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# I. Studies Toward the Synthesis of Echinodithianic Acid and II. The Temperature Dependent NMR Spectrum of Methyl N-Acetylsarcosinate

Alan LeRoy Love
*Utah State University*

# I. STUDIES TOWARD THE SYNTHESIS OF ECHINODITHIANIC ACID

and

# II. THE TEMPERATURE DEPENDENT NMR SPECTRUM OF METHYL N-ACETYLSARCOSINATE

by

Alan LeRoy Love

A dissertation submitted in partial fulfillment
of the requirements for the degree

of

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in

Chemistry

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1971

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I am grateful to Dr. Richard K. Olsen, the research director, for his capable help and advice, and to Dr. Terry D. Alger for his aid on the second part of this thesis.

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And I express appreciation to my wife, Lesley, for her understanding and support.

Alan L. Love

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# ABSTRACT

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and
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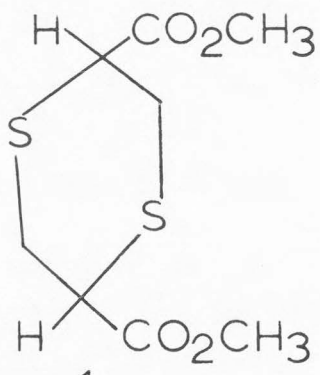
Methyl N-Acetylsarcosinate
by
Alan L. Love, Doctor of Philosophy
Utah State University (1971)

Major Professor: Dr. Richard K. Olsen
Department: Chemistry

Approaches to the preparation of echinodithianic acid (5) from 2,5-dicarbomethoxy-1,4-dithiane (1) were not successful, due to the inability to carboxylate or



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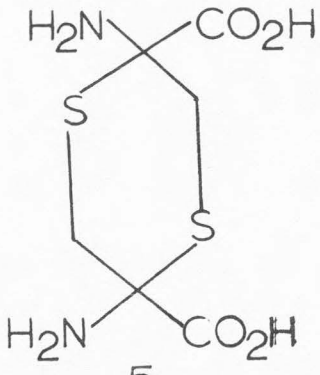
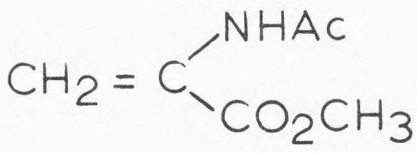


5

carboalkoxylate 1 at carbons 2 and 5. Studies toward the synthesis of 5 utilizing methyl 2-acetamidoacrylate (8) have been investigated. The electrophilic addition of

sulfur dichloride to 8 yielded bis-(2-acetamido-2-carbomethoxyvin-1-yl) sulfide, while the addition of thiocyanogen

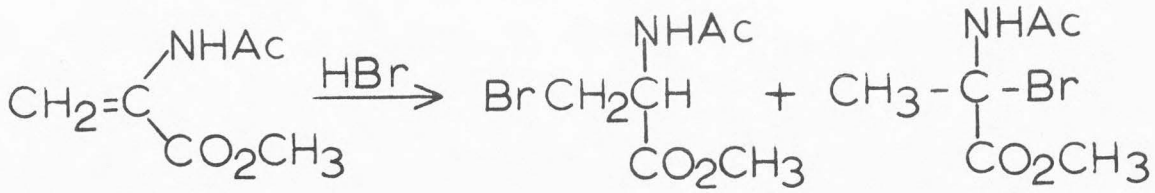


8

chloride to 8 produced methyl 2-acetamido-3-thiocyanatoacrylate.

As electrophilic additions of unsymmetrical dipolar reagents to methyl 2-acetamidoacrylate (8) are not reported in the literature, the addition of hydrogen bromide to 8 was studied to determine the orientation effect of the acetamido group.

Methyl 2-acetamido-2-bromopropionate (69) was found to be the kinetically favored adduct, while under equilibrium conditions the Michael addition product, methyl 2-acetamido-3-bromopropionate (68), was favored.



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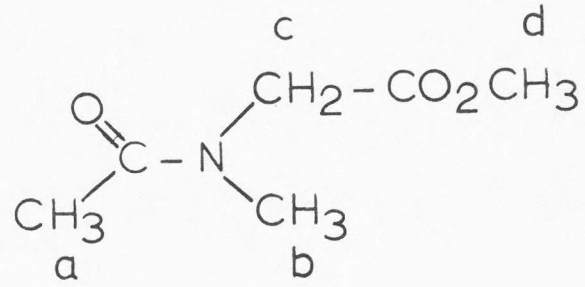
The rates of exchange of the acetyl (a) and the N-methyl (b) protons from the cis to the trans form of methyl N-acetylsarcosinate (72) were measured by a total NMR




72

lineshape method and found to be the same within the limits of the experimental method. Thermodynamic activation parameters are reported.

From these data it was concluded that the exchanges of each of the four types of protons (a,b,c,d) in 72 depend solely on hindered rotation about the amide C-N bond.

(130 pages)

# PART I

# STUDIES TOWARD THE SYNTHESIS OF ECHINODITHIANIC ACID

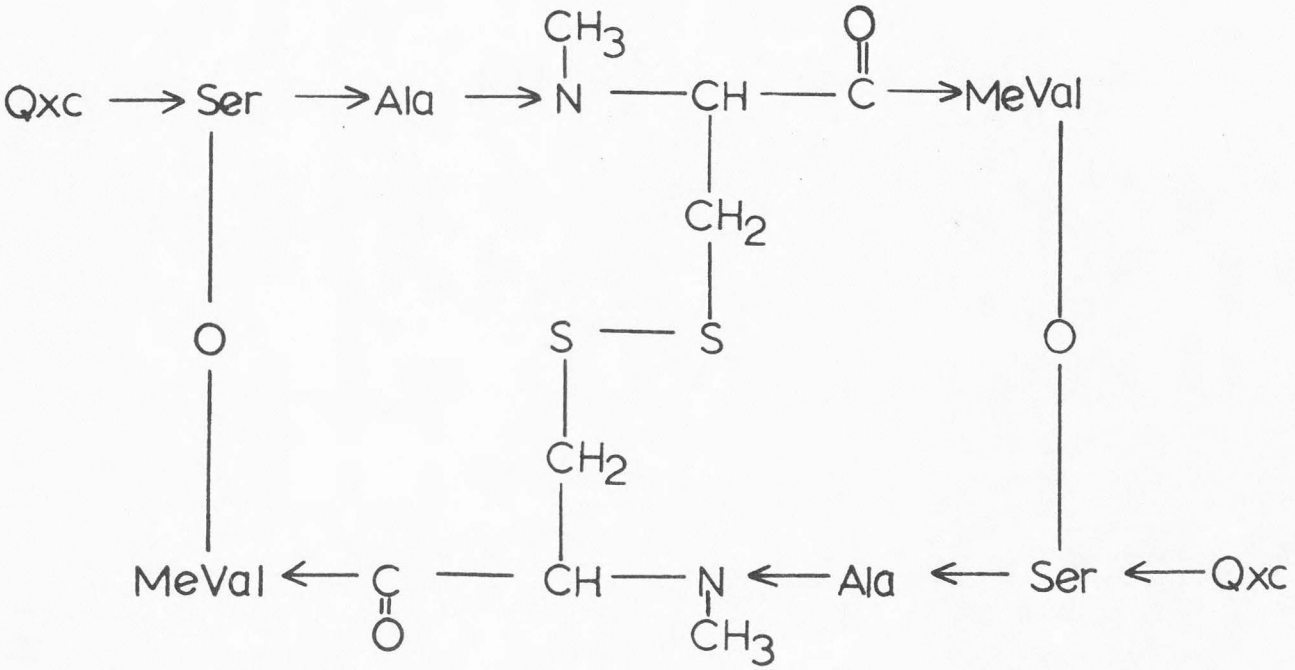
# INTRODUCTION

The quinoxaline antibiotics have been shown to have some interesting biological properties. As a group, they are active *in vitro* against gram-positive bacteria (1), and have been shown to inhibit tumor growth including some types of leukemia in cats, mice, and hamsters (2). One of these compounds, echinomycin, has been shown to inhibit DNA and RNA synthesis (3) and thus is a potential anti-cancer agent.

The common structural features of the quinoxaline antibiotics are a cyclic peptide-lactone ring composed of eight amino acids, and two quinoxaline-2-carboxylic acid moieties attached to the amino group of serine (4). The triostin family, Figure 1, contains a disulfide linkage across the cyclic structure (5). Echinomycin, Figure 2, possesses a 26-membered peptide lactone ring composed of two units each of D-serine, L-alanine, and N-methyl-L-valine interconnected by a 1,4-dithiane ring (4).

Echinomycin was isolated from *Streptomyces echinatus* by Corbaz and co-workers (1a) and Berger and co-workers (1b) both in 1957. Its structure was reported by Keller-Schierlein, Mihailovic, and Prelog in 1959 (4).

It is proposed that echinomycin be synthesized by first preparing *cis*-2,5-di(methylamino)-1,4-dithiane-2,5-dicarboxylic acid (5a) and then adding the appropriate

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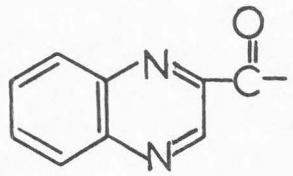



Figure 1. Triostin A

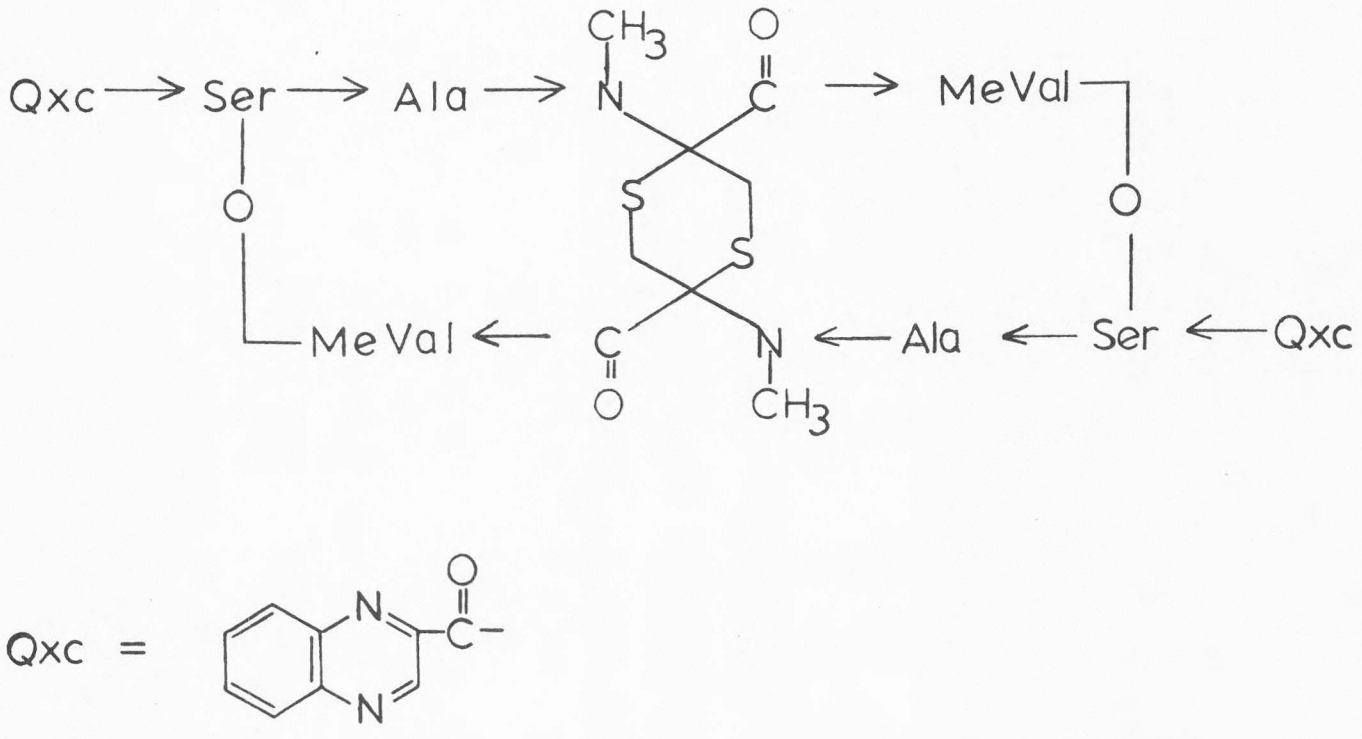
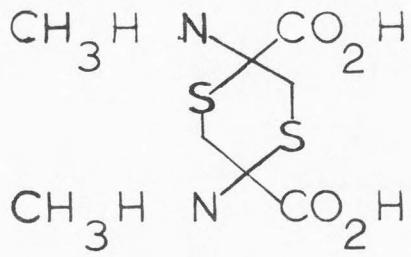



Figure 2. Echinomycin

amino acids in sequence followed by a cyclization reaction.



5a

This thesis is concerned with approaches to the synthesis of a suitable derivative of 2,5-diamino-1,4-dithiane-2,5-dicarboxylic acid (5). One approach would be to convert the previously prepared 2,5-dicarbomethoxy-1,4-dithiane (1) to 2,5-dicarbomethoxy-1,4-dithiane-2,5-dicarboxylic acid (2) by an appropriate carboxylation reaction followed by conversion of the ester functions to amino moieties via the Curtius rearrangement as outlined in Figure 3.

Alternatively, 2,5-dicarbomethoxy-1,4-dithiane (1) could be converted to a 2,2,5,5-tetracarboalkoxy-1,4-dithiane (6), which would then be hydrolyzed to the 2,5-dicarboxylic acid (7) (see Figure 4), followed by conversion to the amino acid 5.

When attempts to carry out the carboxylation of 1 failed, work was begun toward the cyclization of a compound with the amino function already present in the starting material. While an obvious choice, methyl 2-aminoacrylate, is not known, the acetyl derivative, methyl 2-acetamidoacrylate (8) is known.

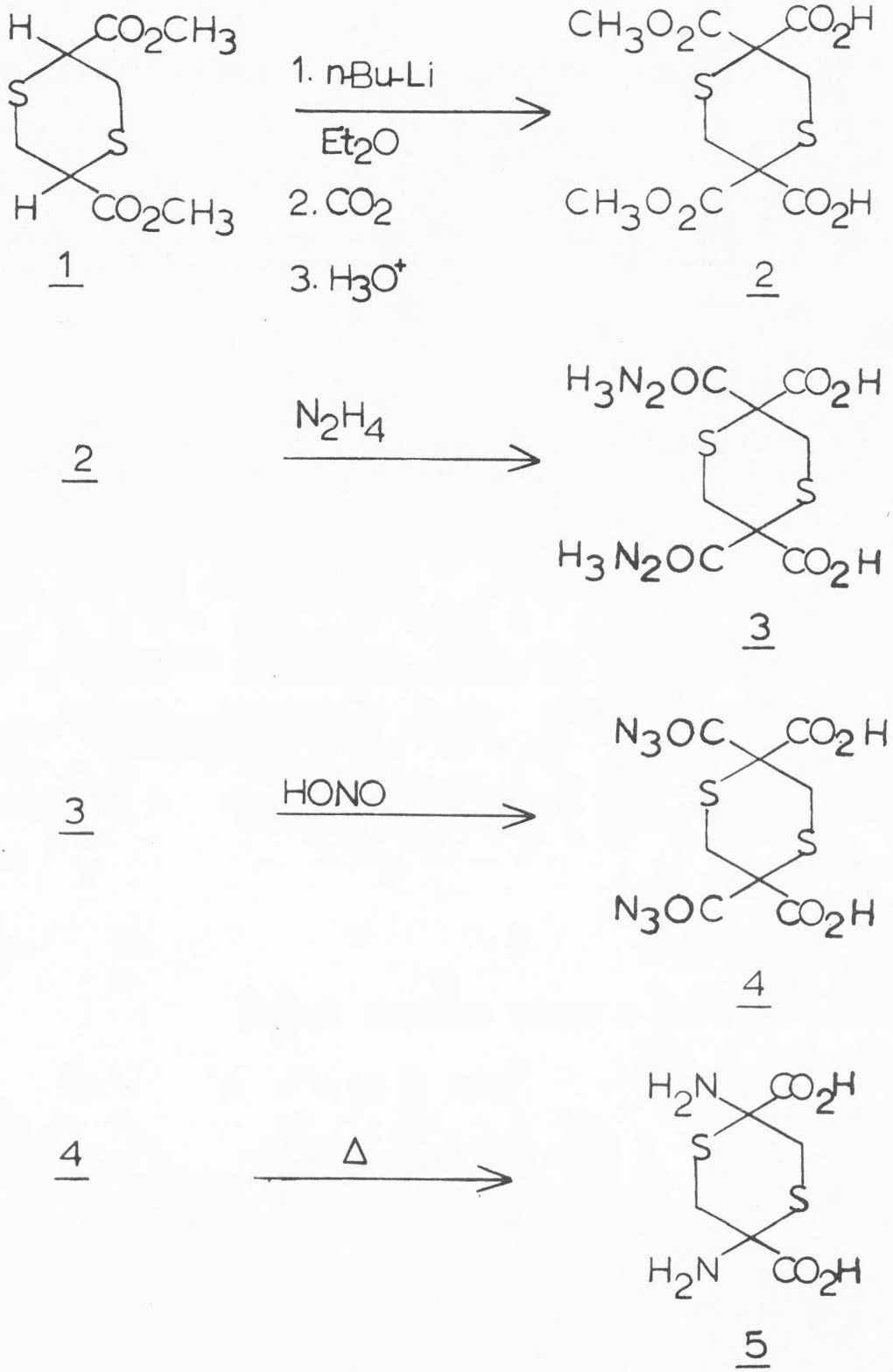



Figure 3. Scheme for synthesis of 2,5-diamino-1,4-dithiane-2,5-dicarboxylic acid via a carboxylation reaction and the Curtius rearrangement.

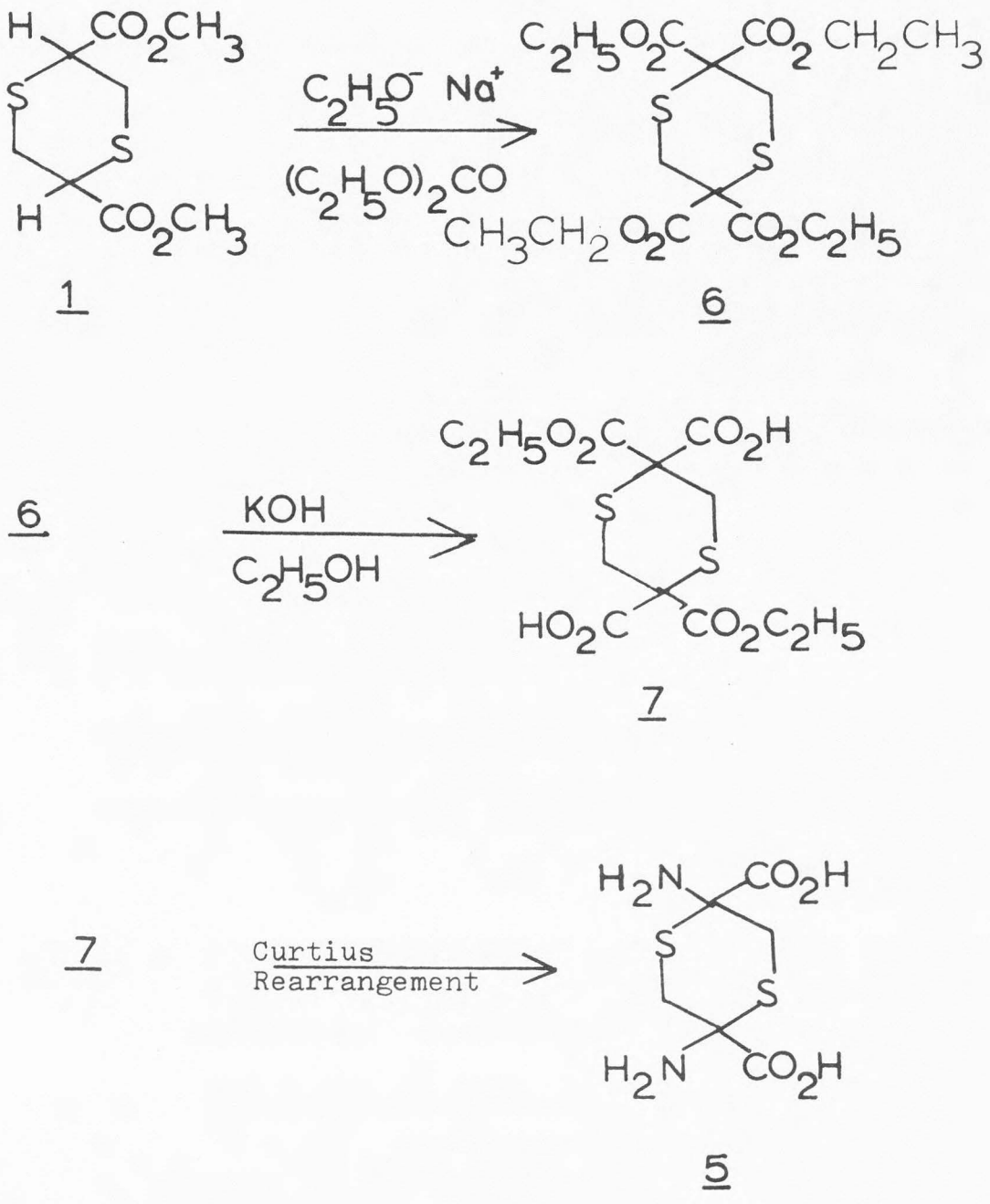
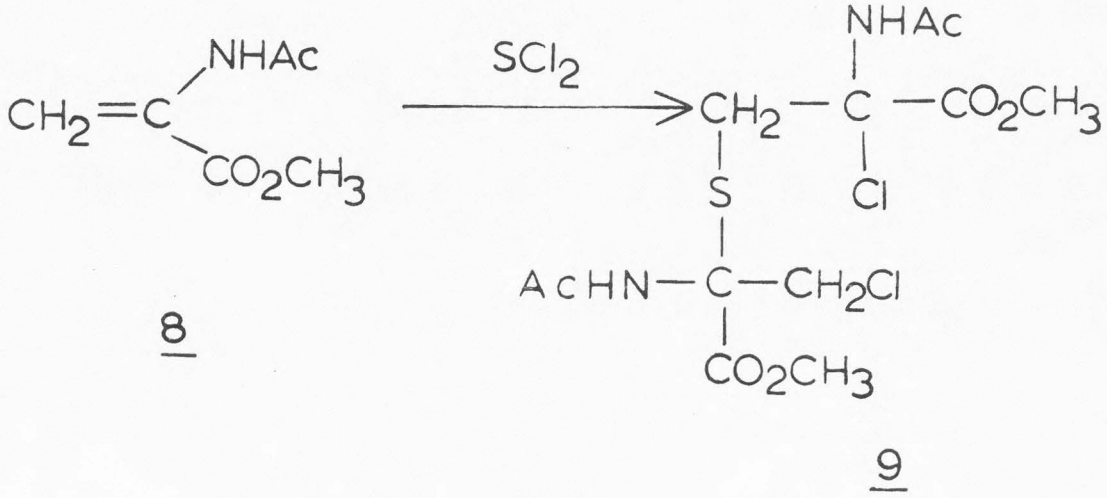



Figure 4. Scheme for synthesis of 2,5-diamino-1,4-dithiane-2,5-dicarboxylic acid via a carbethoxylation reaction and the Curtius rearrangement.

