted with 30 mL $CHCl_3$ twice. The organic layer was evaporated to leave a colorless liquid, which the proton nmr revealed as mostly DMF. The mixture was extracted with water and ether to remove the DMF. The ether layer was evaporated and it left no residue. The aqueous layer was extracted with ethyl acetate which left a thin oil film in the beaker after evaporation. TLC showed that a complex mixture was present, and the ^1H nmr showed no evidence of reduction and that the benzoyl group was no longer present. The aqueous layer was also extracted with dichloromethane to leave a yellow liquid. TLC again showed 3 to 5 components with streaking spots so that it was not possible to separate them by column

chromatography.

3-Benzoyl-5,5-dimethylthiazolidine-4-carboxylic acid (XII) + Borane trifluoride etherate: 0.04 g (0.001 mole) $NaBH_4$ was added to 5 mL of diglyme and to this suspension 0.3 g (0.001 mole) XII was added under nitrogen. The mixture was stirred at r. t. until gas release slowed down. 0.16 g of boron trifluoride etherate was added and the mixture allowed to stir at r. t. for two hours, then it was heated at 50°C one hour. The light yellow solution, which resulted from standing on the lab bench overnight, was added to cold water and left in the refrigerator for three hours. The clear solution was evaporated under a nitrogen stream to leave a mixture of a white solid and an oil. The solid was insoluble in $CHCl_3$ and in DMSO but it was water soluble. The oil had a very complex ^1H nmr spectrum and appeared to be very impure starting material, although it was not conclusive.

Other reactions were carried out, see the following table, and the ^1H nmr of the recovered material showed the presence of the starting acid, except in cases where decomposition occurred.

XII	$NaBH_4$	$BF_3.Et_2O$	Reaction Conditions
1.0	1.0	0.5	r. t. 2 days
1.0	1.2	0.6	r. t. 2 hrs; 50°C, 1 hr; r. t. 2 days
0.6	1.0	0.5	r. t. 15 hrs; 70°C, 6 hrs
0.5	2.0	0.25	50°C, 10 hrs; 65°C, 7 hrs. Dec.

3-Benzoyl-5,5-dimethylthiazolidine-4-carboxylic acid (XII) + Borane Methyl Sulfide (BMS): 0.3 g (0.001 mole) XII was dissolved in 6 mL THF and to this solution 0.6 mL (1 equiv.) of 2M $BF_3.Me_2S$ in THF was added. The reaction mixture was stirred at r. t. for 30 min. under nitrogen then it was heated at 60°C for two hours, and then stirred for two days at r. t. The white suspension was added to ice-cold water in which it dissolved. The solution was left in the refrigerator for a week. No change was noticed and the mixture was evaporated to leave a dry residue mostly soluble in chloroform. The ^1H nmr indicated that it was the starting acid. This reaction was repeated as follows:

XII	BMS	Solvent	Reaction Conditions
0.6	1.0	ether	r. t. overnight
0.6	1.0	ether	r. t. 15 min.; 35°C, 15 hrs
1.0	1.2	THF	r. t. 30 min.; 65°C, 2 hrs
0.6	1.0	THF	65°C, 10 hrs. Dec.

V. BIBLIOGRAPHY

1. E.A. Carr, Jr.. Clin. Pharmacol. Ther. **35**, 94 (1985).

2. D. Sutton. "Radiology and Imaging for Medical Students", 4th Ed., Livingstone, London. 1982; p. 179.

3. I.L. Pykett. Sci. Amer. **246**, 78 (1982).

4. J.P. Whalen, S. Balter. "Radiation Risks in Medical Imaging", Year Book Medical Publishers, Chicago. 1984; p. 49.

5. C.L. Partain, A.E. James, F.D. Rollo, R.R. Price. "Nuclear Magnetic Resonance Imaging", W.B. Saunder Co., Toronto, 1983; p. 355.