Addition of sulfur dichloride to 8, followed by treatment with sodium sulfide (see Figure 5), could lead to 2,5-diacetamido-2,5-dicarbomethoxy-1,4-dithiane (10) in a manner analagous to the preparation of 2,5-dicarbomethoxy-1,4-dithiane from methyl acrylate as reported by Gundermann and Burba (6).

Thiocyanogen chloride could add to methyl 2-acetamidoacrylate (8) to give the thiocyanate, which could then be reduced to the mercaptan (12) (see Figure 6). On treatment with base 12 might cyclize to the desired 1,4-dithiane 10.

Since electrophilic additions of dipolar reagents to methyl 2-acetamidoacrylate are not reported, the addition of sulfur dichloride and thiocyanogen chloride are not only significant as a synthetic route, but also in determining the influence of the acetamido group on such reactions. The addition of hydrogen bromide to methyl 2-acetamidoacrylate is also studied and compared to the addition of hydrogen bromide to methyl acrylate, and conclusions about the effect of the acetamido group are drawn.

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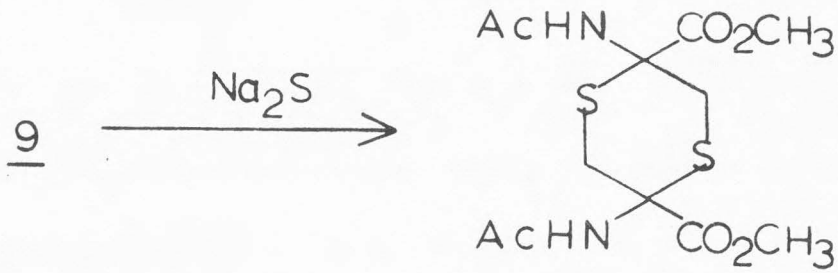


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Figure 5. Scheme for synthesis of 2,5-diacetamido-1,4-dithiane-2,5-dicarboxylic acid dimethyl ester from methyl 2-acetamidoacrylate and sulfur dichloride.

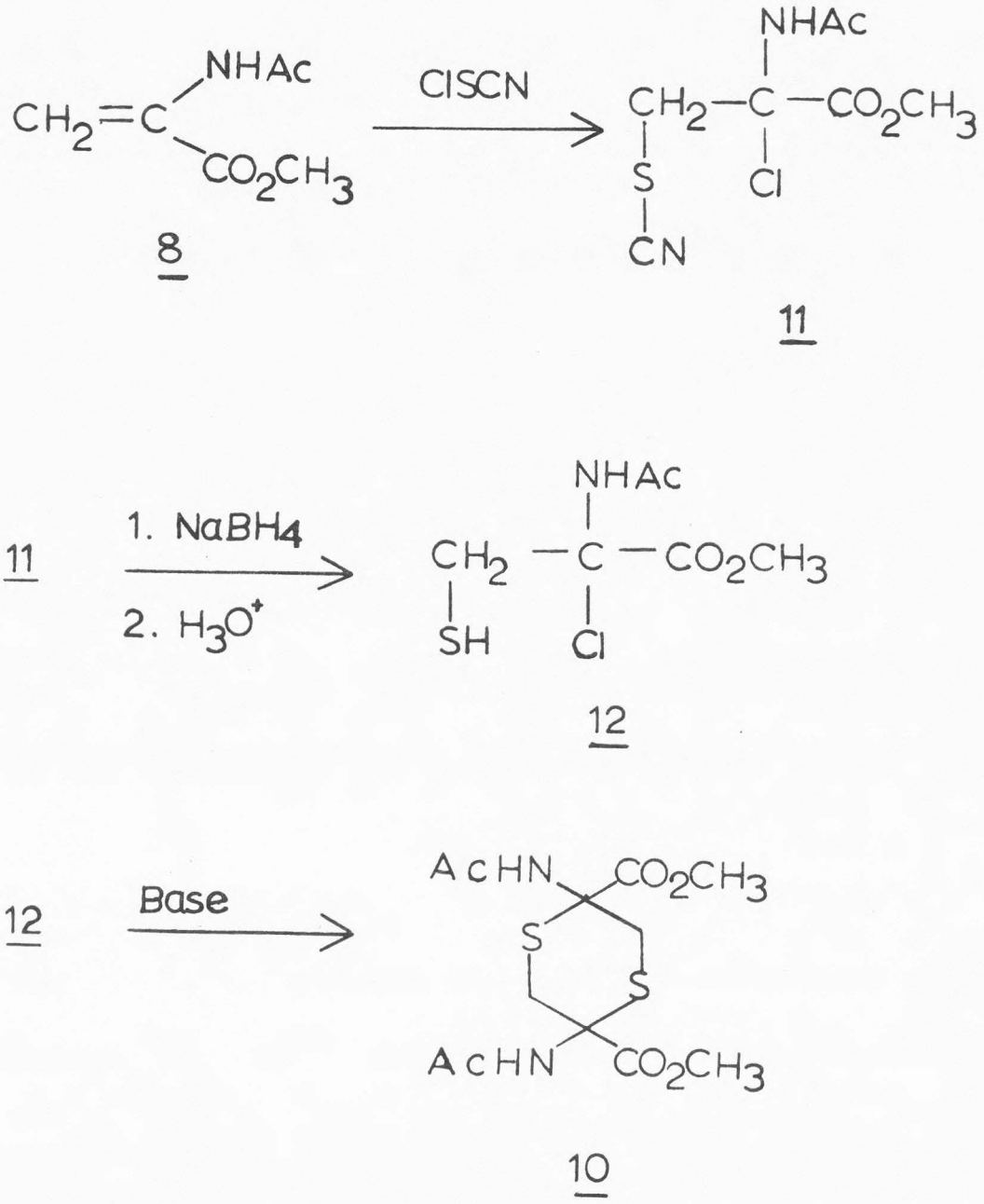



Figure 6. Scheme for synthesis of 2,5-diacetamido-1,4-dithiane-2,5-dicarboxylic acid dimethyl ester from methyl 2-acetamidoacrylate and thiocyanogen chloride.

# LITERATURE REVIEW

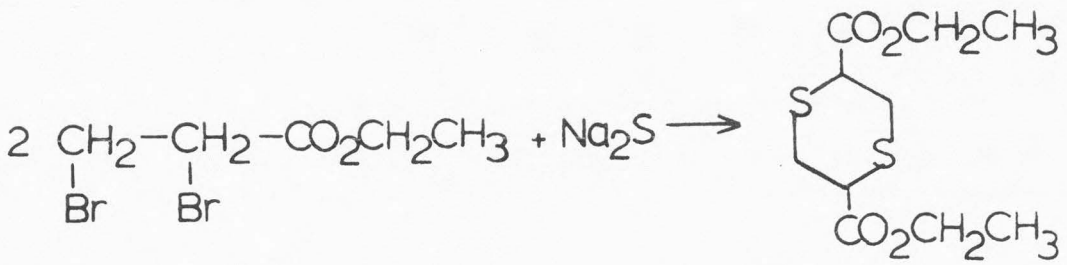
## The structure of echinomycin

In 1957, Corbaz and co-workers extracted Streptomyces echinatus and by chromatography of the extract on an aluminum oxide column isolated the antibiotic echinomycin (1a). From the elemental analysis, the molecular formula was calculated to be $C_{29}H_{37}O_7N_7S$ (1a). Keller-Schierlein and Prelog reported also in 1957 the identification of D-serine, L-alanine, and quinoxaline-2-carboxylic acid after acid and basic hydrolysis of echinomycin (7).

In 1959, Keller-Schierlein, Mihailovic, and Prelog reported the structure of echinomycin (4). After acid hydrolysis a fourth amino acid, N-methylvaline, was identified while a new analysis on a sample of higher purity gave data consistent with a molecular formula of $C_{50}H_{60}O_{12}N_{12}S_2$. It was reported then that echinomycin contained two molecules each of D-serine, L-alanine, N-methyl-L-valine and quinoxaline-2-carboxylic acid. After reduction by sodium in ammonia or lithium aluminum hydride followed by permanganate oxidation, N,N'-dimethylcystine was identified. The structure of echinomycin was reported to be a 26-membered cyclooctapeptide-dilactone ring interconnected by a 1,4-dithiane ring (Figure 2). It was shown by Corbaz that echinomycin is identical to quinomycin A (1a).

Preparation of 1,4-dithianes

There are four feasible methods reported in the literature by which 1,4-dithianes can be prepared. Varvoglis and Tsatsaronis (8) report the reaction of two moles of ethyl 2,3-dibromopropionate (13) with one mole of $H_2S$ to form 2,5-dicarboethoxy-1,4-dithiane (14).



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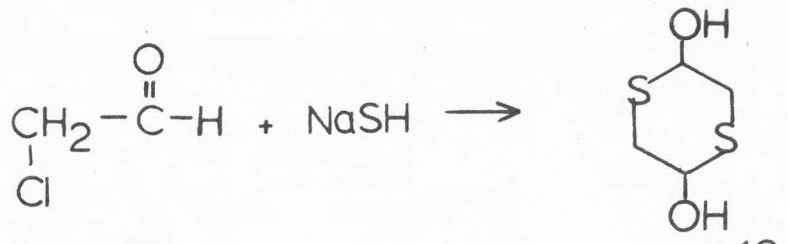
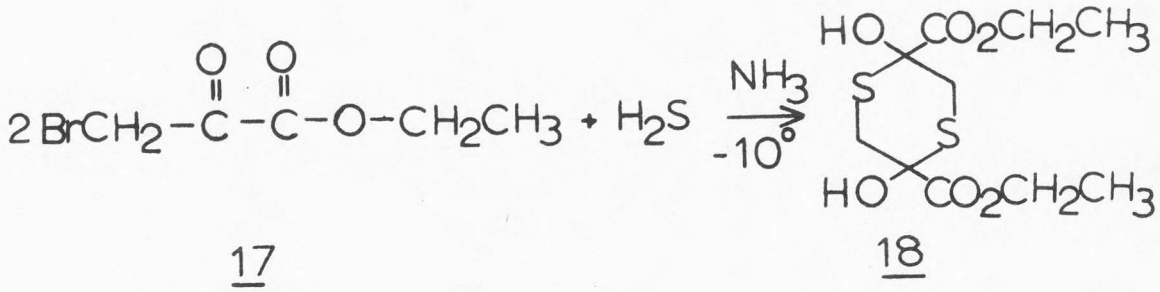
Hromatka and Haberl (9) report the reaction of 2-chloroacetaldehyde with NaSH to give 2,5-dihydroxy-1,4-dithiane (16)



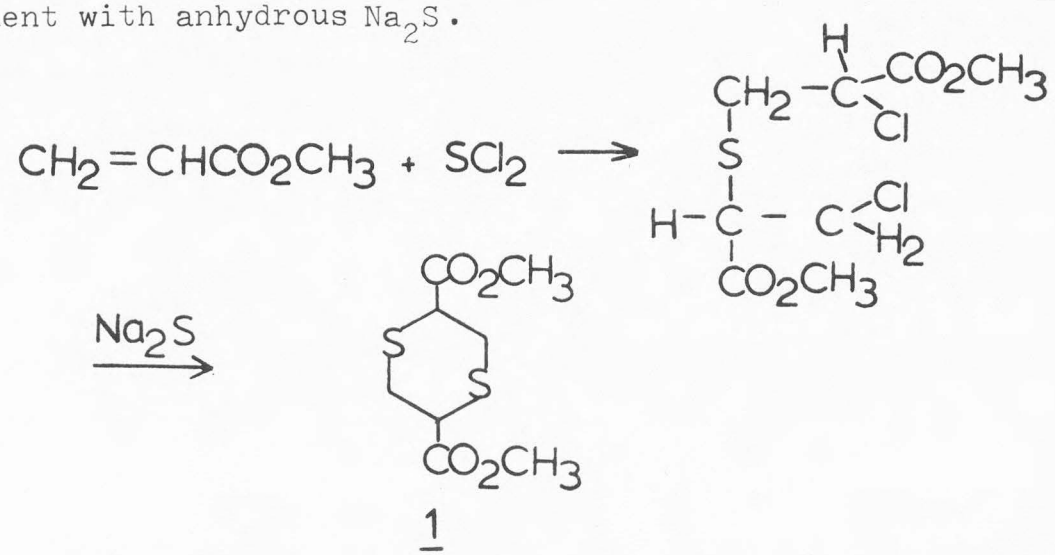
15 16

Asinger and co-workers (10) treated ethyl bromopyruvate (17) with $H_2S$ in the presence of ammonia to obtain a dimer, believed to be 2,5-dihydroxy-1,4-dithiane-2,5-dicarboxylic acid diethyl ester (18).



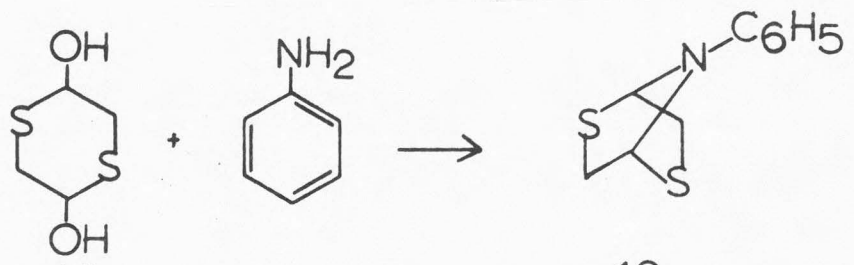
17 18

Gundermann and Burba (6) reported in 1961 the preparation of 2,5-dicarbomethoxy-1,4-dithiane (1) by the addition of sulfur dichloride to methyl acrylate followed by treatment with anhydrous $Na_2S$.



The reaction of the dibromide (13) with $Na_2S$ is reported by Gundermann and Burba (6) to give the dithiane (14) in low yield. The product (16) reported by Hromatka and Haberl (9a) is not useful in the proposed synthetic scheme.

Hromatka and Haberl (9a,b) report the reaction of aniline with 2,5-dihydroxy-1,4-dithiane (16) to give the bicyclic adduct (19).



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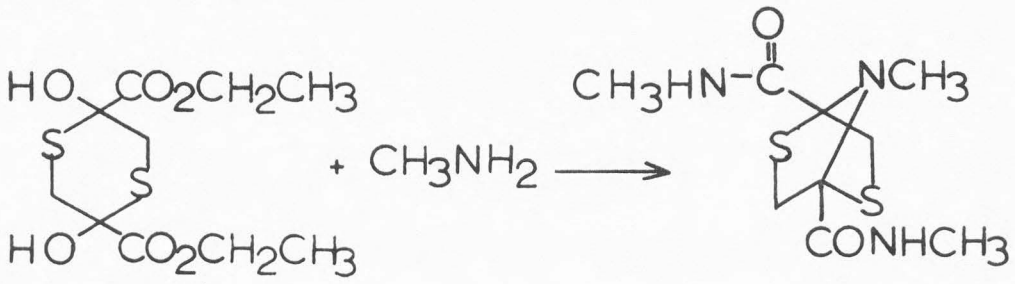
From work in this laboratory (11) a compound that appears to be the 2,5-N,N'-dimethyl dicarboxamide analog (20) has been prepared by the reaction of the dithiane (18) with monomethylamine.



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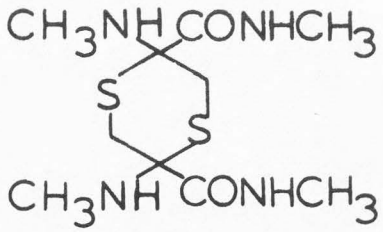
An attempt will be made to find conditions under which (18) would react with monomethylamine to give the monocyclic dithiane (21).



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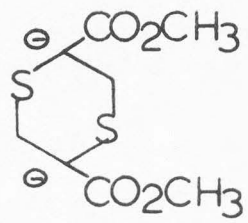
Another approach utilizing 2,5-dicarbomethoxy-1,4-dithiane (1), prepared by the method of Gundermann and Burba (6), is to generate the carbanion at positions 2 and 5 (22), which should be stabilized by the sulfur as well as the carbonyl group (12), and then to carry out a suitable reaction with the anion (22), as outlined in Figures 3 and 4.



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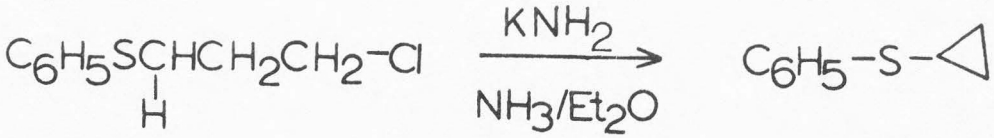
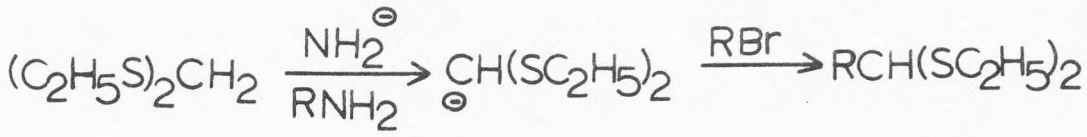
Carbanion reactions of sulfides

There are several examples of carbanions stabilized by sulfur in the literature. Truce, Hollister, Lindy and Parr (13) report the reaction of 1-chloro-3-phenylthiopropane (23) with $KNH_2$ to give the cyclopropyl sulfide (24).



23 24

Arens, Froling and Froling (14) reported the reaction of formaldehyde dithioacetal (25) with amide ion to give the carbanion (26) which on treatment with an alkyl bromide gave the new thioacetal (27).



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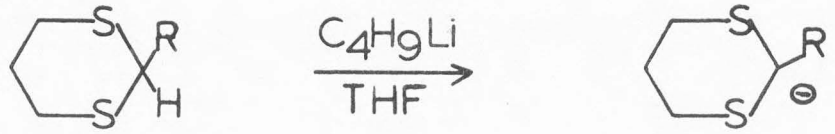
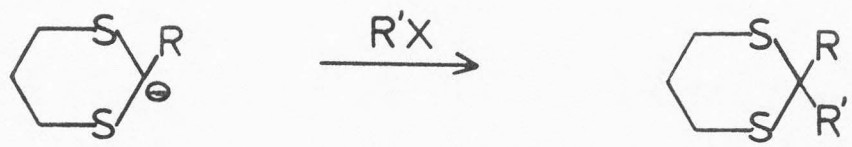
The preparation of the carbanion of various 1,3-dithianes (28) has been reported by Corey and Seebach (15) where R is a primary, secondary or tertiary alkyl, allyl, benzyl



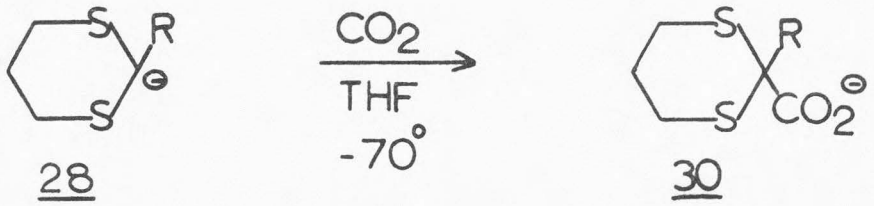
28

or aromatic substituent. The carbanion (28) was also reacted with alkyl halides to give the disubstituted dithiane (29).



28 29

Corey and Seebach (15) also report the reaction of the carbanion (28) with carbon dioxide to give the carboxylic acid (30).



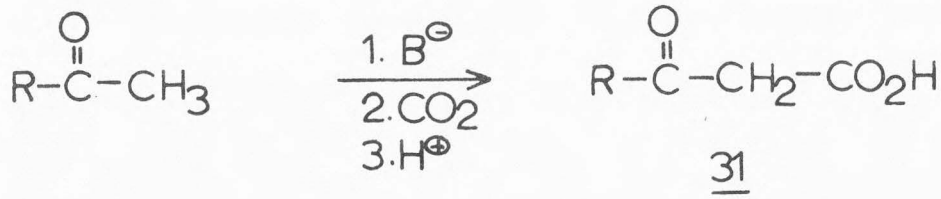

28 30

$R = CH_3,\ t\text{-}C_4H_9$

Thus it appears reasonable that 2,5-dicarbomethoxy-1,4-dithiane (1) might undergo a carboxylation reaction.

The carboxylation of carbanions

Levine and Hauser (16) reported in 1944 that methyl ketones, when caused to react with strong base followed by treatment with carbon dioxide, form 3-oxocarboxylic acids (31).

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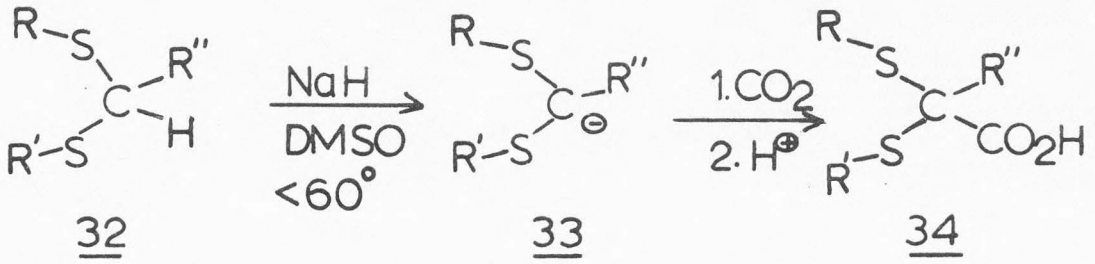
The bases used were sodium or potassium triphenylmethide and sodium amide. Of the many papers found in the literature (15-18) the findings of Tagaki and co-workers (18)

are, along with the previously mentioned work of Corey and Seebach (15), most relevant to this thesis. Tagaki and co-workers report the reaction of the dithioacetal (32) with sodium hydride in dimethyl sulfoxide (DMSO) to give the carbanion (33), which reacts with carbon dioxide to give the carboxylic acid (34).



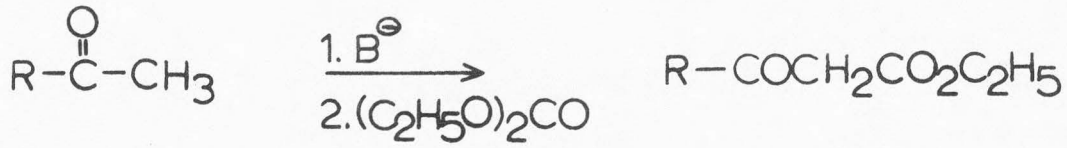

32 33 34

R = phenyl, alkyl R' = phenyl, alkyl R" = H, phenyl

It is reported in the same paper that the substituted acids (34) decarboxylate more readily than the unsubstituted acids of the type R-$CH_2CO_2H$.

Carbethoxylation of carbanions

Levine and Hauser (16) also reported in 1944 the reaction of methyl ketones with strong base followed by treatment with diethyl carbonate to give the ethyl 3-oxocarboxylates (35). The bases used were potassium and sodium triphenylmethide and sodium amide.



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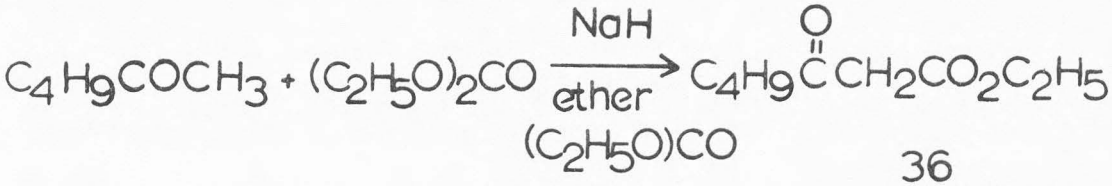
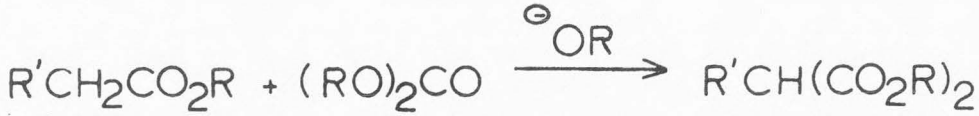
Soloway and LaForge (19) reported in 1947 that 2-hexanone dropped slowly into a mixture of sodium hydride, ether, and diethyl carbonate gave ethyl 3-oxoheptanoate (36) in good yield.



36

Wallingford, Homeyer and Jones reported the reaction of ketones (20) with diethyl carbonate and ethoxide ion to give the ethyl 3-oxocarboxylates and the reaction of esters (21) with dialkyl carbonate and alkoxide ion to give the malonates (37).



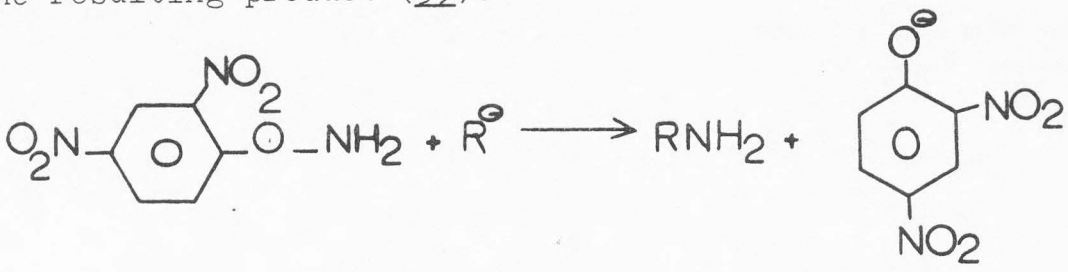
37

R = $CH_3$, $C_2H_5$

Swamer and Hauser (22) reported sodium hydride to be the superior base for this reaction and it is commonly used (23).

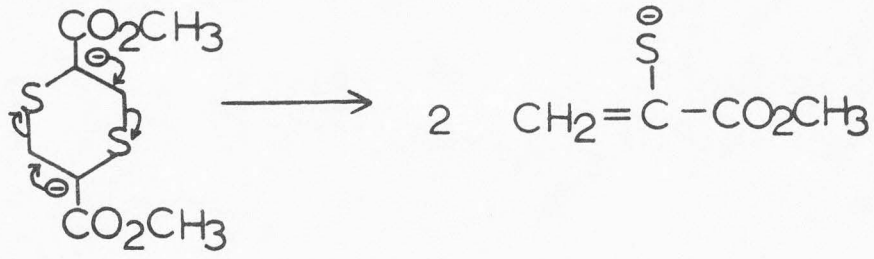
Direct amination of carbanions

Sheradsky (24) recently prepared O-2,4-dinitrophenylhydroxylamine (38) which undergoes nucleophilic attack at nitrogen. When reacted with carbanions (25), amines are the resulting product (39).



38 39

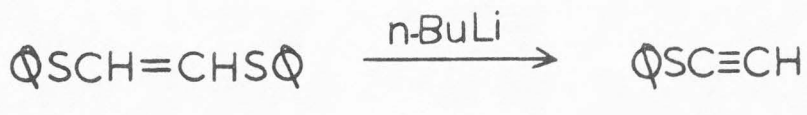
One potential problem with the reactions of the dicarbanion (22) is the possible cleavage of the dithiane ring to give 2-thiopyruvate derivatives as shown in Figure 7. This cleavage is an internal elimination for which analogies are found in the literature (26, 27).



22

Figure 7. The cleavage of the dianion (22) by internal elimination.

Parham and Stright (26) reported that both cis and trans-1,2-diphenylthioethylene (40) eliminate thiophenol on treatment with n-butyllithium to give phenylmercapto-acetylene (41).



40 41

Escales and Baumann (27) reported in 1886 that the dithioketal of ethyl butanoate (42) eliminated ethyl mercaptan on treatment with potassium hydroxide to give potassium 3-ethylmercapto-3-methylacrylate (43).

$$CH_3C(SC_2H_5)_2CH_2CO_2C_2H_5 \xrightarrow[350^\circ]{KOH} CH_3(C_2H_5S)C{=}CHCO_2K$$

42 43

In view of the possibility of this elimination, it is proposed to attempt a deuterium exchange reaction under strongly basic conditions to test the stability and the reactivity of the carbanion (22) of 2,5-dicarbomethoxy-1,4-dithiane (1).

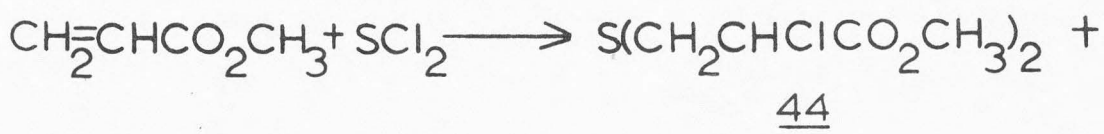
Another reasonable precursor to derivatives of echinodithianic acid (5) is methyl 2-acetamidoacrylate (8). Two possible synthetic schemes are outlined in Figures 7 and 8. As there is little data published regarding polar additions to this compound, it is proposed to study the additions of hydrogen bromide, sulfur dichloride and thiocyanogen chloride to determine the suitability of (8) as a precursor to echinodithianic acid, and to compare these addition reactions with similar additions to methyl acrylate to obtain information of the effect of the acetamido group.

Additions of aprotic reagents to methyl acrylate

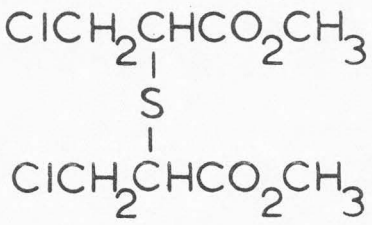
The addition to methyl acrylate of polar reagents such as sulfur dichloride and alkylsulfenyl chlorides results in a mixture of products.

Gundermann and Burba (6) indicate that sulfur dichloride adds to methyl acrylate to give a statistical distribution

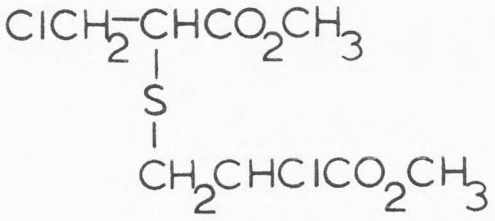
of the products (44), (45) and (46).



44

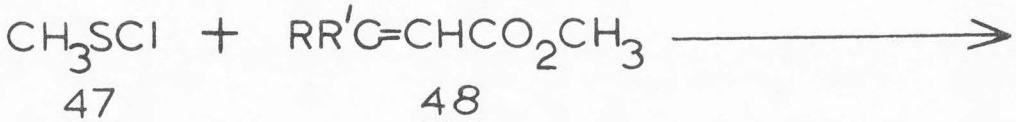


45



46

Other authors (28) have reported the addition of methanesulfenyl chloride (47) to methyl acrylate derivatives (48) to give the products (49) and (50) in a 1:1 ratio.

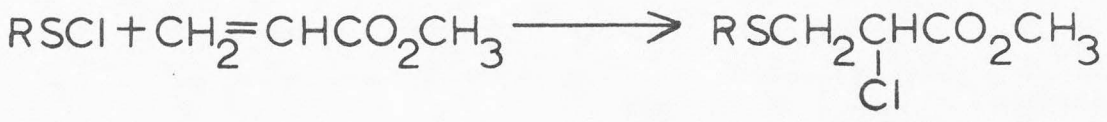


47 48

49 50

However, Brintzinger, Langheck and Ellwanger (29) report the 2-chloro compound (51) to be the only product

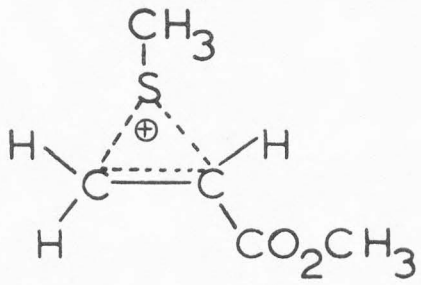
of the addition of ethanesulfenyl chloride and of 2-propanesulfenyl chloride to methyl acrylate.



51

R = ethyl, 2-propyl

Thaler, Mueller, and Butler (30) have reported that the reaction proceeds through the episulfonium ion (52).



52

This intermediate reacts with chloride ion to give the 2-chloro adduct (53a) as the major product when care is taken to exclude traces of acid during the addition. Upon addition of acid and heating, the product rearranges to the more thermodynamically stable beta-chloro adduct (53b). (See figure 8)

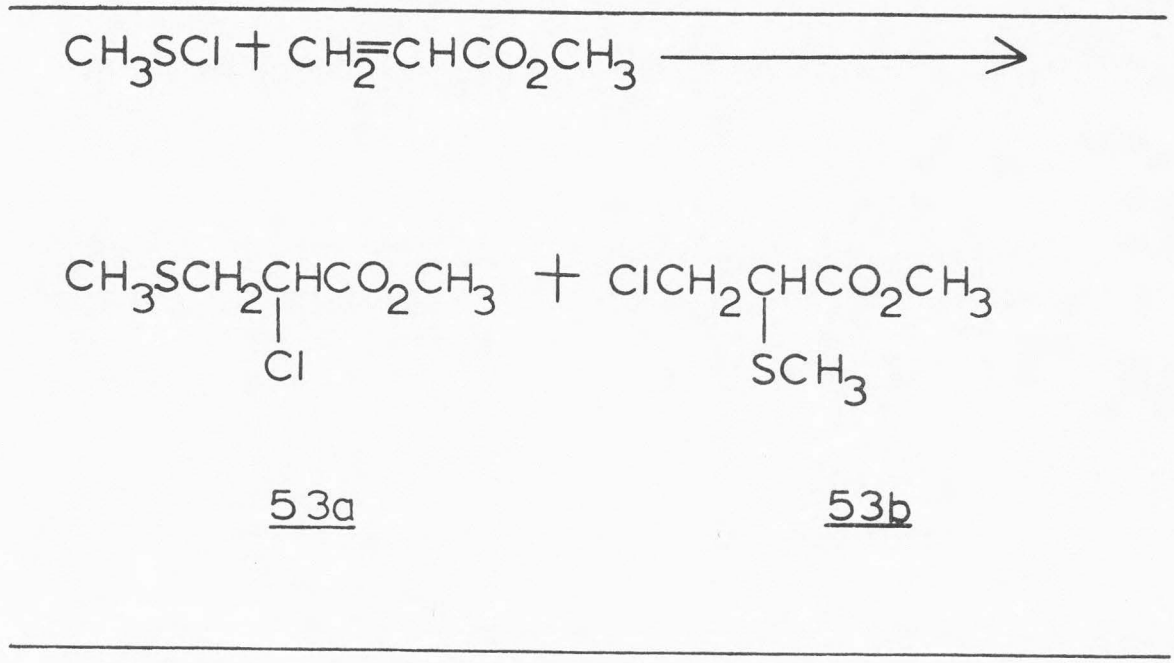



Figure 8. The addition of methanesulfenyl chloride to methyl acrylate.

It is concluded that the alkylsulfenyl chlorides add to methyl acrylate under kinetic control to give the 2-chloro adduct (53a), which under equilibrium conditions rearranges to give dominantly the 3-chloro adduct (53b) (30).

Michael additions to methyl acrylate

If the reagent is of the type HX, where X may be halogen, potential carbanion, sulfur or nitrogen, then only the products of the type $XCH_2CH_2CO_2CH_3$ are observed (31-43). Some specific examples of these compounds are listed in Table 1. Of special note is the addition of

Table I. Michael additions to methyl acrylate

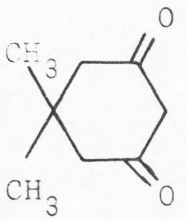
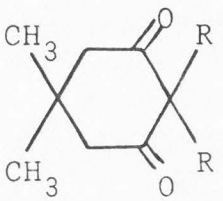
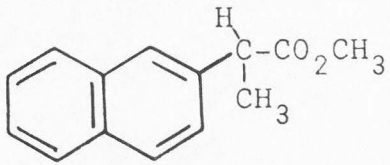
| Reagent | Conditions, Solvent | Product[a] | Reference |
|---|---|---|---|
| $NaHSO_3$ | pH 4-6 | $HSO_3R$ | Morton & Landfield (31) |
| HCl, HBr, HI | acid | XR | Moureu, Murat, & Tampier (32) |
| HBr | acid MeOH | BrR | Monzingo & Patterson (33) |
|  | basic $H_2O$/Dioxane |  | Nazarov & Zav'yalov (34) |
|  | NaOMe | $ArC(R)(CH_3)CO_2CH_3$ (H) | Dasgupta & Antony (35) |
| $HC(NO_3)_3$ | acid | $(NO_3)_3C\text{-}R$ | Kaplan & Kamlet (36) |

Table 1. Continued

| Reagent | Conditions, Solvent | Product[a] | Reference |
|---|---|---|---|
| $HC(NO_3)_3$ | basic | $NO_2(NO_3)_2C(R)CH_2CH(OH)CO_2CH_3$ + $KC(NO_3)_2CH{=}CHCO_2CH_3$ + $(NO_3)_3CR$ | Kaplan & Kamlet (36) |
| $O_2N(CH_2)_4NO_2$ | 85% Triton B | $NO_2CH(R)CH_2CH_2CH(R)NO_2$ | Fever & Harmetz (37) |
| $C_6H_5CH_2CN$ | $HCO_2Na$ or 2N KOH in $CH_3OH$ | $C_6H_5CH(R)CN$ | Bertocchio & Dreux (38) |
| $CH_3COCH_2CH_3$[b] | $HCO_2Na$ or 2N KOH in Alc. | $CH_3COCH(R)CH_3$ | Bertocchio & Dreux (38) |
| $NH_3$ | liq. $NH_3$ | $H_2NR$, $HNR_2$, $NR_3$ | Morsch (39) |

Table I. Continued

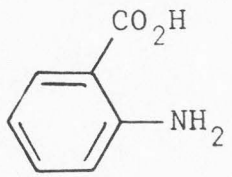
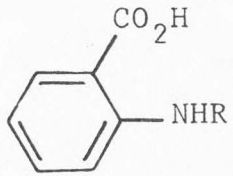
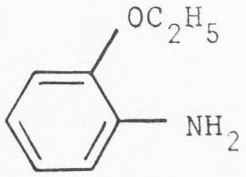
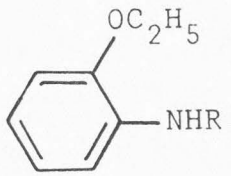
| Reagent | Conditions Solvent | Product[a] | Reference |
|---|---|---|---|
| $CH_3NH_2$ | liq. $NH_3$ | $CH_3HNR$, $CH_3NR_2$ | Morsch (39) |
| $(C_2H_5)_2NH$ | liq. $NH_3$ | $(C_2H_5)_2NR$ | Morsch (39) |
|  | catalyzed by $Ac_2O$ |  | Baltrosis, Maciulis, & Purenas (40) |
| p-$H_2NC_6H_4CH_2CO_2H$ | catalyzed by $Ac_2O$ | $RHNC_6H_4CH_2CO_2H$ | Baltrosis, Maciulis, & Purenas (40) |
|  | catalyzed by $Ac_2O$ |  | Baltrosis, Maciulis, & Purenas (40) |

Table 1. Continued

| Reagent | Conditions Solvent | Product[a] | Reference | |
|---|---|---|---|---|
| p-$BrC_6H_4NH_2$ | | p-$BrC_6H_4NHR$ | Baltrusis, Zubiene, & Purenas | (41) |
| $R'NHNO_2$[c] | Triton B or Na, K salt of Nitramine in 50% aq. MeOH | $R'N(R)NO_2$ | Kissinger & Schwartz | (42) |
| $C_6H_5CH_2SH$ | $N(CH_2CH_2OH)_3$ or NaOAc | $C_6H_5CH_2SR$ | Mallik & Das | (43) |
| $C_8H_{17}SH$ | $N(CH_2CH_2OH)_3$ or NaOAc | $C_8H_{17}SR$ | Mallik & Das | (43) |
| p-$ClC_6H_4SH$ | acid, base, or neutral | p-$ClC_6H_4SR$ | Mallik & Das | (43) |

[a] $R = -CH_2CH_2CO_2CH_3$

[b] Several other ketones were employed by these authors.

[c] $R' = CH_3-$, $C_2H_5-$, butyl-

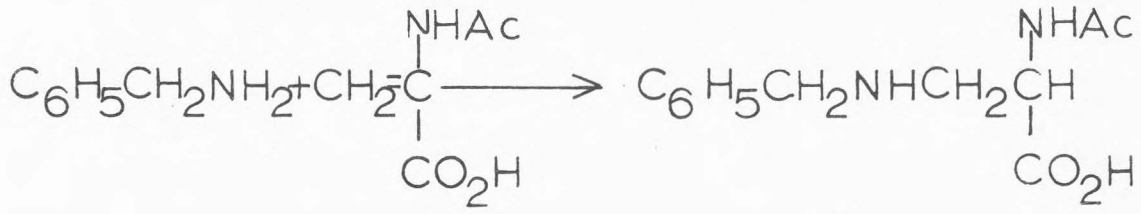
hydrogen bromide to methyl acrylate which gives only methyl 3-bromopropionate, the Michael addition product (32,33).

In summary, reagents which can donate a proton add to methyl acrylate, generally independant of pH, in a Michael addition to give the 3-substituted propionate, while aprotic reagents add to methyl acrylate to give a distribution of isomers dependant on reaction conditions.

Additions to 2-amidoacrylic acid derivatives

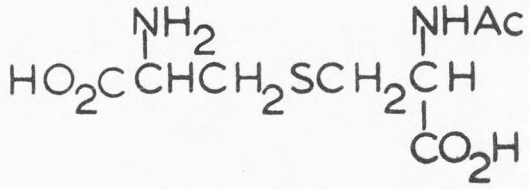
Amines (44,45,46), mercaptans (45,47,48,49,50,51), thiophenols (45,48) and halogens (45,52,54) have been reported to add to the double bond of 2-amidoacrylic acid derivatives. The resulting products are beta-substituted alanine derivatives.

Eiger and Greenstein (45) reported the reaction of benzylamine with 2-acetamidoacrylic acid (8a) to give 2-acetamido-3-benzylaminopropionic acid (54).