6. F.A. Mettler, Jr., A.G. Williams, J.H. Christie, R.D. Moselly, C.A. Kelsey. J. Nucl. Med. **26**, 201 (1985).

7. M.E. Phelps, E.H. Hoffman, S.C. Huang, D.E. Kuhl. J. Nucl. Med. **19**, 635 (1978).

8. M.H. Lewis, J.T. Willerson, S.E. Lewis, et al.. J. Nucl. Med. **23**, 1121 (1982).

9. M.T. Madsen, C.H. Park. J. Nucl. Med. **26**, 395 (1985).

10. C.F. Meares, T.F. Wensel. Acc. Chem. Res. **17**, 202 (1984).

11. E.A. Deutsch, B.L. Barnett in "Inorganic Chemistry in Biology and Medicine", A.E. Martell (Edr.), American Chemical Society Symposium Series, No. 140, A.C.S., Washington, D.C., 1980; p. 103.

12. L.G. Marzilli, R.F. Dannals, H.D. Burns. ibid.; p. 91.

13. E.A. Deutsch, K. Libson, S. Jurisson, L.F. Lindoy. Prog. Inorg. Chem. **30**, 75 (1982).

14. A. Davison in "Technetium in Chemistry and Nuclear Medicine", E.A. Deutsch, M. Nicolini, H.N. Wagner, Jr. (Eds.), Cortina International, Verona. 1983; p. 3.

15. L.G. Marzilli, A.V. Kramer, H.D. Burns, L.A. Epps. ibid.; p. 63.

16. B.A. Khaw, J.T. Fallon, H.W. Strauss, E. Haber. Sci. **209**, 295 (1980).

17. E.A. Deutsch, K. Libson. In ref. 11; p. 29.

18. J.G. McAffee, C.F. Fueger, H.S. Stern, H.N. Wagner, Jr., T. Migita. J. Nucl. Med. **25**, 811 (1984).

19. L. Bellito, C. Donadio, G. Tramonti, P. Lorusso, F. Lunghi, F. Zito, C. Bianchi. In ref. 14; p. 171.

20. H.F. Kung, M. Blau. J. Nucl. Med. **21**, 147 (1980).

21. H.F. Kung, K.M. Tramposch, M. Blau. J. Nucl. Med. **24**, 66 (1983).

22. A. Yokoyama, K. Horiuchi. Int. J. Appl. Rad. Isot. **33**, 929 (1982).

23. R.G. Robinson, D. Bradshaw, B.A. Rhodes, J.A. Spicer, R.J. Visentin, A.H. Gobuty. Int. J. Appl. Rad. Isot. **28**, 105 (1977).