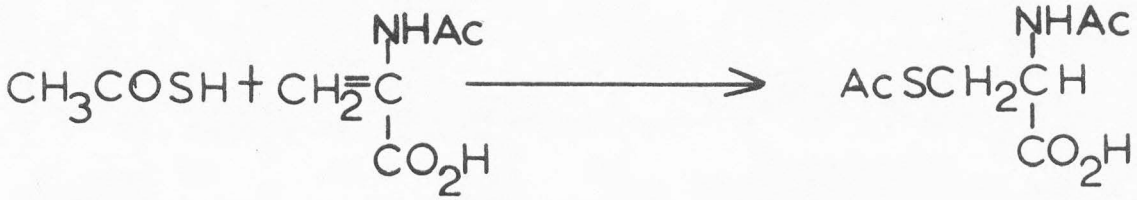
8a 54

The addition of cysteine to (8a) was reported by Schoeberl and Wagner (49) to give S-(2-acetamido-2-carboxyethyl)-cysteine (55).



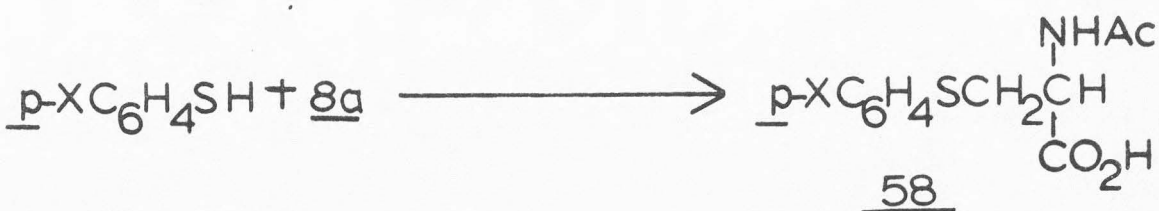
55

Thiolacetic acid (56) adds to (8a) to give N,S-diacetylcysteine (57) as reported by M. Farlow (53).



56 8a 57

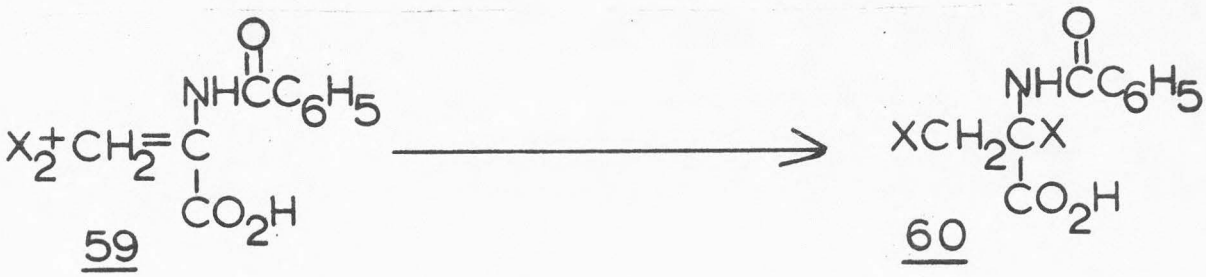
Behringer and Fackler (48) report the addition of para-substituted thiophenols to (8a) to give the cysteine derivatives (58).



58

X=H, Cl, Br, $CH_3$, $NO_2$

The addition of bromine to (8a) was reported by Eiger and Greenstein (45) to give N-acetyl-2,3-dibromoalanine. Similarly Kil'disheva, Rasteikene, and Knunyants (52a) report the addition of chlorine and bromine to 2-benzamido-acrylic acid (59) to form the 2,3-dihalo compounds (60).

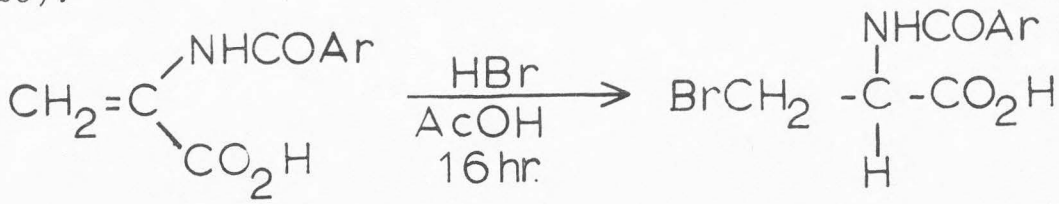


59 60

X = Br, Cl

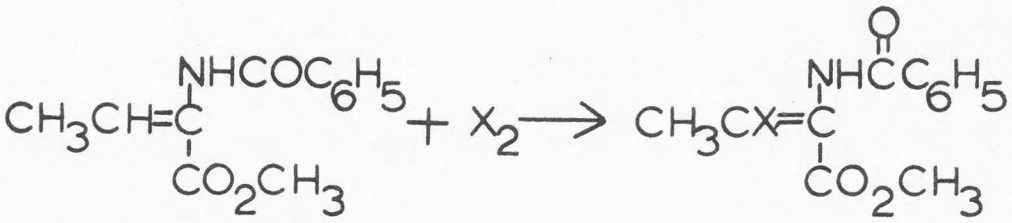
The products are reported to readily dehydrohalogenate (52b).

Knunyants and Shokina have reported the addition of hydrogen bromide to the 2-(acylamino)acrylic acid derivatives (59,59a) to form N-acyl-3-bromoalanine derivatives (52c).



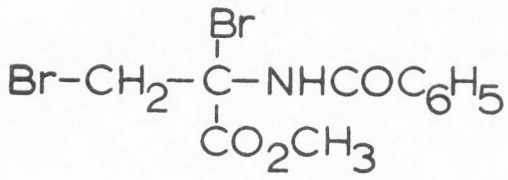
59 Ar = phenyl
59a Ar = benzyl

Pfleger and Strandtmann (54) report the addition of halogen to methyl 2-benzamidomethacrylate (61) to give the 3-halomethacrylate (62) and not the 2,3-dihalo esters.



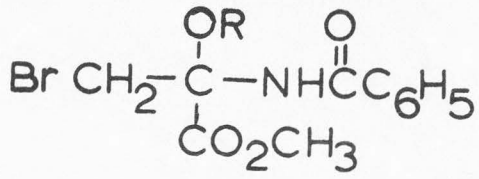
61 62

However, Kil'dishova, Linkova, and Knunyants (52b) obtained methyl 2-benzamido-2,3-dibromopropionate (63) by



63

reacting the dibromo acid (60) with diazomethane. The ester (63) reacted with alcohol to yield the 2-alkoxy ester (64).



64

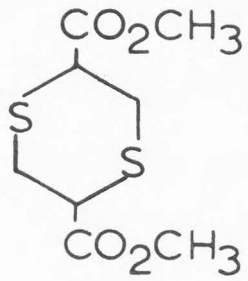
R= methyl, ethyl

In summary, the results reported in the literature indicate that protic reagents add to amidoacrylic acid derivatives in a manner similar to the Michael addition of hydrogen bromide to methyl acrylate. But it is not expected that the amido group would not influence electrophilic additions and indeed some influence is indicated by the enhanced reactivity of the 2-halo adducts (60,63)(52), and by the longer reaction time required for the addition of hydrogen bromide to the 2-(acylamino)acrylic acid derivatives (52c).

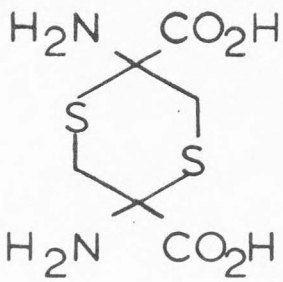
# RESULTS AND DISCUSSION

## The preparation of 2,5-dicarbomethoxy-1,4-dithiane (1)

The method reported by Gundermann and Burba (6) was employed in the synthesis of 1, but the overall yields obtained by this method were very low. The difficulty of the preparation of 1 proved to be a major obstacle to this approach to the synthesis of echinodithianic acid (5). The reactions attempted were selected first because of potential utility in the synthesis of 5, and second because of the




1




5

possibility of gaining information about the carbanionic properties of 1.

## The deuterium exchange of 1

The exchange of deuterium for the hydrogens at the 2 and 5 positions of 2,5-dicarbomethoxy-1,4-dithiane (1) proceeded cleanly and quantitatively in methanol-d containing a catalytic amount of sodium methoxide. That the exchange reaction occurred was shown by analysis of the NMR and

mass spectra of the resulting product (see Figures 9 & 10).

The ring methylene protons of 1 appear in the NMR spectrum as complicated pattern centered at 6.7 $\tau$, probably due to the non-equivalence of axial and equatorial positions. The 2 and 5 protons absorb near 6.2 $\tau$, which is very close to the absorption due to the methyl ester protons.

The 2,5-dideuterocompound shows only the methyl ester absorption at 6.22 $\tau$, and a greatly simplified absorption at 6.71 $\tau$, with the relative intensity being 3:2 ($CH_3O$-: -$CH_2S$-).

The mass spectra also are consistent with exchange at the 2 and 5 positions. The molecular ion for 1 is m/e 236, (100%), with p+1=(11.0%) and p+2=(10%), while the molecular ion of the dideuterated compound is m/e 238, (100%) with p+1=(10.0%) and p+2=(10.0%).

Molecular ions from esters commonly show fragment ion peaks due to loss of .OR and $\cdot CO_2R$ fragments (55). These peaks are present in the mass spectra of both 1 and the deuterated molecule at M-31 and M-59. Both spectra contain peaks which could be an ion fragment due to the loss of methyl acrylate and peaks at m/e equalling one-half the molecular weight which could be an ion fragment resulting from alpha cleavage of the sulfide functions (55).

The attempted carbonylation of 2,5-dicarbomethoxy-1,4-dithiane (1)

The treatment of 1 with butyllithium or sodium hydride followed by treatment with carbon dioxide failed to give the

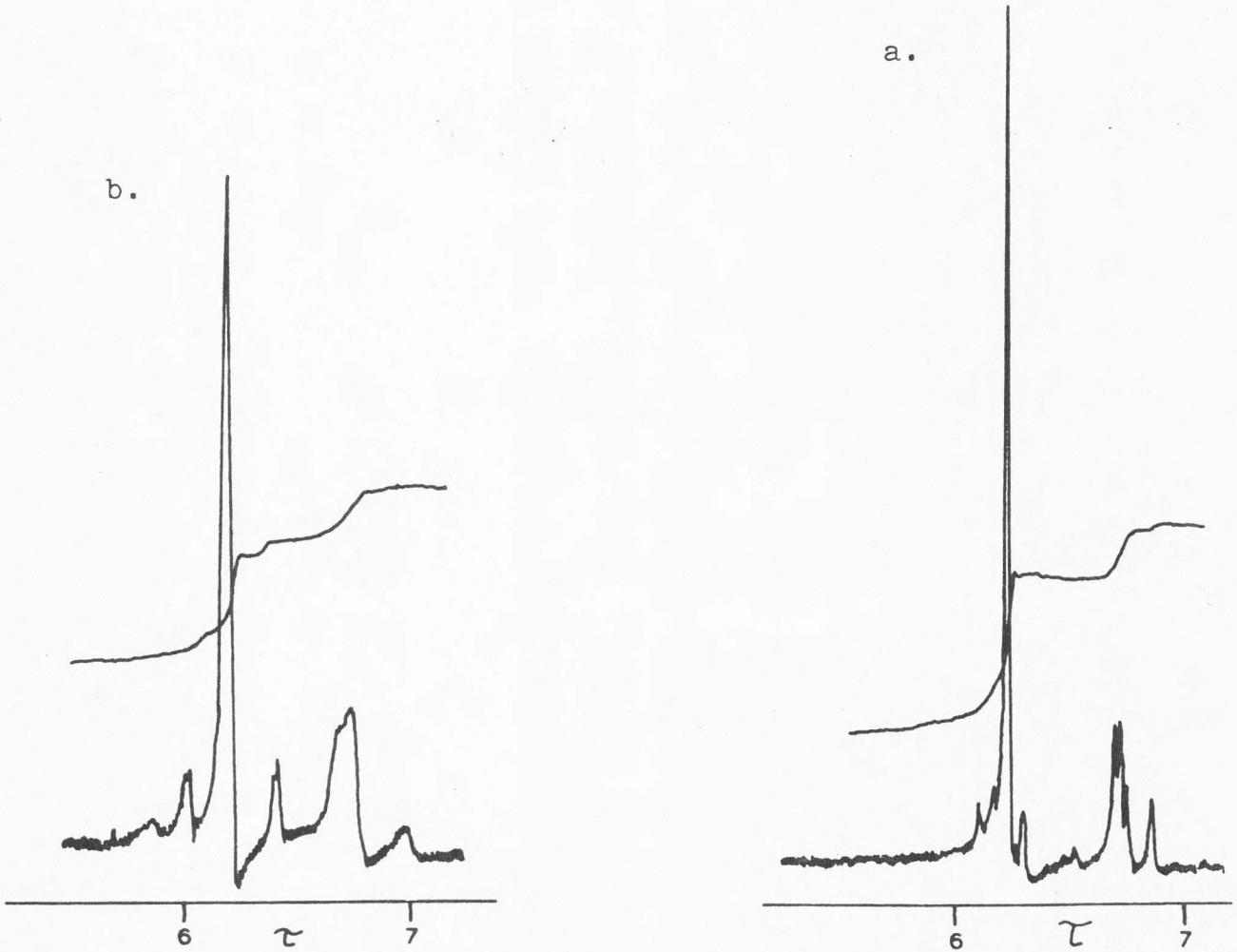



Figure 9. The NMR Spectrum of a) 2,5-dicarbomethoxy-1,4-dithiane (1) and b) the deuterium exchange product.

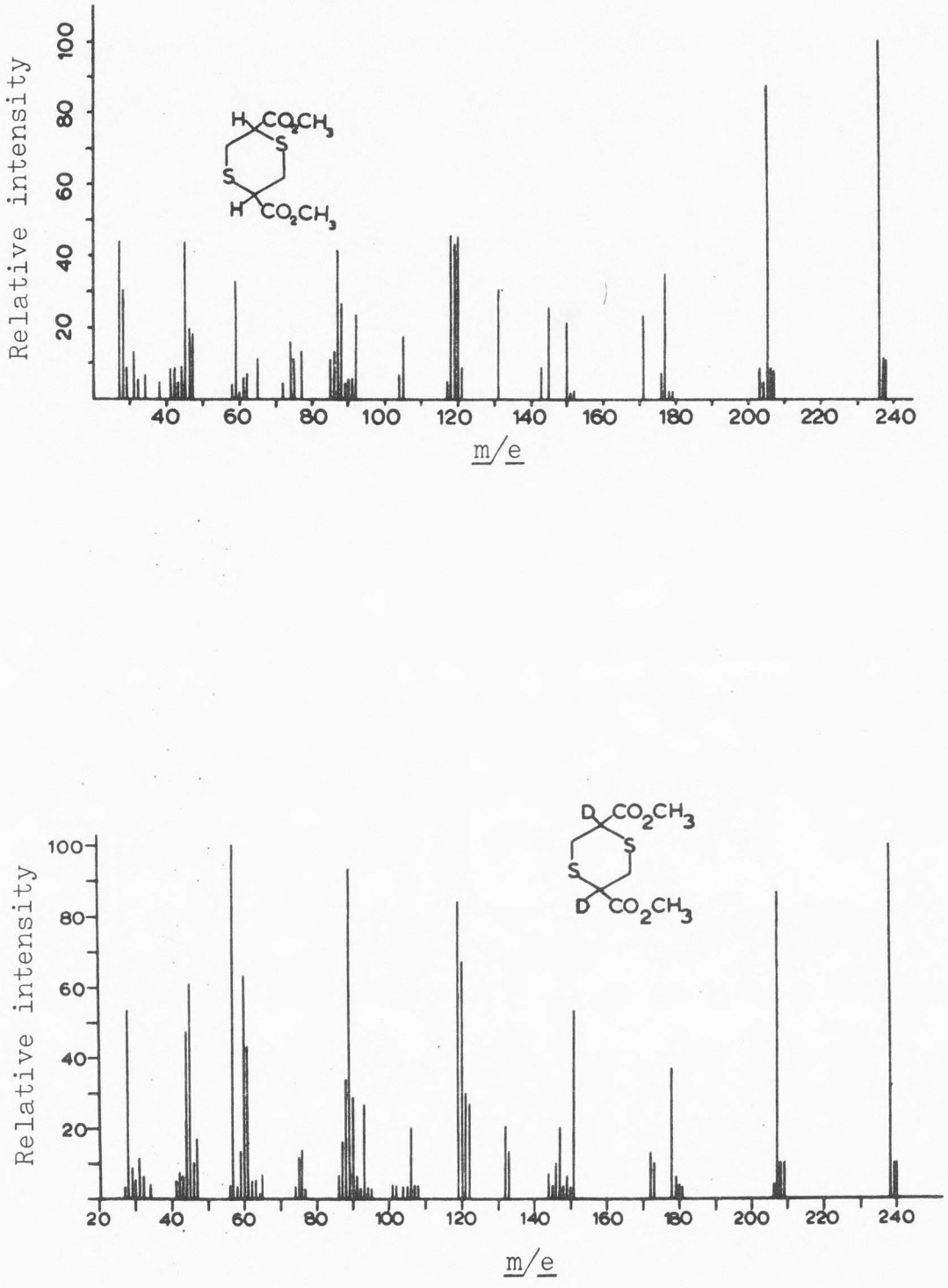
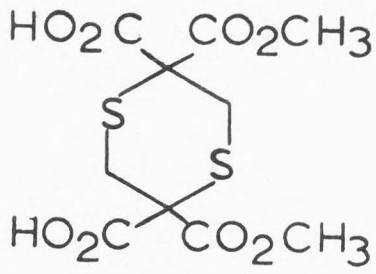



Figure 10. Mass spectra of 2,5-dicarbomethoxy-1,4-dithiane (1) and the deuterium exchange product.

desired product 2.



2

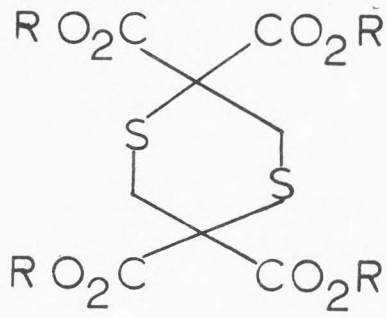
From the melting points and thin layer chromatography, summarized in Table (2), it was established that only starting material was recovered.

Table 2. Melting point and TLC data from attempted carbonylation of 2,5-dicarbomethoxy-1,4-dithiane (1)

| | mp | rf (4:1 benzene:methanol) |
|---|---|---|
| 1 | 117°-118° | 0.85 |
| Product | 117°-118° | 0.85 |
| Product +1 | 117°-118° | 0.85 |

The attempted carbalkoxylation of 2,5-dicarbomethoxy-1,4-dithiane (1)

Treatment of 1 with sodium hydride or sodium alkoxide and dimethyl or diethyl carbonate failed to produce the desired tetra-ester 6.



6

The attempted carbethoxylation of 2,5-dicarbomethoxy-1,4-dithiane (1)

The product isolated from the treatment of 1 with base and diethyl carbonate was shown not to be the desired tetra-ester 6, R=ethyl. The elemental analysis of the reaction product did not correspond with the percentage composition calculated for 6, R=ethyl. Mass spectral data indicated loss of one sulfur atom from the molecule as the P+2 peak was only 5.6% of the parent peak, while a molecule containing two sulfur atoms gives rise to a P+2 peak which is 10% of the parent peak (55). The molecular weight of this product, obtained from the mass spectrum, was 228.

The presence of the ethyl ester function in the product was suggested by the triplet at 8.6 $\tau$ and the quartet at 5.6 $\tau$ in a 3:2 ratio, and further by the m-45 peak in the mass spectrum (see Figure 11). There is

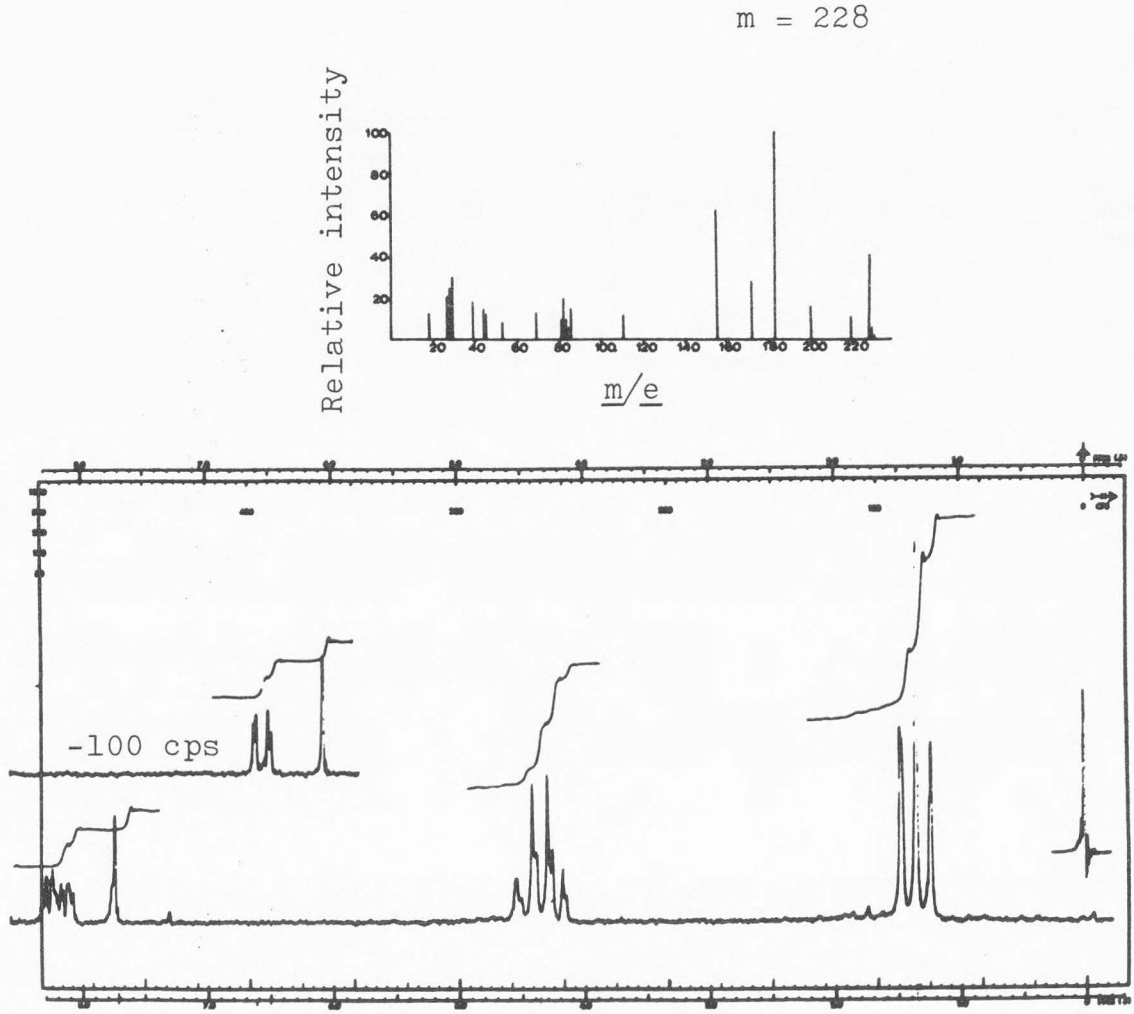



Figure 11. The spectra of the carbethoxylation product of 2,5-dicarbomethoxy-1,4-dithiane.

no evidence of the methyl ester moiety in the product although it was present in the starting material 1. The low field signals in the NMR spectrum could arise from aromatic or vinyl protons (55).

The attempted carbomethoxylation of 2,5-dicarbomethoxy-1,4-dithiane (1)

When 1 was treated with strong base and dimethyl carbonate, the desired tetra-ester 6, R=methyl, was not obtained. The mass spectrum of the product indicated the presence of one sulfur atom in the molecule as the P+2 peak was 5.6% of the parent peak.

The elemental analysis was inconsistent with the tetra-ester 7, R=methyl, but was consistent with the empirical formula $C_8H_8O_4S$ and a molecular weight of 200.

The presence of the methyl ester moiety was suggested by a signal at 6.1 $\tau$ in the NMR spectrum, and by the M-31 and M-58 peaks in the mass spectrum (55). An ester function was further indicated by the presence of a strong band at 1730 $cm^{-1}$ in the IR spectrum (see Figure 12). The presence of vinyl or aromatic protons was indicated by the low field signals in the NMR spectrum (see Figure 13).

Summary of the attempted carbalkoxylation reactions

The difference in molecular weights between the product from 1 plus diethyl carbonate (228) and 1 plus dimethyl carbonate (200) was 28, the combined weight of

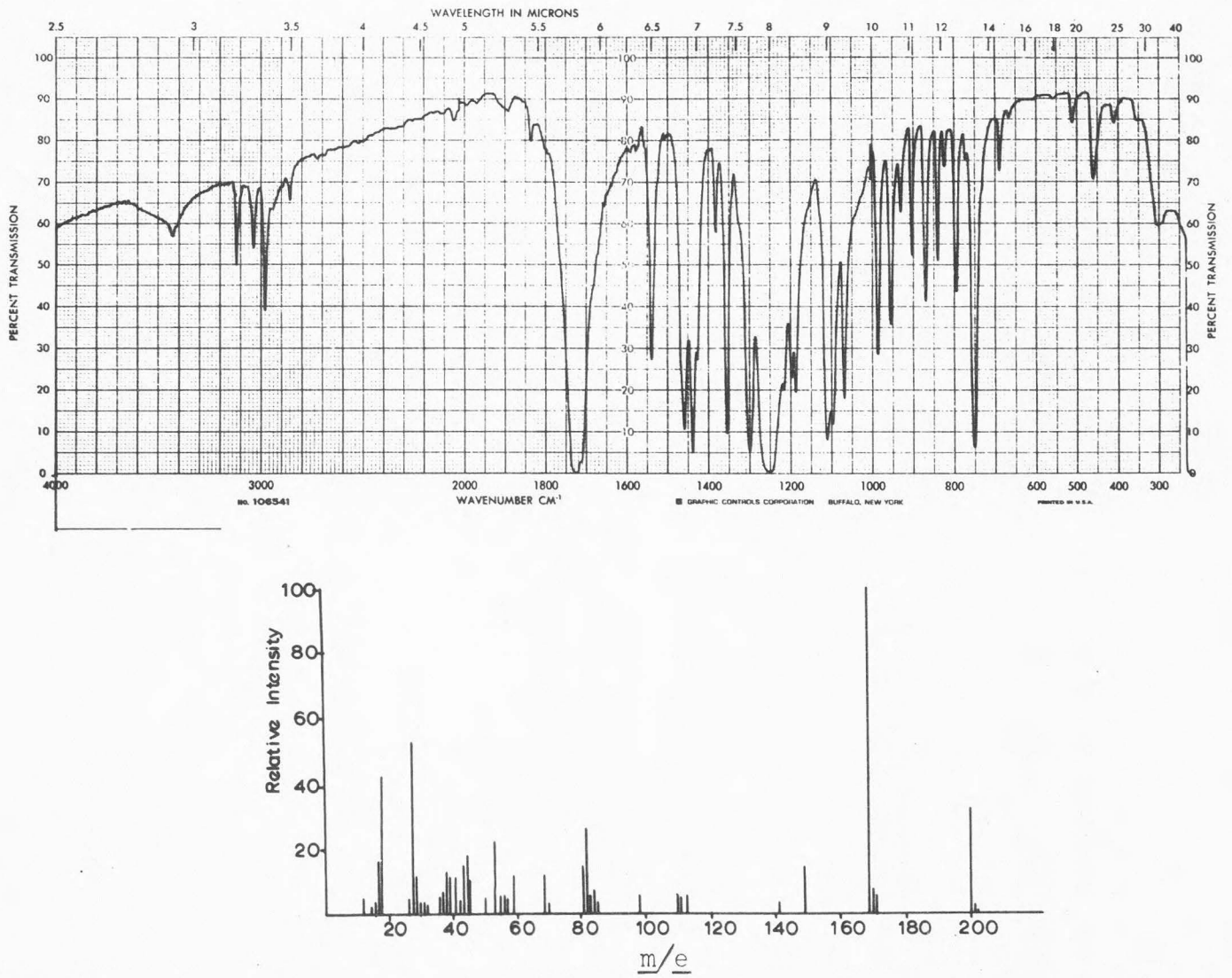



Figure 12. The IR and mass spectrum of the carbomethoxylation product of 2,5-dicarbomethoxy-1,4-dithiane.

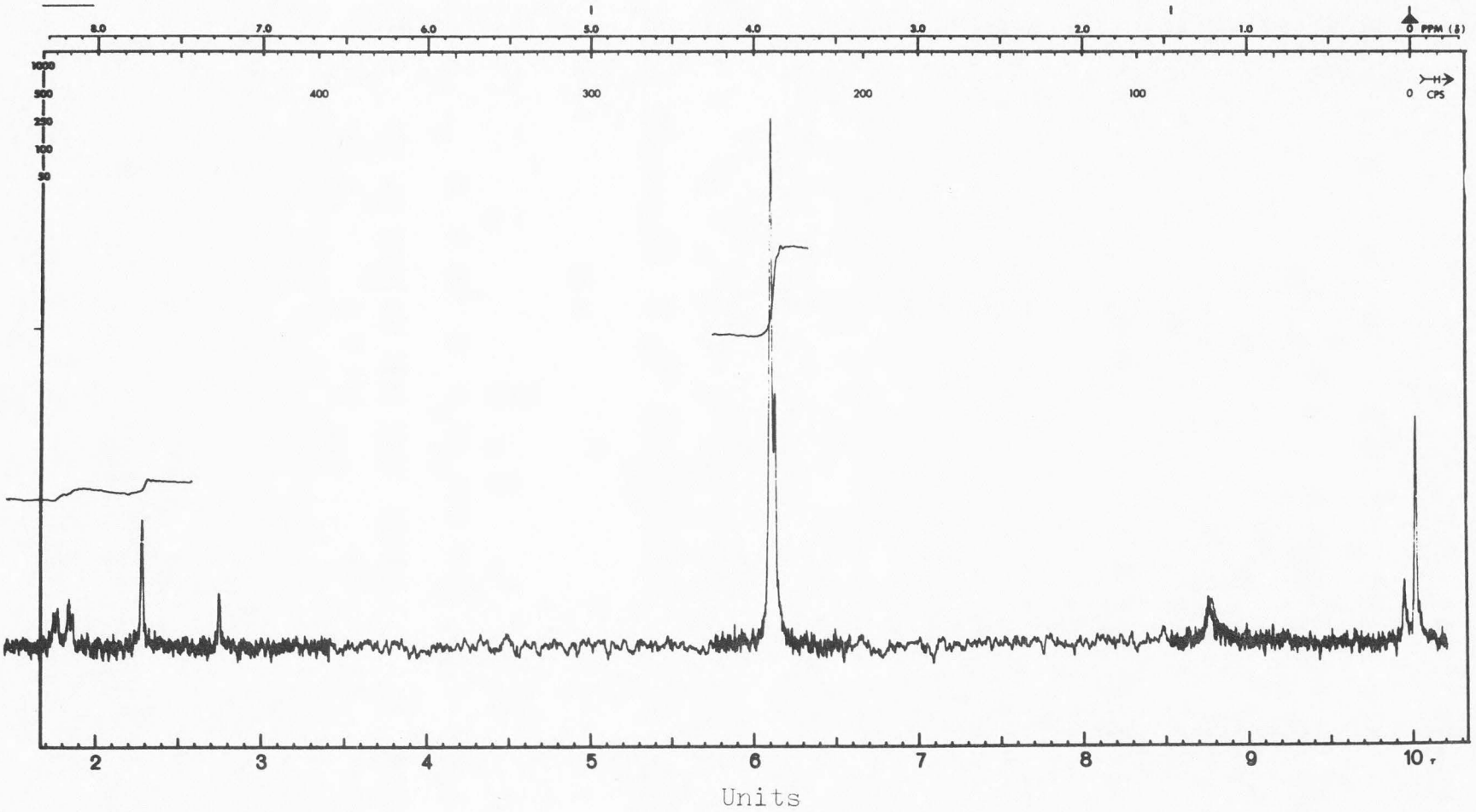



Figure 13. The NMR spectrum of the carbomethoxylation product of 2,5-dicarbomethoxy-1,4-dithiane.

two methylene groups. The differences in the spectra of the two products may be due to the presence of two ethyl ester moieties in the one molecule and two corresponding methyl ester moieties in the other. This is a reasonable conclusion if 2,5-dicarbomethoxy-1,4-dithiane (1) underwent similar reactions in both diethyl carbonate and dimethyl carbonate, and in addition underwent transesterification during the attempted carbethoxylation.

Attempts to identify these products were frustrated by the very small quantity of 2,5-dicarbomethoxy-1,4-dithiane available.

The reaction of 1 with sodium ethoxide

The reaction of 1 with sodium ethoxide in ethanol resulted in a waxy solid which appeared to be a polymer. The expected transesterification product, 2,5-dicarbethoxy-1,4-dithiane was not obtained.

The attempted amination of 1

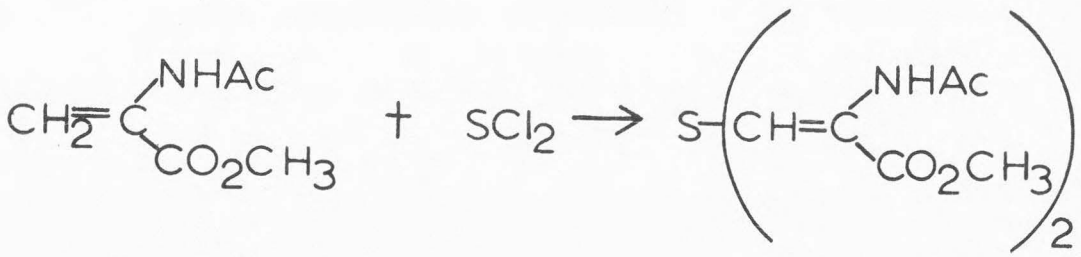
The reaction of 1 with O-2,4-dinitrophenylhydroxylamine (24) gave a mixture of several products as shown by thin-layer chromatography. Due to the lack of sufficient quantities of the dithiane 1, this approach was not pursued further.

Summary of the reactions of 2,5-dicarbomethoxy-1,4-dithiane (1)

Although the protons at the 2 and 5 positions of 1 were sufficiently acidic to undergo base-catalyzed exchange in methanol-d, the other attempted reactions involving the carbanion intermediate (22)led only to ring-opened products, as evidenced by the presence of only one sulfur atom in the products. The exchange reaction was carried out with a catalytic amount of base, while the other reactions were carried out with equivalent amounts of base. When carbonylation, carbalkoxylation and amination were attempted with catalytic amounts of base only, the starting material 1 was recovered.

The additions to methyl 2-acetamidoacrylate (8)

Sulfur dichloride was added to 8 and the resulting product then underwent dehydrohalogenation to form the vinyl sulfide (65).

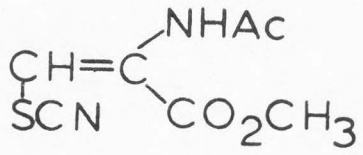


8 65

The structure of 65 is consistent with the NMR spectrum, and is in excellent agreement with the elemental analysis. The

assignment of the NMR signals is as follows: acetyl protons, 8.14; methyl ester protons, 6.51; vinyl protons, 2.40; and the amide protons, 2.05 $\tau$ (see Figure 14).

The addition of thiocyanogen chloride to 8 resulted in the formation of methyl 2-acetamido-3-thiocyanatoacrylate (66).



66

The infrared spectrum showed a peak at 3280 $cm^{-1}$ due to the amide N-H absorption, a sharp peak at 2120 $cm^{-1}$ due to the thiocyanate group, and two carbonyl absorptions at 1661 and 1677 $cm^{-1}$ (see Figure 15).

The mass spectrum of 66 showed a molecular ion at m/e 200, with the p+2 peak being 5.6% of the parent peak indicating the presence of only one sulfur atom in the molecule (see Figure 15). The intense peak at m/e 142 is due to loss of the thiocyanate group as reported by Jensen, Holm, Wentrup, and Moller (56) for alkyl thiocyanates, while the base peak at m/e 110 can be rationalized by loss of the thiocyanate group and the elements of methanol. The elemental analysis agreed well with the formula $C_7H_8N_2O_3S$.

These additions are proposed to proceed through a carbonium ion intermediate (67) followed either by loss of

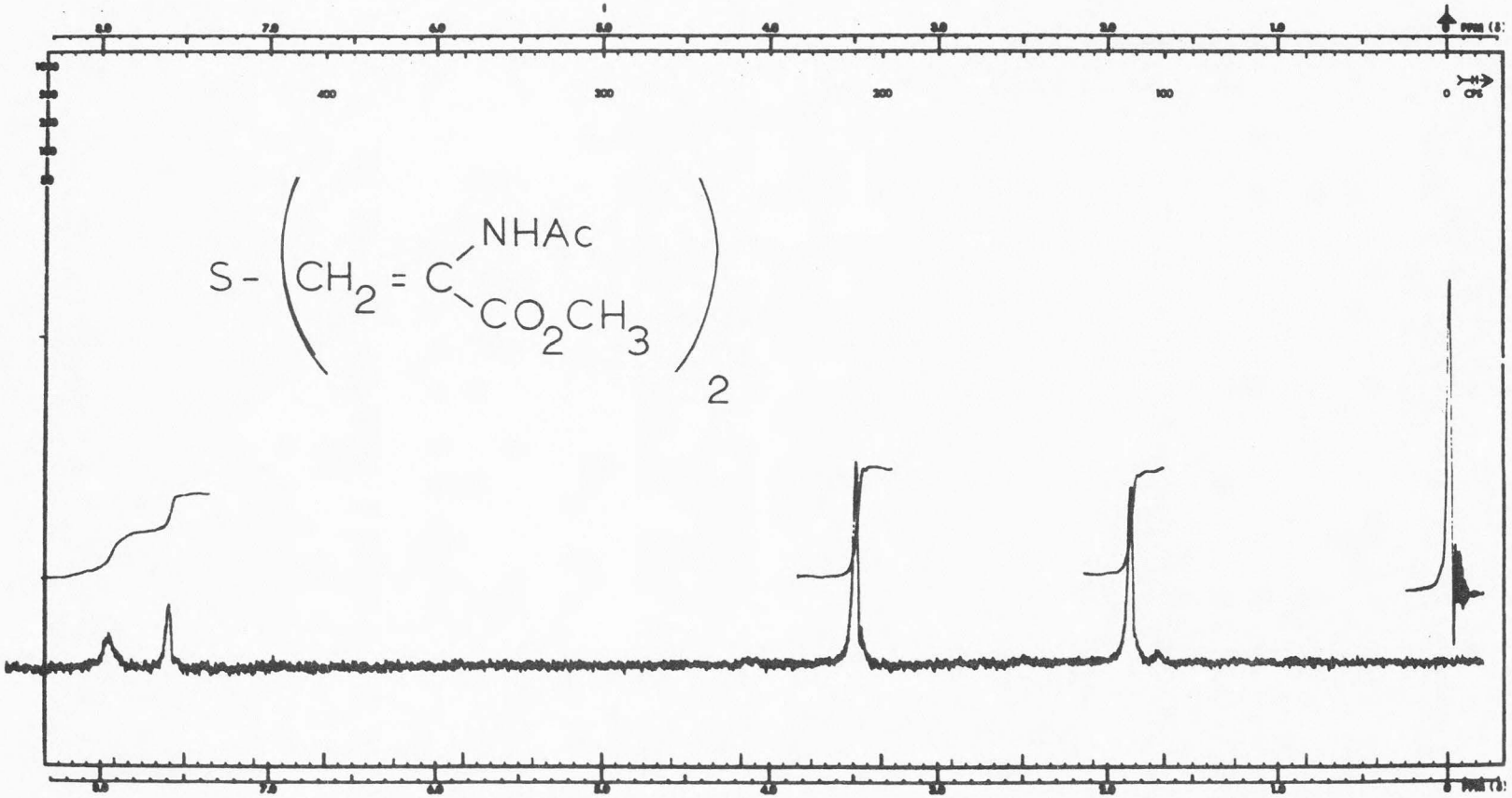



Figure 14. The NMR spectrum of bis-(2-acetamido-2-carbomethoxyvinyl) sulfide (65).

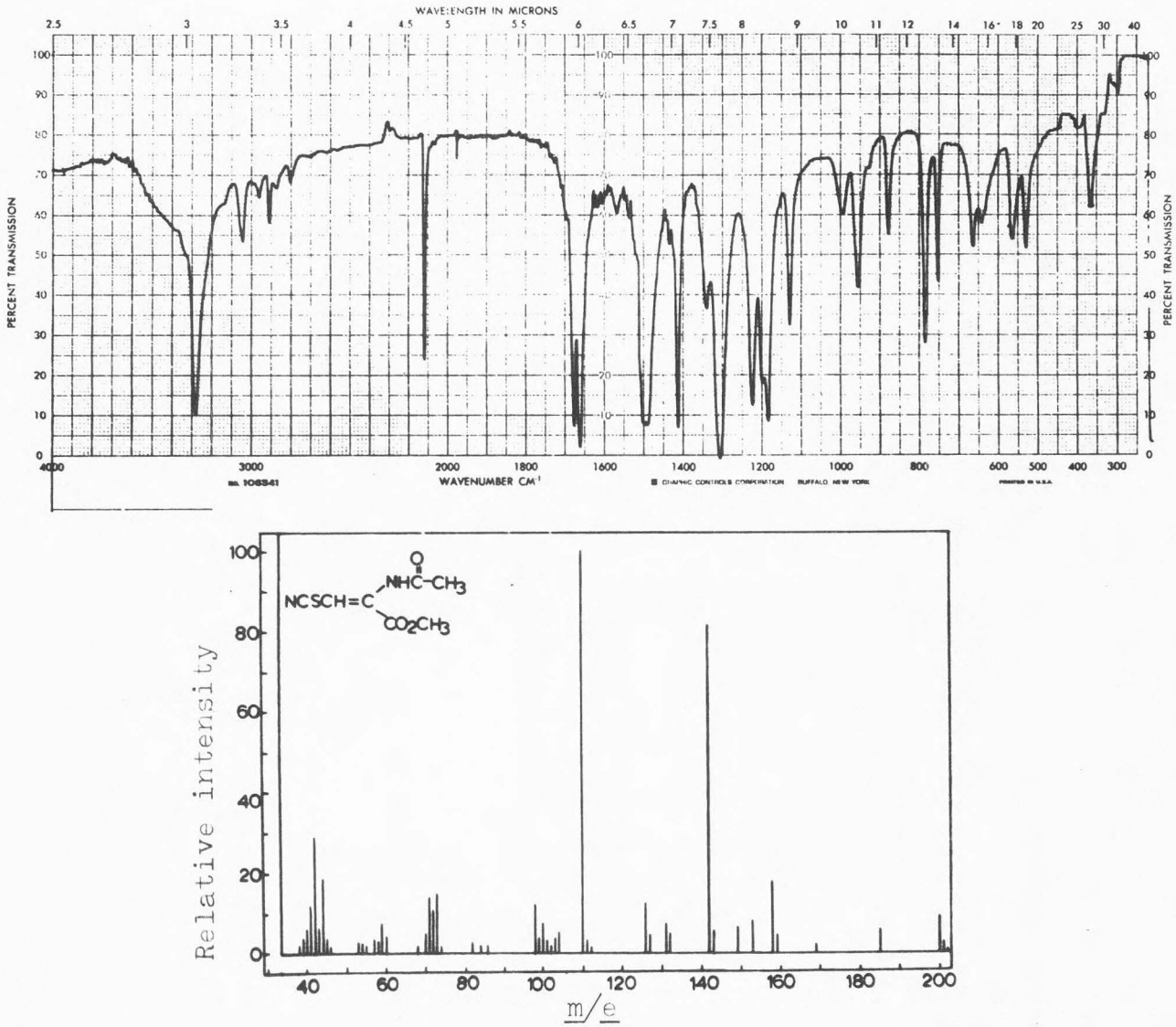



Figure 15. IR and mass spectra of methyl 2-acetamido-3-thiocyanatoacrylate (66).