24. D.L. Johnson, A.R. Fritzberg, B.L. Hawkins, S. Kasina. Inorg. Chem. **23**, 4204 (1984).

25. A.G. Jones, A. Davison. In ref. 14; p. 25.

26. A. Davison, B.V. DePamphilis, R. Faggiani, A.G. Jones, C.J.L. Lock, C. Orvig. Can. J. Chem. **63**, 319 (1985).

27. C.E. Costello, J.W. Brodack, A.G. Jones et al.. J. Nuc. Med. **24**, 353 (1983).

28. A.G. Jones, M.J. Abraams, A. Davison. In ref. 14; p. 27.

29. S. Seifert, R. Munze, B. Johannsen. In ref. 14; p. 19.

30. J.C. Crawhall, E.F. Scowen, R.E. Watts. Brit. Med. J. **1963**, 588.

31. M. Friedman in "Advances in Experimental Medicine and Biology", Plenum Press, **86B**, 36

32. W.F. Kean, T.P. Anastassiades, I. L. Dwosh, P.M. Ford, W.G. Kelly, C.M. Dok. J. Am. Geriatr. Soc. **30**, 94 (1982).

33. W.M. Weigert, H. Offermanns, P. Scherberich. Angew. Chem. Int. Ed. **14**, 330 (1975).

34. K.J. Franklin, H.E. Howard-Lock, C.J.L. Lock. Inorg. Chem. **21**, 1941 (1982).

35. L. Stryer, "Biochemistry", 2nd. Ed., Freeman & Co., San Francisco, CA. 1983; p. 867.

36. H.T. Nagasawa, D.J.W. Goon, E.G. DeMaster. J. Med. Chem. **21**, 1274 (1978).

37. S. Ratner, H.T. Clarke. J. Am. Chem. Soc. **59**, 200 (1937).

38. J. Heller. Biochem. **7**, 2914 (1968).

39. R.G. Kallen. (a)J. Am. Chem. Soc. **93**, 6227 (1971), (b) J. Am. Chem. Soc. **93**, 6236 (1971).

40. V.R. Riemschneider, G.A. Hoyer. Z. Naturforsch. **18b**, 25 (1963).

41. J.J. Peset, J.H. Frost. Tetrahedron, **31**, 907 (1975).

42. J.F.W. McOmie, Adv. Org. Chem.**3**, 191 (1963).

43. J.P. Greenstein, M. Winnitz. "Chemistry of the Aminoacids", Vol. 3, Wiley and Sons, New York. 1961.

44. A. Berger, J. Noguchi, E. Katchalsky. J. Am. Chem. Soc. **78**, 4483 (1956).

45. F. Weygang, R. Geiger. Chem. Ber. **90**, 634 (1957).

46. R.A. Boissonas, Adv. Org. Chem. **3**, 159 (1963).

47. H. Zahn, K. Hammerstrom. Chem. Ber. **102**, 1048 (1969).

48. G. Amiard, R. Heimes, L. Velluz. Bull. Soc. Chim. France **23**, 698 (1956).

49. L. Zervas, I. Photaki, I Phocas. Chem. Ber. **101**, 3332 (1968).

50. L. Zervas, I. Photaki. J. Am. Chem. Soc. **84**, 3887 (1962).

51. G.H.L. Nefkens, G.I. Tesser, R.J.F. Nivard. Rec. Trav. Chim. Pays-Bas **79**, 668 (1960).

52. L. Zervas, I. Photaki, N. Ghelis. J. Am. Chem. Soc. **85**, 1339 (1983).

53. D.F. Veber, J.D. Milkowsky, S.L. Varga, R.G. Denkewalter, R. Hirshmann. J. Am. Chem. Soc. **94**, 5456 (1972).

54. T.R.C. Boyd, J. Chem. Soc., Chem. Comm. **1968**, 2751.

55. T.J. deBoer, H.J. Backer. Org. Syn. Coll. Vol. **4**, 943 (1963).

56. B. Lippert, C.J.L. Lock, B. Rosenberg, M. Zvagulis. Inorg. Chem. **16**, 1525 (1977).

57. R.P. Hughes, N. Khrishnamachari, C.J.L. Lock, J. Powell, G. Turner. Inorg. Chem. **16**, 314 (1977).

58. V.R. Riemschneider, G.A. Hoyer. Z. Naturforsch. **17b**, 765 (1962).

59. J.C. Sheehan, D.D.H. Yang. J. Am. Chem. Soc. **80**, 1158 (1957).

60. M. Iwakawa, B.M. Pinto, W.A. Szarek. Can. J. Chem. **56**, 326 (1978).

61. A.H. Cook, I.M. Heilbron in "The Chemistry of Penicillin", H.T. Clarke, J.R. Johnson, R. Robinson, Eds., Princeton University Press, Princeton, N.J. 1949; (a)p. 962, (b)p. 959, (c)p. 958, (d)p. 961.

62. H.E. Howard-Lock, C.J.L. Lock, P.S. Smalley. Can. J. Chem. **63**, 2411 (1985).

63. A. Hajos, "Complex Hydrides", Elsevier, Budapest. 1979.

64. H.O. House, "Modern Synthetic Reactions", W.A. Benjamin Inc., New York. 1965.

65. G.R. Pettit, T.R. Kasturi. J. Org. Chem. **26**, 1686 (1961).

66. R.A. Bell, M.B. Gravestock. Can. J. Chem. **47**, 2099 (1969).

67. This work and crystal structure is under review by Can. J. Chem for publication.

68. S. Toppet, P. Claes, J. Hoogmartens. Org. Magn. Res. **6**, 48 (1974).

69. M. Guiliano, D. Davidovics, J. Chouteau, J.L. Larice, J.P. Roggero. (a)J. Mol. Struct. **25**, 329 (1975); (b)J. Mol. Struct. **25**, 343 (1975).