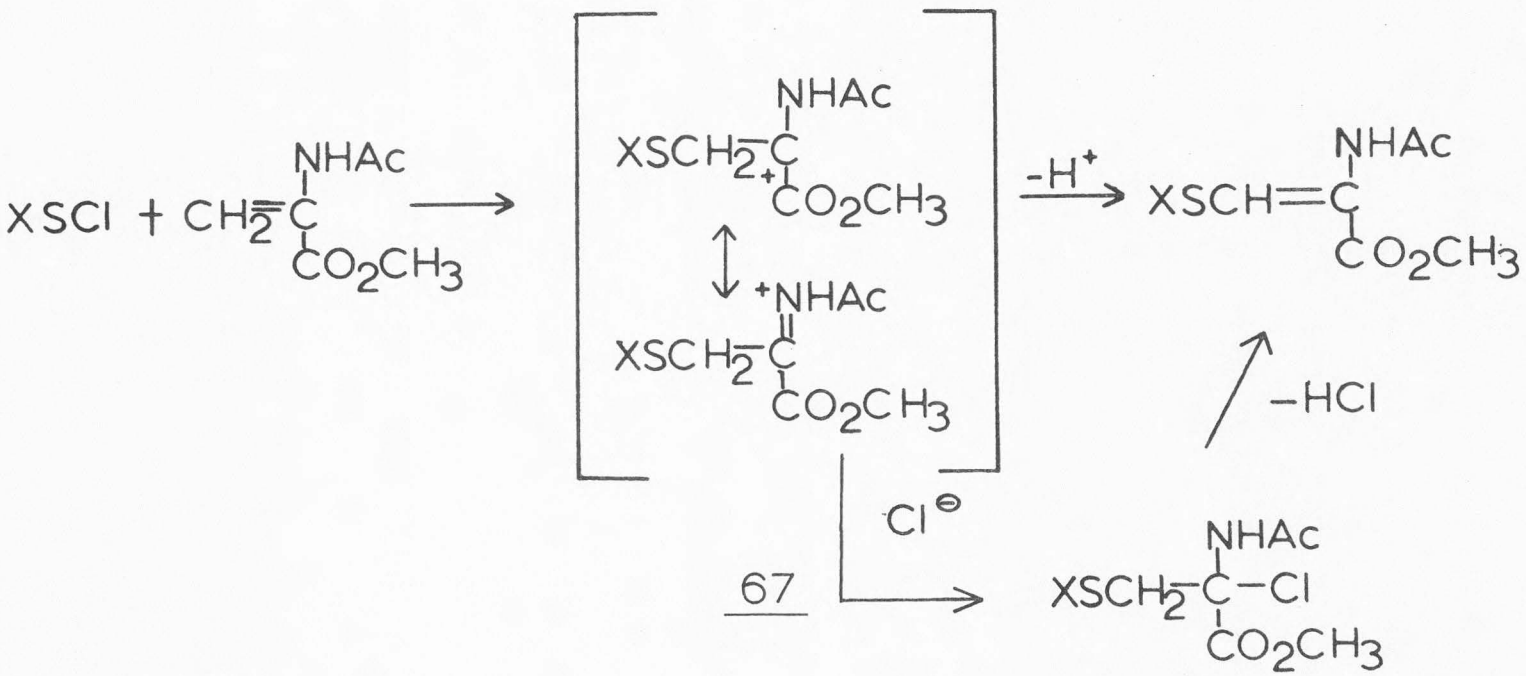
a proton or addition of chloride ion followed by elimination of hydrogen chloride (see Figure 16).

A comparison of these results with similar additions to the parent methyl acrylate discussed earlier (pages 22 to 30) indicate that the acetamido group strongly influences the direction of the addition of these reagents to 8. It is proposed that this directing influence is the result of stabilization of the carbonium ion 67 by resonance involving the nonbonded electrons on nitrogen as shown in Figure 16.

The reaction of methyl 2-acetamidoacrylate (8) with hydrogen bromide gas in chloroform led to three products which were identified as methyl pyruvate, acetamide·hydrogen bromide, and methyl 2-acetamido-3-bromopropionate (68) (see Figure 17).

As hydrogen bromide gas was passed through a solution of 8 in chloroform, acetamide.hydrogen bromide crystallized from the reaction mixture. The acetamide·hydrogen bromide was identified by comparison of the IR spectrum with that of material prepared from acetamide and hydrogen bromide gas (see Figure 18). Both products melted over the range 112-116° (lit. acetamide·hydrogen bromide, 140° (79)), and the IR spectra of the two were superimposable.

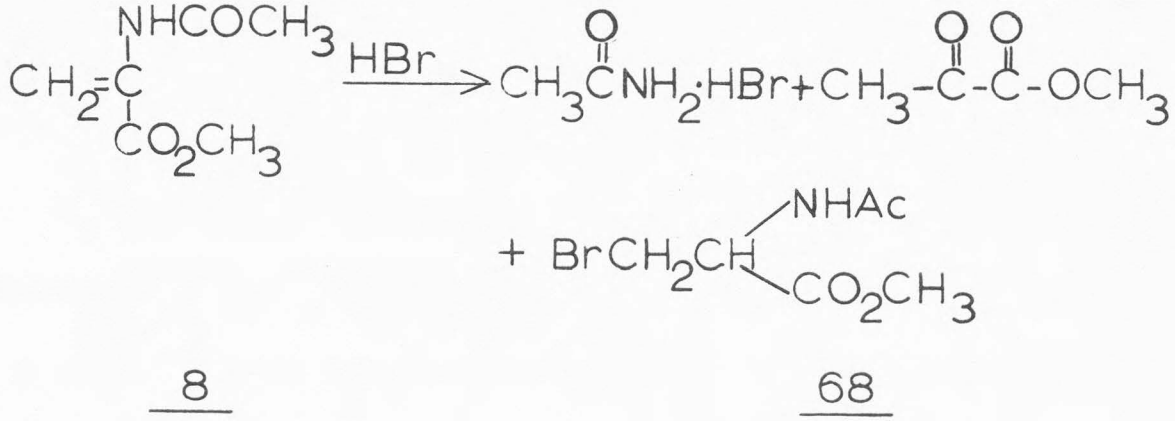
The methyl pyruvate obtained from the reaction of methyl 2-acetamidoacrylate with hydrogen bromide was treated with 2,4-dinitrophenylhydrazine following a modification




x = Cl, CN

Figure 16. The addition of sulfur chlorides to methyl 2-acetamidoacrylate (8).

of the method of Strain (59). The IR spectrum of the material thus obtained was identical to that of a material prepared by treating a known sample of methyl pyruvate with 2,4-dinitrophenylhydrazine in the same manner (see Figure 19). The two dinitrophenylhydrazones were hydrolyzed to the acids and had identical melting points, 219-220° (lit. 218° (59)).




8 68

Figure 17. The reaction of 8 with hydrogen bromide.

The formation of acetamide and methyl pyruvate requires the presence of water in the reaction solution or water added during work-up of the reaction and could represent the reverse of the condensation by which 2-acetamidoacrylic acid is prepared. Likewise, the reaction of water with

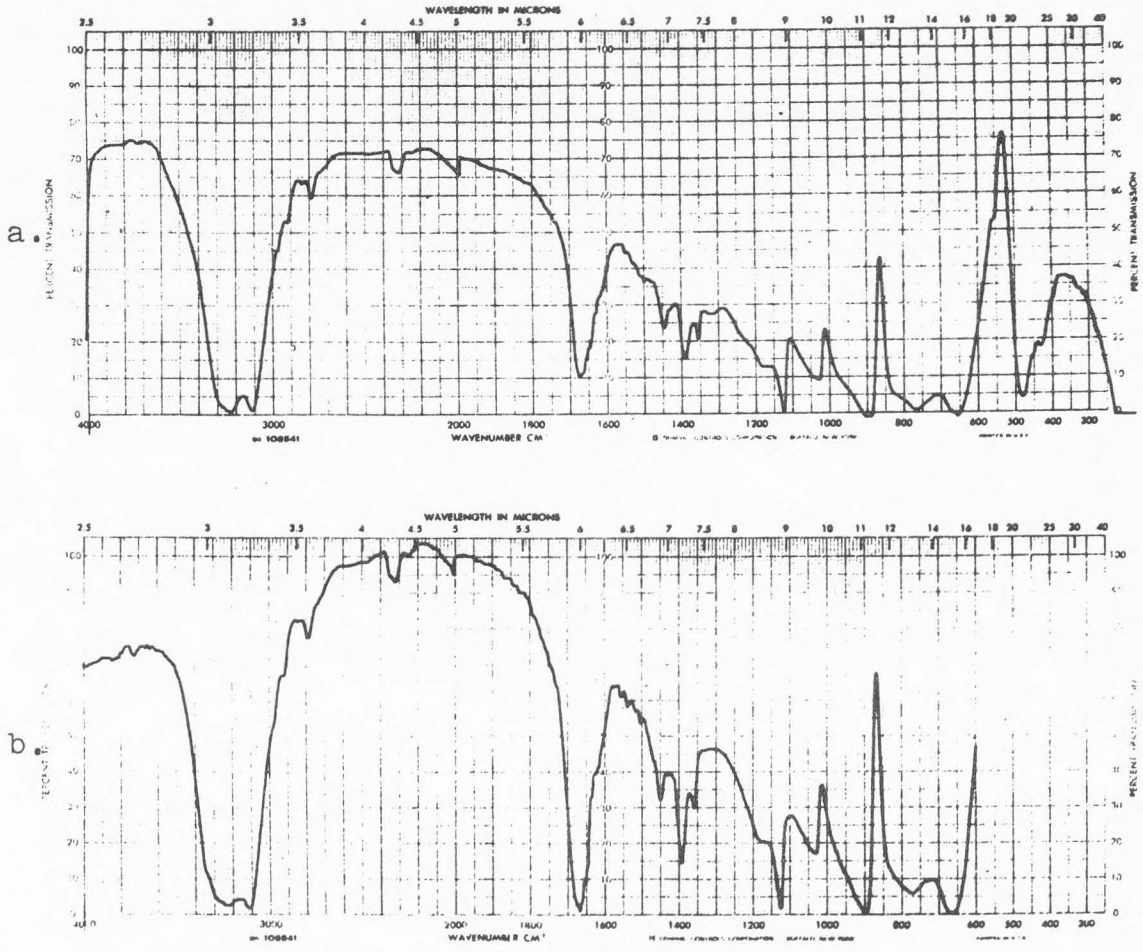


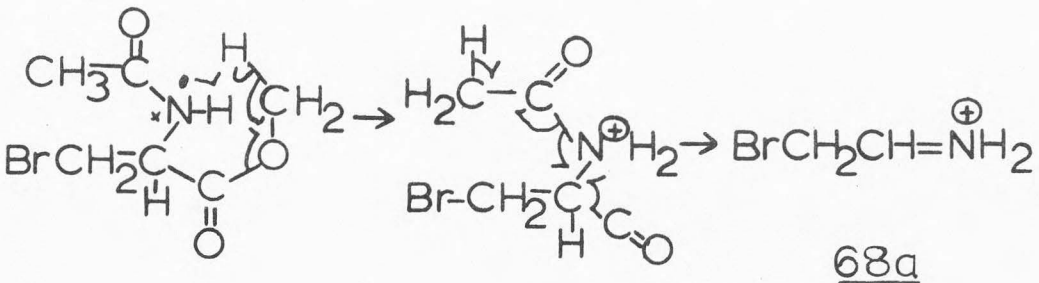

Figure 18. The IR spectra of acetamide·hydrogen bromide a) from 8 + HBr, b) from acetamide + HBr.

the addition product methyl 2-acetamido-2-brompropionate (69) could also yield acetamide and methyl pyruvate.

When the reagents, solvents, and glassware were carefully dried, the addition of hydrogen bromide to methyl 2-acetamidoacrylate (8) led to the formation of methyl 2-acetamido-3-bromopropionate (68), the Michael addition product (see Figure 17). The spectral data were consistent with this structure (see Figure 20).

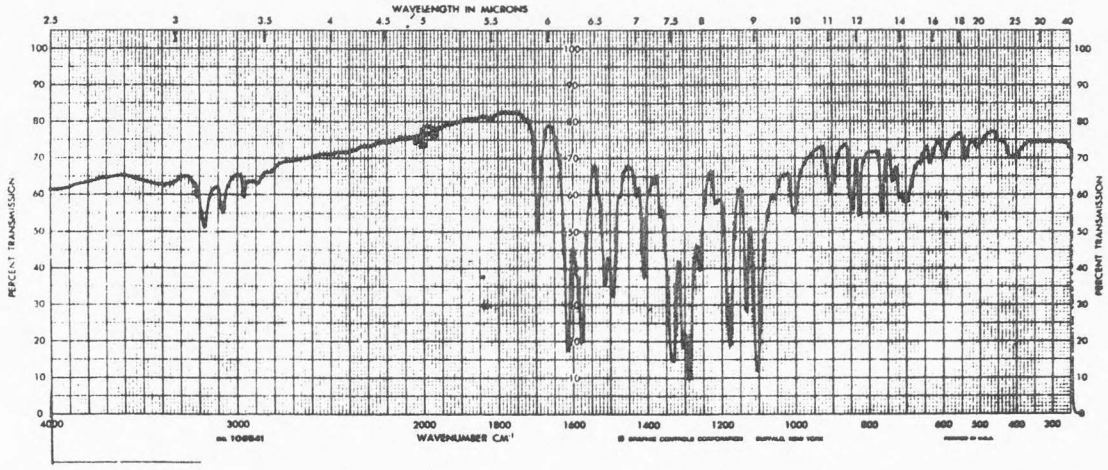
The assignment of peaks in the NMR spectrum of 68 is as follows: the amide proton appears as a broad singlet at 3.35 $\tau$ , the methine proton as a multiplet at 4.96 $\tau$ , the bromomethylene protons as a doublet at 6.20 $\tau$ , the methyl ester protons as a singlet at 6.19 $\tau$ , and the acetyl protons as a singlet at 7.93 $\tau$ .

The mass spectrum of 68 contains molecular ion peaks at m/e 223 (3.3) and 225 (3.0) as expected of monobromo compounds (210). The base peak at m/e 43 is most likely the acylium ion arising from amide cleavage. The M-59 peaks could arise from the loss of acetamide (55), while the M-101 peaks are possibly the fragment ion 68a arising from the loss



68a

a




b

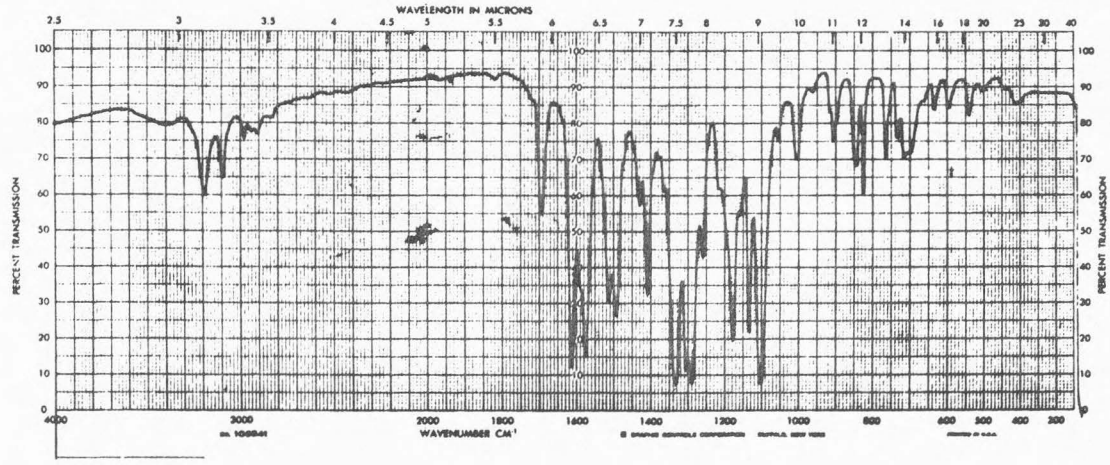
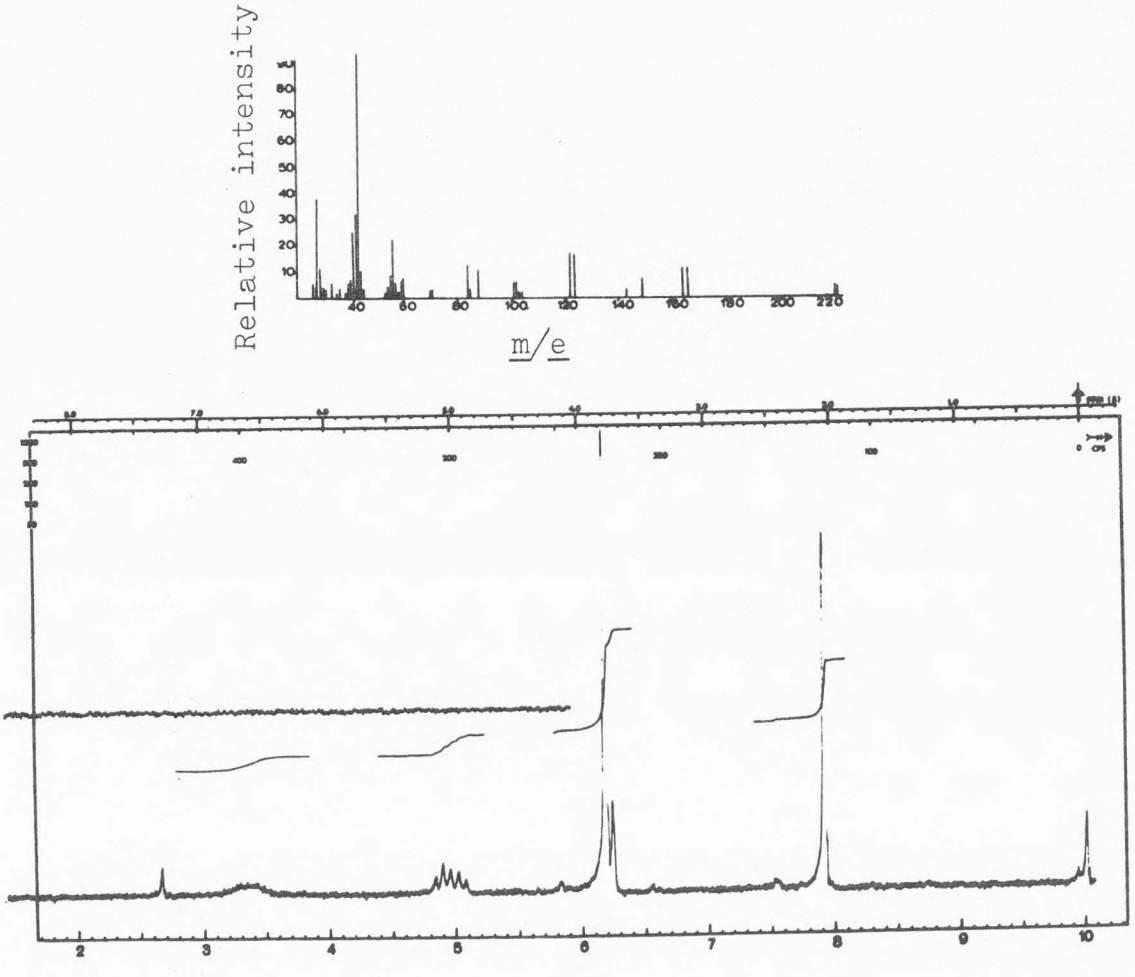
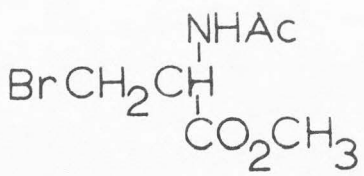



Figure 19. The IR spectra of methyl pyruvate 2,4-dinitrophenylhydrazone, a) from methyl 2-acetamidoacrylate + HBr, b) from an authentic sample.




68

Figure 20. The spectral data of methyl 2-acetamido-3-bromopropionate (68).

of the acyl group and the carbomethoxy group.

In order to explain the products from the addition of hydrogen bromide to methyl 2-acetamidoacrylate (8), two modes of addition are proposed as shown in Figure 21.

One mode of addition is protonation of the ester carbonyl followed by reaction with bromide ion and tautomerization to give the Michael addition product 68. The alternative mode of addition is protonation of the double bond in a manner analagous to the enamine reaction reported by Stork, et al (57), to give a highly reactive intermediate which reacts with water to give acetamide and methyl pyruvate, or with bromide ion to give 69.

The addition of hydrogen bromide to 8 was carried out in deuterochloroform and the progress of the reaction was followed by NMR. The changes in the spectrum are shown in Figure 22.

Immediately upon addition of hydrogen bromide to the chloroform solution of 8, the vinyl peaks at 3.50 and 4.20 $\tau$ disappeared, the amide proton signal shifted from 2.30 to -1.04 $\tau$ , and a peak at 7.22 $\tau$ appeared, equal in intensity to the methyl ester and acetyl peaks at 6.1 and 7.6 $\tau$ respectively. This peak at 7.2 $\tau$ is assigned to the methyl protons beta to the ester function of 69 (see Figure 21).

With the passage of time, the peaks at 7.2 and 7.6 $\tau$ diminished, while a singlet at 7.1 $\tau$, a singlet at 6.2 $\tau$, a shoulder on the peak at 6.1 $\tau$ , and a quartet at 4.85 $\tau$

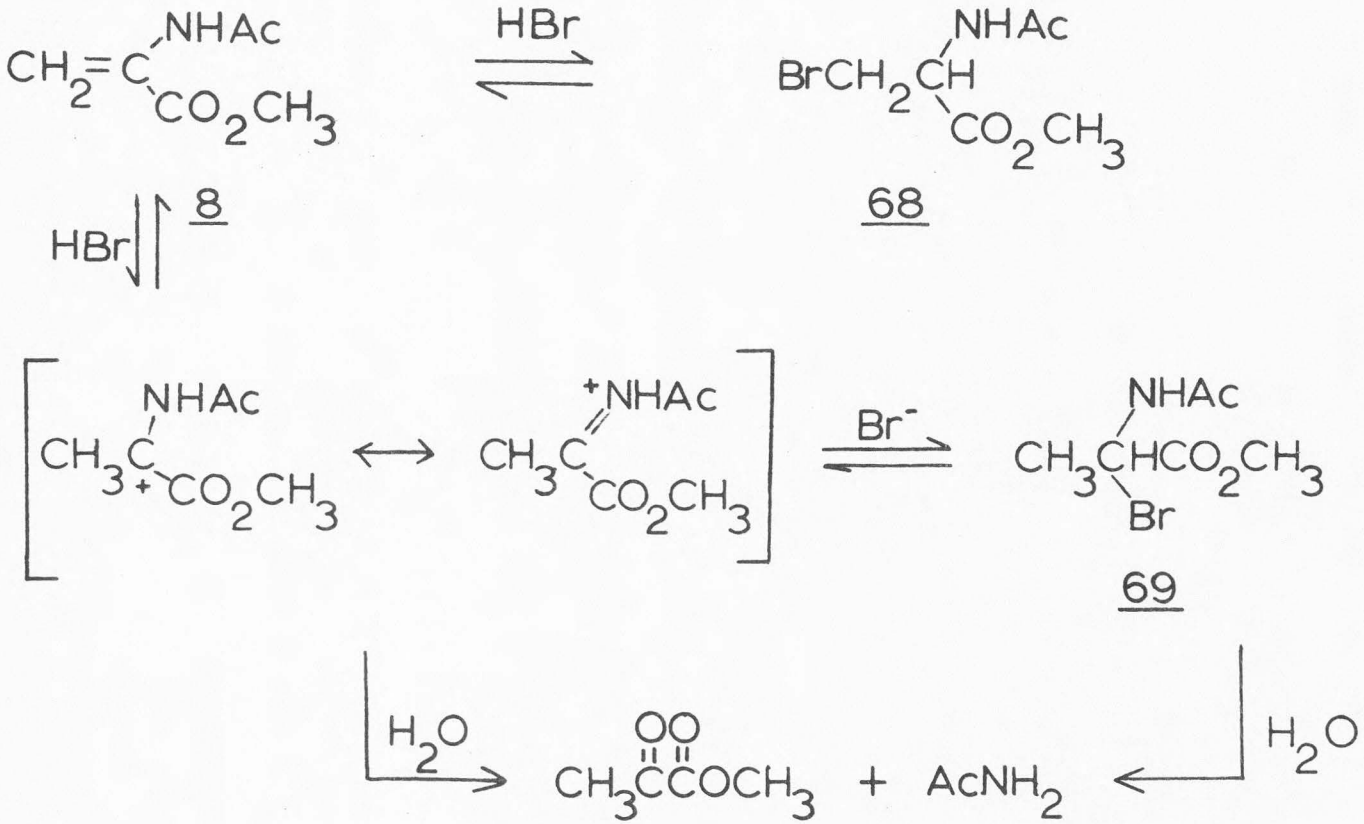



Figure 21. Proposed modes of addition of hydrogen bromide to 8.

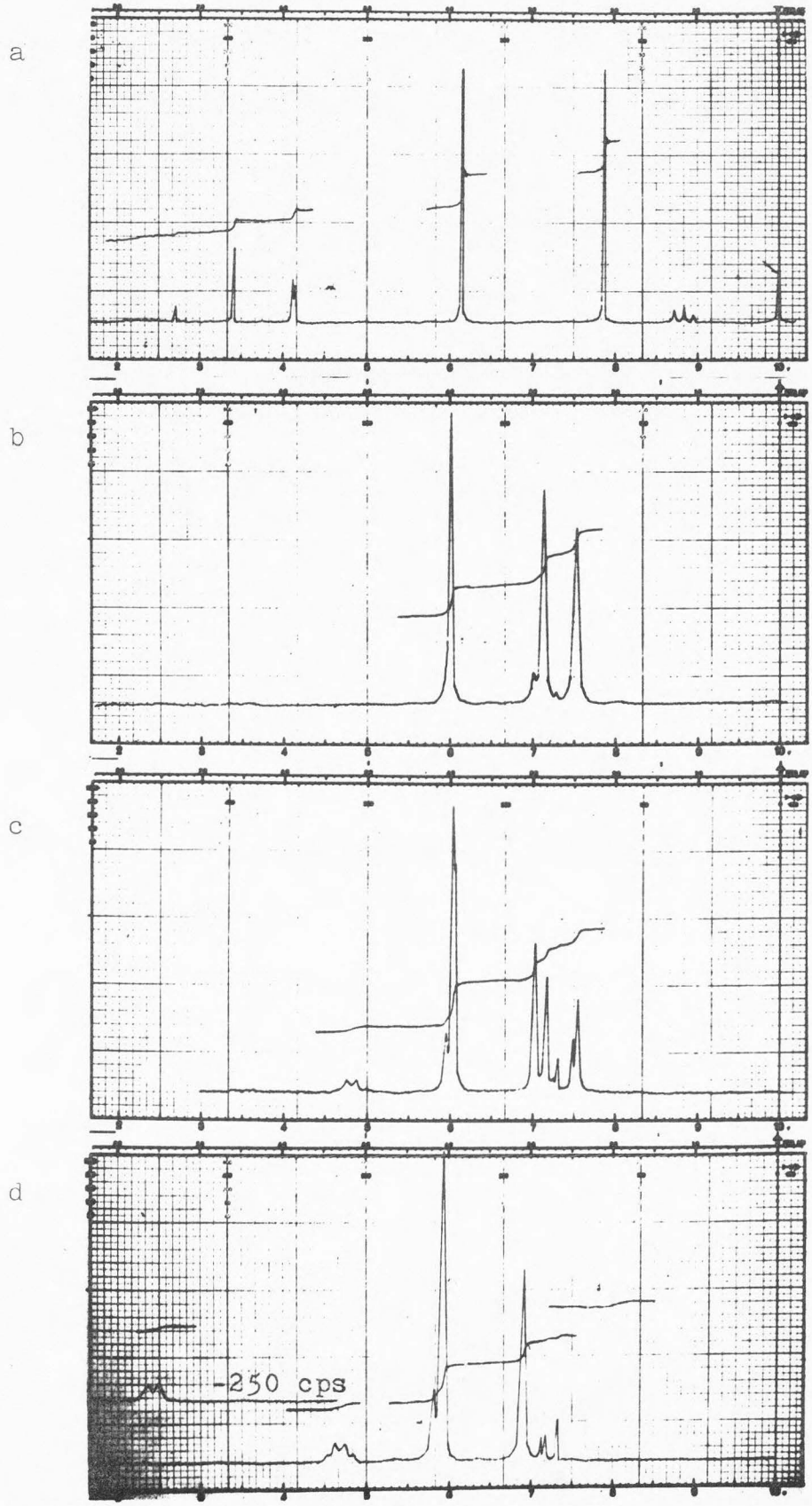
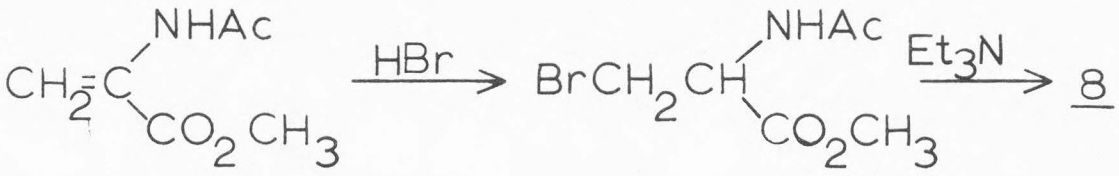



Figure 22. The time-dependant NMR spectrum of methyl 2-acetamidoacrylate plus hydrogen bromide in deuterochloroform, a) 8 before addition, b) t = 2 min, c) t = 12 hr, d) t = 2 days.

appeared, and the amide peak at -1.0 τ transformed into a doublet. The observed changes in the NMR spectrum were attributed to a decrease in the amount of 69, consistent with the assignment of the signals of 68 and 69.

After 48 hrs, the addition product was isolated and found to be methyl 2-acetamido-3-bromopropionate (68). This compound on treatment with triethyl amine produced a quantitative yield of methyl 2-acetamidoacrylate (8).




8 68

From these data it is concluded that the addition of HBr to 8 to give the species 69 is the faster reaction, but this reaction is reversible and the Michael addition product 68 is thermodynamically more stable, which is to say that 69 is favored by kinetic control while 68 is favored by equilibrium control.

When the addition of hydrogen bromide to methyl acrylate was carried out in deuterochloroform and followed by NMR spectroscopy, the vinyl protons clustered around 4.0 disappeared and triplets at 6.25 and 7.0 τ appeared immediately. No further change in the spectrum over a period

of two days was observed. These results are interpreted as a very fast Michael addition leading to methyl 3-bromopropionate (70) (see Figure 23).

Thus, the effect of the acetamido group of 8 appears to greatly increase the rate of protonation of the double bond and to slow down the rate of the Michael addition, while the Michael addition products 70 and 68 are thermodynamically more stable.

Summary

2,5-Dicarbomethoxy-1,4-dithiane (1) proved to be unsuitable as a precursor to echinodithianic acid (5) in view of the instability of the dithiane ring in the presence of strong base and in view of the difficulty encountered in the preparation of 1. Methyl 2-acetamidoacrylate (8) proved to add dipolar reagents cleanly and predictably, and in view of the enhanced reactivity of the alpha-halo group as reported by Kil'dishova, Linkova, and Knunyants (52b), 8 is a potential precursor to the corresponding derivative of 5.

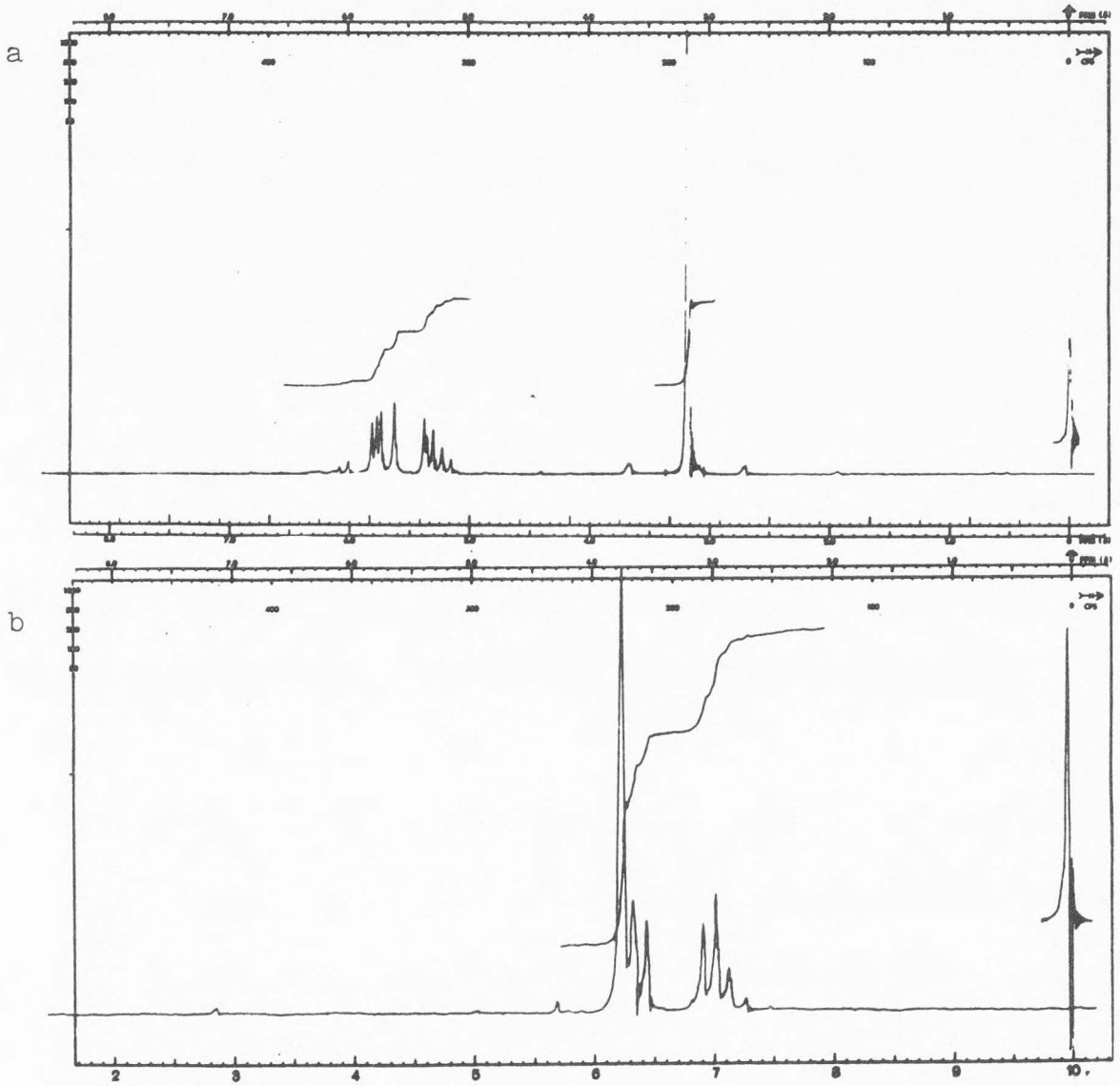



Figure 23. The NMR spectra of a) methyl acrylate, b) methyl 3-bromopropionate.

# EXPERIMENTAL

## Methods

The melting points were determined with a Thomas Hoover capillary melting point apparatus and are not corrected. Evaporation *in vacuo* was carried out with a Buchler rotary evaporator with the vacuum provided by a water aspirator. The infrared spectra were recorded on a Beckman I.R. 20A spectrophotometer in potassium bromide pellets or as neat liquids. Nuclear Magnetic Resonance spectra were obtained on a Varian A-60 Analytical NMR Spectrometer. The solvents are specified. The format of the data report is: chemical shift (multiplicity, integral intensity). Mass spectral data were determined with a Hitachi-Perkin-Elmer RMU-6E single focusing instrument. Thin-layer chromatography was done on commercially available silica gel plates containing flourescence indicator. Compounds were located under ultra-violet radiation, and with iodine. All elemental analyses were performed by M-H-W Laboratories, Garden City, Michigan.

## Preparation of (2-carbomethoxy-2-chloroethyl)-(1-carbomethoxy-2-chlorethyl) sulfide, (1a)

Following the method of Gundermann and Burba (6), to 182 ml (2.0 mol) of freshly distilled methyl acrylate was added dropwise 63.3 ml (1.0 mol) of sulfur dichloride, which had been freshly distilled from phosphorous

trichloride, while maintaining the temperature of the reaction solution at 65 to 70°C. After the addition was complete, the solution was allowed to stand overnight at room temperature.

The unreacted methyl acrylate was evaporated *in vacuo* and the remaining yellow oil was distilled under high vacuum. The fraction boiling between 164° and 166° at 3 torr (6) was collected to yield 121 g of **1a** (44%).

Preparation of 2,5-dicarbomethoxy-1,4-dithiane (**1**)

The method of Gundermann and Burba (6) was followed. The yield of **1** was not improved by varying the temperature, the rate of addition of **1a** to sodium sulfide, the total reaction time, or the reflux time.

A solution of 8.4 g (0.365 mol) of sodium in 600 ml of absolute methanol was divided into two 300 ml portions. One portion was saturated with dry hydrogen sulfide gas and then the two portions were combined to give an anhydrous solution of sodium sulfide. This solution was cooled in an ice bath, and a second solution of 50.0 g (0.18 mol) of **1a** in 600 ml of absolute methanol was added dropwise over a period of 8 hr.

After standing at room temperature for one week, the reaction mixture was refluxed for 5 hr and the methanol was distilled under atmospheric pressure. To the residue was added 250 ml of water and 250 ml of chloroform. The chloroform layer was separated, washed twice with water,

dried over magnesium sulfate, and evaporated *in vacuo* to leave a yellow oil.

The oil was distilled under vacuum and the fraction boiling between 150°-170° at 1.5 torr was collected (6). After cooling this fraction in a freezer for two days, a crystalline material was isolated by filtration.

The solid material was extracted with 75 ml cold acetone and the acetone evaporated *in vacuo* to leave a white powder. This powder was recrystallized from methanol to give 0.73 g of 1, mp 119.5°-120° (1.7%), lit mp 118°-119°, (6). The maximum overall yield obtained based on methyl acrylate was 1.5 g (0.31%).

IR 3010, 2990, 1725, 1440, 1290, 1270, 1245, 1200, 1150, 1005, 915, 880, 805, 790, 700, 650 $cm^{-1}$

NMR ($CDCl_3$) 6.22 (S, 6H); 6.20 (M, 2H); 6.70-6.85 (M, 4H) (see Figure 9)

Mass Spec. parent peak m/e 236 (100); p+1 (11.3) p+2 (10.9) (see Figure 10)

Reaction of 2,5-dicarbomethoxy-1,4-dithiane (1) with deuteromethanol

To a solution of 0.107 g (0.45 mmol) of 1 in 20 ml of deuteromethanol was added a solution of 0.05 g of sodium in 10 ml of deuteromethanol. After stirring with a magnetic stirrer for 4 hours, this solution was evaporated *in vacuo* and the residue dissolved in 20 ml of chloroform. The chloroform solution was washed with 20 ml of dilute hydrochloric acid, dried over magnesium sulfate, and evaporated to leave a yellow solid. The solid was extracted with methanol, and as the hot extract cooled, 2,5-dideutero-2,5-dicarbomethoxy-1,4-dithiane precipitated as

white crystals, 0.1 g, (93%), mp 117°-118°.

NMR: $\tau$ 6.21 (S,3H); 6.74 (S,2H) (See Figure 9)
Mass Spectrum: parent peak, m/e 238 (100), p+1 (10), p+2 (10) (See Figure 10)

Attempted carbonylation of 2,5-dicarbomethoxy-1,4-dithiane (1)

To a carefully dried flask flushed continuously with nitrogen was added 150 ml of tetrahydrofuran, previously dried over calcium hydride, and 0.354 g (1.5 mmol) of 1. The reaction flask was cooled in a Dry Ice-isopropanol bath and 3.2 mmol of n-butyllithium in 1.6 ml of hexane was added. After 15 min, the solution was poured into a Dry Ice-ether slurry, and the mixture warmed to room temperature. The ether was evaporated *in vacuo* and the residue dissolved in 50 ml of chloroform, washed with 50 ml of 0.075 N acetic acid and 50 ml of water. The chloroform was evaporated to leave a yellow oil (0.2 g); thin-layer chromatography (TLC) (4:1 benzene:methanol) rf (product) = 0.85, (1) = 0.85, (mixed) = 0.85. The yellow oil was recrystallized from ethanol to yield white crystals, mp 117°-120°, mmp with (1) 117-120°. (See Table 2)

Attempted carbethoxylation of 2,5-dicarbomethoxy-1,4-dithiane (1)

Five ml of dry ethanol was placed into a 500 ml flask and 2.5 mmol of sodium metal added. After the reaction ceased, the excess ethanol was removed *in vacuo* and a solution of 0.40 g (1.27 mmol) of 1 in 250 ml of dry diethyl carbonate was added. The flask was fitted with a

distillation head and condensor. The reaction solution was subjected to a slight vacuum to remove product ethanol while being stirred for 5 hr at room temperature. The solution was then warmed to boil gently under vacuum for 20 minutes. After the addition of 10 ml of glacial AcOH, the solution was allowed to stand at room temperature overnight whereupon sodium acetate precipitated as long colorless needles (mp 321°). The solution was filtered and the filtrate washed twice with water, once with 300 ml of aqueous sodium bicarbonate, twice with water, dried over magnesium sulfate and evaporated to leave 0.41 g of white solid, mp 37°-38°. Recrystallization from ethanol did not improve the melting point.

TLC (1:5 MeOH:benzene) rf = 0.62
IR Ester Bands, 1710 $cm^{-1}$, 1738 $cm^{-1}$
Mass Spec. m/e 228, 41; 229, 6; 230, 2.5; 183, 100
NMR $\tau$ 1.71 (D, 1H); 1.84 (D, 1H): 2.50 (S, 1H); 5,61 (Q, 6H); 8.62 (T, 9H)
Anal. Calc. for $C_{13}H_{18}O_6S$: C, 51.6; H, 5.9; S, 10.6.
Found: C, 49.6; H, 5.00; S, 12.6.

Although the structure of this compound was not established, the spectra clearly indicate that it was not the desired tetra-ester 6.

The attempted carbomethoxylation of 2,5-dicarbomethoxy-1,4-dithiane (1)

To 150 ml of dry ether was added 0.5 g of sodium hydride (20 mmol) and 75 ml of methyl carbonate. A solution of 0.29 g (1.25 mmol) of 1 in 40 ml of dry ether was added dropwise over a period of 5 hours at room

temperature. The resulting solution was stirred at room temperature for an additional 5 hours, and poured into 100 g ice. Twenty ml acetic acid was added, the ether layer was separated, washed with 250 ml water, dried over sodium sulfate and evaporated to leave a tan solid. Recrystallization from ethanol afforded 0.2 g of white crystals, mp 126.5°-127.5°.

NMR τ 1.83 (S,1H); 1.93 (S,1H); 6.17 (S,9H)
Mass Spec. p m/e 200, 32.8 ; p+1 3.7 ; p+2 1.8
Anal. Calc. for $C_8H_8O_4S$: C, 48.0 ; H, 4.0 ; S, 16.0
Found: C, 48.13 ; H, 4.06 ; S, 15.89 .

The analysis and spectral data indicate that this compound was not the desired product. No structure was assigned to this compound.