70. E. Catrina. Rev. Roum. Chim. **21**, 81 (1976).

71. H.E. Howard-Lock, C.J.L. Lock, P.S. Smalley. J. Cryst. Spectrosc. Res. **13**, 333 (1983).

72. H.E. Howard-Lock, C.J.L. Lock, M.L. Martins, P.S. Smalley. Submitted to Can. J. Chem. (1986).

73. H.E. Howard-Lock, C.J.L. Lock, M.L. Martins, P.S. Smalley. Submitted to Can. J. Chem. (1986).

74. S.K. Freeman. "Applications of Laser Raman Spectroscopy", J. Wiley and Sons, New York. 1974.

75. N.B. Colthup, L.H. Daly, S.E. Wiberley. "Introduction to Infrared and Raman Spectroscopy", Academic Press, New York. 1964.

76. W.C. Hamilton, J.A. Ibers. "Hydrogen Bonding in Solids", W.A. Benjamin Inc., New York. 1968.

77. A. Novak. Structure and Bonding, **18**, 177 (1974).

78. G.C. Levy, G.L. Nelson. "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York. 1972.

79. R.A. Archer, R.D.G. Cooper, P.V. DeMarco, L.F. Johnson. J. Chem. Soc., Chem. Comm. **1970**, 1291.

80. R.D.G. Cooper, P.V. DeMario, J. C. Cheng, W.D. Jonas. J. Am. Chem. Soc. **91**, 1908 (1969).

81. M.M. Vestling, R.L. Ogren. J. Heterocyclic Chem. **12**, 243 (1975).

82. J. Loscalzo, R.G. Kallen, D. Voet. Arch. Biochem. Biophys. **157**, 426 (1973).

83. P.W. Borthwick. Acta Crystallogr. **B36**, 628 (1980).

84. H.E. Howard-Lock, C.J.L. Lock, M.L. Martins, R. Faggiani, M. Duarte. Submitted to J. Am. Chem. Soc. (Dec. 1985).

85. M. Catti, G. Ferraris. Acta Crystallogr. **B32**, 2754 (1976).

86. R.D. Ellison, H.A. Levy. Acta Crystallogr. **19**, 260 (1965).

87. M.D. Joester, L.J. Schaad. "Hydrogen Bonding", Dekker Inc., New York. 1974.

88. M.S. Brown, H. Rapoport. J. Org. Chem. **28**, 3261 (1963).

89. H. Seki, K. Kenji, H. Matsuo, S. Ohki, I. Matsuo, S. Yamada. Chem. Pharm. Bull. **13**, 995 (1965).

90. H.C. Brown, B.C. Subba Rao. J. Am. Chem. Soc. **78**, 2582 (1956).

91. P. Karrer, P. Portmann, M. Sutter. Helv. Chim. Acta, **31**, 1617 (1948).

92. T. Fujisawa, T. Mori, T. Sato. Chem. Lett. **1983**, 835.

93. R.H. Manske. Org. Syn. Coll. Vol. II, 154.

94. H.C. Brown, P. Heim, N.M. Yoon. J. Am. Chem. Soc. **92**, 1637 (1970).

95. M.L. Anhoury, M. Arickx, P. Crooy, R. Neys, J. Eliaers. J. Chem. Soc. Perkin I **1974**, 191.

96. G.S. Poindexter, A.I. Meyers. Tetrahedron Lett. **1977**, 3527.

97. R.E. Dessy, J.-Y. Kim. J. Am. Chem. Soc. **82**, 681 (1960).

98. S. Khrishnamurthy, K.L. Thompson. J. Org. Chem. **54**, 778 (1977).