The attempted amination of (1)

To 150 ml of 1:10 methanol:benzene was added 1.0 g (4.29 mmol) of 1 and 1.0 g of 50% sodium hydride in mineral oil. After 20 min, a large excess of the previously prepared O-2,4-dinitrophenylhydroxylamine (24) was added and the solution stirred at room temperature for 4 hours. The solution was washed with water, dried over magnesium sulfate, and evaporated to leave orange material. This material was extracted with chloroform; the chloroform solution was concentrated and applied to a silica gel column. The column was eluted with benzene, then chloroform, and finally with ethyl ether. Organic material was found only in the chloroform fractions. These were combined, washed with base, concentrated and streaked on a preparative

thick-layer plate and eluted with 1:10 MeOH:benzene to give 8 bands of rf = 0.95, 0.89, 0.71, 0.57, 0.16, 0.08, 0.04, and 0.0. No further work-up was attempted.

Preparation of 2-acetamidoacrylic acid (8a)

Following the procedure of Wieland, Ohnacker and Ziegler (58), to a flask fitted with a liquid-liquid extractor was added 12 g of acetamide, 67 g of pyruvic acid and 250 ml of 1,1,2-trichloroethane. The solution was refluxed using a liquid-liquid extraction apparatus whereby the heavier than water solvent was returned to the reaction vessel as the water was azeotropically distilled. After refluxing five hours, the solution was cooled and filtered to remove the precipitated acid. The filtrate was extracted with 250 ml aqueous sodium bicarbonate to recover any unprecipitated acid and the previously removed acid was added to this extract. After evolution ceased, just enough solid potassium hydroxide was added to completely dissolve the acid. The basic solution was placed on a rotary evaporator to remove the last traces of 1,1,2-trichloroethane and made just acid to congo red with dilute hydrochloric acid. The 2-acetamidoacrylic acid was filtered off, air dried overnight and recrystallized from 95 per cent ethanol, mp 196.5°-197°, (lit 196-198° (58)), yield 8 g (21%).

The preparation of methyl 2-acetamidoacrylate (8)

Using the method reported by Wieland, Ohnacker and Ziegler (58), 2.80 g of potassium hydroxide (0.05 mol) were dissolved in 300 ml of water; 5.0 g (0.0387 mol) of 8a were dissolved in this solution and 11.90 g of silver nitrate (0.07 mol) dissolved in 30 ml of water was added. The mixture was cooled and the silver salt of (8a) was removed by filtration and air dried in the dark. The dry salt was covered with methyl iodide and refluxed for four hrs. The solution was filtered hot; the filter cake was washed with chloroform, and the chloroform and methyl iodide were evaporated *in vacuo* to leave a white solid. This solid was extracted with 2 x 100 ml of boiling 60-70° petroleum ether. The combined extracts were cooled in the freezer for two days. Filtration yielded methyl 2-acetamidoacrylate (8), 2.7 g (48.7%), mp 50-52°, (lit 50-52°, (78)).

NMR ($CDCl_3$) τ 2.3, (S,1H); 3.4, (S,1H); 4.1, (D,1H); 6.1, (S,3H); 7.8, (S,3H).

The addition of sulfur dichloride to methyl 2-acetamido acrylate (8)

To a solution of 1.4 g (0.01 mol) of 8 in 75 ml of chloroform was added 1.0 g of sulfur dichloride (0.01 mol). The solution refluxed spontaneously. The solution was frozen (Dry Ice-acetone bath) for 5 hrs. An additional 1.4 g (0.01 mol) of 8 were added and the solution warmed to room temperature and stirred for 8 hrs. On cooling overnight, solid material precipitated. The solid was filtered

and the filtrate concentrated by evaporation *in vacuo* to leave an oil which was recrystallized twice from ethanol to yield 2 g (63%) of bis(2-acetamido-2-carbomethoxyvinyl) sulfide (*65*), mp 202.5-204°.

NMR τ 2.04, (S,1H); 2.41, (S,1H); 6.52, (S,3H); 8.13, (S,3H); (see Figure 14).
Qualitative Analysis: N pos., S pos., Cl neg.
Anal. Calc. for $C_{12}H_{18}N_2O_6S$: C, 45.6; H, 5.1; N, 8.8; S, 10.1.
Found: C, 45.16; H, 5.28; N, 8.72; S, 10.20.

The addition of thiocyanogen chloride to methyl 2-acetamidoacrylate (*8*)

Acetic acid (125 ml) containing 2 ml of acetic anhydride was refluxed for 2½ hours. After cooling, 1.5 g of chlorine (0.021 mol) and 2.0 g of potassium thiocyanate (0.021 mol) were added and the mixture was stirred 45 minutes at room temperature. Two grams of *8* (0.014 mol) were added and the mixture stirred 1.5 hours. The acetic acid solution was concentrated *in vacuo* and filtered. The filtrate was dissolved in 200 ml of chloroform and the resulting solution was washed with 3 x 300 ml of water, dried over magnesium sulfate, and evaporated *in vacuo* to yield 1.6 g of crude product. This material was recrystallized twice from chloroform to yield pure methyl 2-acetamido-3-thiocyanato-acrylate (*66*), mp 153°, (57%).

IR 3280, 2120, 1677, 1661 $cm^{-1}$ (see Figure 15)
Mass Spectrum m/e 110 (100); 142 (81); 200 (9.44); p+1 (2.28) p+2 (0.57)
Anal. Calc. for $C_7H_8N_2O_3S$: C, 42.0; H, 4.0; N, 14.0
Found: C, 42.1; H, 3.93; N, 13.8.

The addition of hydrogen bromide to methyl 2-acetamidoacrylate (8)

Hydrogen bromide gas was passed through a solution of 8 in 50 ml of spectral grade chloroform until the solution ceased to gain weight, after which the solution was stirred for four hrs at room temperature.

The isolation of acetamide·hydrogen bromide. Acetamide·hydrogen bromide precipitated from the chloroform solution as white crystals, mp 112-116°.

IR 3230, 3110, 1678, 1450, 1390, 1122, 895, 770, 665 $cm^{-1}$ (see Figure 18)
NMR ($CF_3CO_2H$) $\tau$ 1.60, (S,2H); 7.80, (S,3H)
Mass Spectrum m/e 82 (16.6); 80 (16.9); 59 (37.5); 44 (100); 28 (37.5)

The isolation of methyl 2-acetamido-3-bromopropionate. After filtering off the acetamide·hydrobromide, the chloroform solution was washed with 2 x 100 ml water, dried over magnesium sulfate, and evaporated to leave 0.16 g of methyl 2-acetamido-3-bromopropionate, mp 94-95°, (51%).

Mass Spectrum, molecular ion m/e 223, (3.3); 225, (3.0)
NMR ($CDCl_3$) $\tau$ 3.35, (S,1H); 4.96, (M,1H); 6.19, (S,3H); 6.20, (D,2H); 7.93, (S,3H).

The isolation of methyl pyruvate. After filtering off the acetamide·hydrogen bromide, the chloroform solution was extracted with water (2 x 100 ml). The aqueous extracts were combined and evaporated under a dry air stream to yield 2.1 g of methyl pyruvate, (74%), which was characterized as the 2,4-dinitrophenylhydrazone (see below).

The reaction of methyl pyruvate with 2,4-dinitrophenylhydrazine

Following a modification of the method of Strain (59), the methyl pyruvate obtained from the reaction of hydrogen bromide with methyl 2-acetamidoacrylate was dissolved in a solution of 100 ml of methanol, 100 ml of water, and 10 ml of conc hydrochloric acid. An excess of 2,4-dinitrophenylhydrazine was added and the mixture heated on a steam bath for 0.5 hr and slowly cooled to room temperature. The yellow crystals were removed by filtration and recrystallized once from methanol, mp 145-160°.

IR 3190, 3090, 1695, 1612, 1575, 1492, 1330, 1290, and 1102 $cm^{-1}$.
NMR ($CDCl_3$) $\tau$ 0.86 (D); 1.84 (M); 6.04 (S); 7.68 (S).

Reagent grade methyl pyruvate was treated with 2,4-dinitrophenylhydrazine in the same manner (59) to yield yellow crystals, recrystallized once from methanol, mp 145-155°, (lit 186.5-187.5 (59)).

IR 3190, 3090, 1695, 1612, 1575, 1492, 1330, 1290, and 1102 $cm^{-1}$.

The IR spectra of the two samples were superimposible.

Strain reports this product to be a mixture of the 2,4-dinitrophenylhydrazones of methyl pyruvate and pyruvic acid (59). Accordingly, the two samples were hydrolyzed to the 2,4-dinitrophenylhydrazone of pyruvic acid as follows: the material was placed in aqueous sodium hydroxide and stirred at room temperature for 0.5 hr. The solution was filtered and acidified with conc hydrochloric

acid. The resulting solid was removed by filtration and air dried, mp 219-220° (both samples), (lit. 218° (59)).

The elimination of hydrogen bromide from methyl 2-acetamido-3-bromopropionate (68)

To a solution of 0.2 g of (68) in 10 ml of chloroform was added 2 ml of triethylamine. After the reaction mixture was allowed to stand for ½ hr at room temperature, 50 ml of chloroform was added and the solution washed twice with water, dried over magnesium sulfate, and evaporated in vacuo to leave 0.12 g of methyl 2-acetamidoacrylate (8). An NMR spectrum of this material was superimposable with that of a previously prepared sample of 8.

Preparation of acetamide·hydrogen bromide

Fifty ml of dry chloroform was saturated at room temperature with hydrogen bromide gas. To this solution was added 1.0 g (0.017 mol) of acetamide. Upon standing at room temperature overnight, acetamide.hydrogen bromide precipitated as pure crystals, mp 112-116°.

IR 3230, 3120, 1670, 1392, 1125, 1030, 898, 775, 665 $cm^{-1}$ (see Figure 18).

The addition of hydrogen bromide to methyl 2-acetamidoacrylate (8): The NMR study

To 1.0 ml of deuterochloroform was added 0.200 g (1.4 mmol) of 8. Hydrogen bromide was passed over the solution for two min following which the solution was immediately transferred to an NMR sample tube by means of

a capillary dropper. The sample tube was capped and the NMR spectrum was traced at intervals as follows, (t=time elapsed from the beginning of the addition of hydrogen bromide):

t = 5 min, 40 min, 1.3 hr, 14 hr, 21.1 hr, 38.5 hr, 68 hr.

At t = 5 min peaks at 7.6 and 7.1 $\tau$ appeared, and the peaks at 3.4 and 4.1 $\tau$ had disappeared. After 15 hr a multiplet at 4.85 $\tau$ had appeared, the peaks at 7.2 and 7.6 $\tau$ had disappeared, the peak at 7.1 $\tau$ had greatly increased, a shoulder on the peak at 6.1 $\tau$, and a singlet at 6.2 $\tau$ had appeared.

After three days the contents of the NMR tube were emptied into a separatory funnel, diluted with 10 ml chloroform, washed with 10 ml water, dried over magnesium sulfate, and evaporated <u>in vacuo</u> to leave 0.16 g of methyl 2-acetamido-3-bromopropionate, mp 94-95° (67%).

NMR ($CDCl_3$) $\tau$ 3.34 (S,1H); 4.96 (P,1H); 6.19 (S,3H); 6.21 (D,2H)
Mass Spectrum m/e 223 (3.3%); 225 (3.0%)

<u>The attempted addition of thiocyanogen chloride to methyl acrylate</u>

a. Acetic acid (100 ml) was refluxed with acetic anhydride for 1 hr and then cooled in an ice bath. To the dry acetic acid was added 2.8 g (0.04 mol) of chlorine and 3.9 g (0.04 mol) of potassium thiocyanate. After stirring at room temperature for 45 hr, 2.0 g (0.023 mol) of methyl acrylate were added, the solution stirred an additional 3 hr, and the solvent evaporated <u>in vacuo</u>.

NMR spectra taken periodically during the course of the reaction remained identical to the NMR spectrum of methyl acrylate, (see Figure 23).

b. To 100 ml dry carbon tetrachloride was added 2.8 g (0.04 mol) of chlorine and 3.9 g (0.04 mol) of potassium thiocyante. After stirring at room temperature for 1 hr, 2.0 g (0.023 mol) of methyl acrylate were added and the reaction mixture stirred at room temperature for 2 days. NMR spectra of the solution taken periodically during this period were identical to the spectrum of methyl acrylate (see Figure 23). No attempt was made to further characterize the methyl acrylate as it appeared that no reaction had occurred.

The addition of hydrogen bromide to methyl acrylate

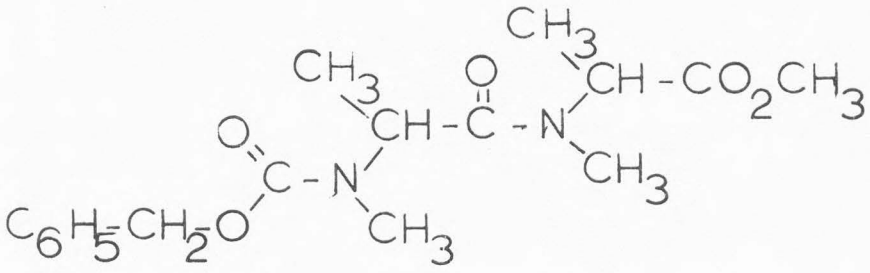
Hydrogen bromide gas was passed over a solution of 0.20 g of methyl acrylate in 0.5 ml of deuterochloroform for two minutes. The sample was then placed in an NMR tube, and NMR spectra were recorded over a period of two days. Immediately the vinyl proton peaks disappeared and peaks due to methyl 3-bromopropionate appeared, but no further change was observed. After washing the sample with water and drying over magnesium sulfate, methyl 3-bromopropionate (70) was isolated. (0.19 g, 51%) NMR ($CDCl_3$) $\tau$ 6.10 (S,3H); 6.25 (T,2H); 7.0 (T,2H); (see Figure 23).

# PART II

## THE TEMPERATURE DEPENDENT NMR SPECTRUM OF METHYL N-ACETYLSARCOSINATE

# INTRODUCTION

It has been observed that the methyl ester protons of N,N'-dimethylcarbobenzoxyalanylalanine methyl ester (71) give rise to a doublet in the nuclear magnetic resonance spectrum, (NMR), centered at 6.33 $\tau$ (60). Since this doublet cannot be produced by spin-spin coupling, the molecule must undergo a slow conformational change providing non-equivalent magnetic environments for the methyl ester protons.

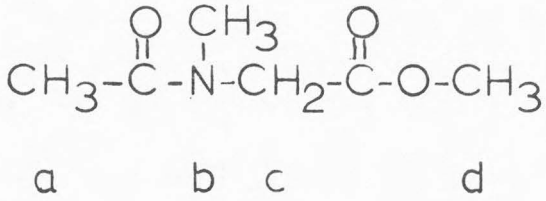


71

It is known that the rotation about the carbonyl-nitrogen bond of amides is restricted (61,62) and this could be the source of the conformational rigidity in the dipeptide. An alternative source of the two magnetic sites is the barrier to exchange between the extended and folded conformers as described by Marraud, Neel, Avignon, and Huong (63) for various dipeptides, and by Bystrov et al. (64) for alanylalanine derivatives.

While the N-methyl proton signals of the dipeptides are adequately described by hindered rotation about the amide bonds, the interpretation of the doublet rising from the methyl ester protons is not clearly defined. A comparison of the rates of exchange of the N-methyl and the methyl ester protons on the N,N'-dimethylcarbobenzoxy-alanylalanine methyl ester using NMR spectroscopy is not feasible since the signals of the two N-methyl groups interfere with each other while the two peaks of the methyl ester protons are not sufficiently separated. A model compound suitable for study would be a simple molecule containing an amide bond, and having N-methyl protons and methyl ester protons each giving rise to simple doublets.

A suitable molecule is methyl-N-acetylsarcosinate (72). The NMR spectrum of 72 in dimethyl sulfoxide-$d_6$ has been reported by Bovey, Ryan, and Hood (65). Each of the four




72

types of protons (labeled a, b, c, d) gives rise to a doublet. A rate study could help derive a physical interpretation of these splittings.

# LITERATURE REVIEW

## Amide resonance and exchange

In many molecules a nucleus can have two or more possible magnetic environments as the molecule can have two or more stable conformations. As a molecule exchanges between conformations, so a nucleus exchanges between magnetic environments or magnetic sites. This exchange was observed in dimethylformamide and reported by Phillips (61). The origin of the nonequivalent sites was reported to be restricted rotation about the C-N bond as previously postulated by Pauling (62). At a field strength of 30 Mc, the N-methyl protons give rise to a doublet with a separation of six cps at room temperature. This separation is greater by a factor of 4/3 at a field strength of 40 Mc and thus the splitting is due to different chemical environments and not to spin-spin coupling. Similar results were reported for dimethylacetamide (61). The restricted rotation of the amide bond is due to a resonance form placing considerable double bond character in the C-N bond giving rise to "cis" and "trans" isomers. (See Figure 24) (62).

The data obtained for a variety of amides is summarized in Table 3 as reported by Siddall, Stewart and Knight (66).

Table 3. Barriers to rotation in various amides[a] $RCON(R')_2$

| R | R' | Solvent | Method[b] | $\Delta F^*$ (T) kcal/mole |
|---|---|---|---|---|
| H | Me | Neat | S.S. | 20.9 (119) |
| H | Me | 0.04 mol. fraction $CHCl_2CHCl_2$ | A.S.S. | 20.9 (115) |
| Me | Me | Neat | S.S. | 18.1 (75) |
| Me | Me | $CD_3SOCD_3$ | S.S. | 18.3 (75) |
| H | Et | Neat | A.S.S. | 20.4 (100) |
| Me | Et | Neat | A.S.S. | 16.9 (25) |
| Me | 2-Pr | Neat | A.S.S. | 15.7 (25) |

[a] Siddall, Stewart, and Knight; reference (66).
[b] S.S. = complete signal shape analysis; A.S.S. = approximate signal shape analysis.

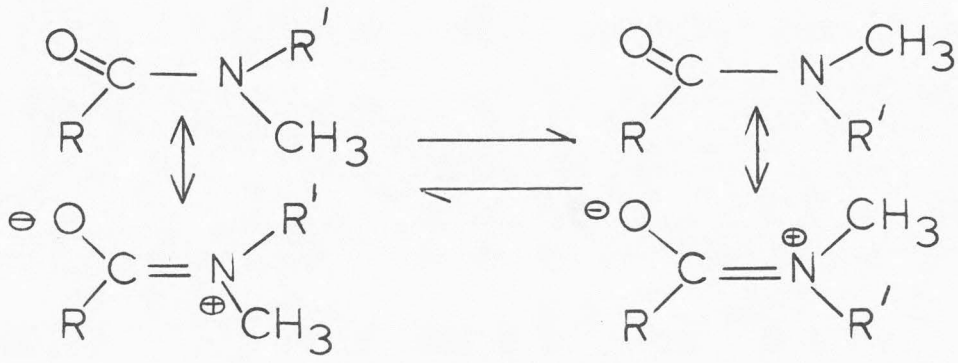
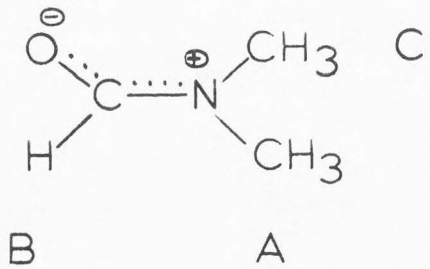


Figure 24. Amide resonance

Correlation of structure to signal

Anet and Bourn (67) conducted studies on the nuclear Overhauser effect of dimethylformamide (73). This effect is explained simply as follows, (67) (and references 2b, 6, and 7 contained therein); if protons A and B are coupled through space, each affects the relaxation time of the other. If proton B is spin saturated as in double resonance, there occurs an enhancement of the integrated intensity of the signal from proton A.



B A C

73

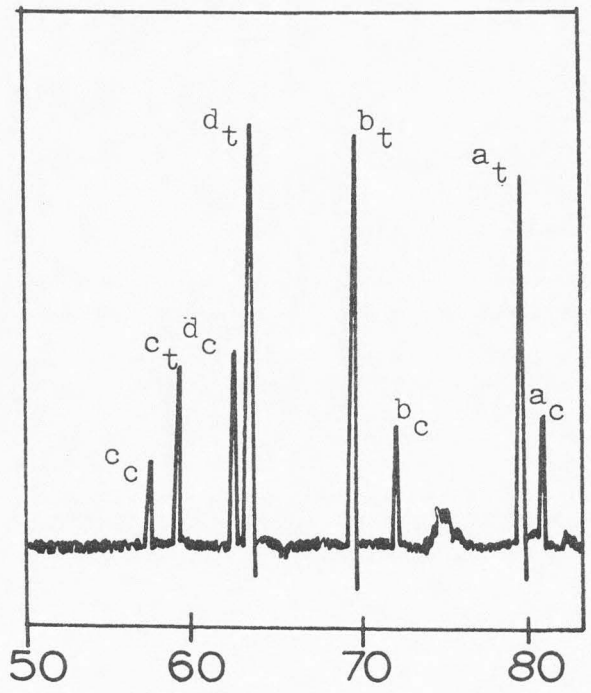
When proton B is irradiated, protons A should show a nuclear Overhauser effect while protons C should not. The results of this study (67) prove the low field signal to arise from the methyl group trans to the oxygen (A). This is in agreement with results of previous authors (68).

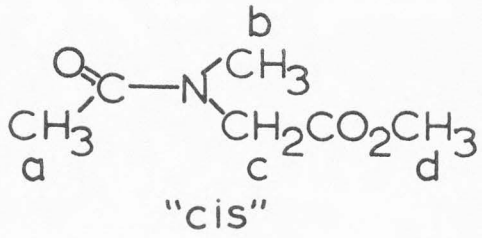
Bovey, Ryan and Hood (65) assigned the various signals in methyl N-acetylsarcosinate (72) as in Figure 25. This assignment is made on the basis of data reported by Anet and Bourn (67) and on populations of the signals. The splitting of all four types of protons was attributed to cis-trans isomerism as in Figure 25. No rate study on this compound has been reported.

Liberek, Steporowska and Jereczek (69) report the isomerism about the sarcosine amide bond in methyl carbobenzoxysarcosinate and in dipeptide derivatives of sarcosine as a function of dilution with aromatic solvents. This study confirms the assignment of the higher intensity low field signal to the N-methyl group trans to oxygen.

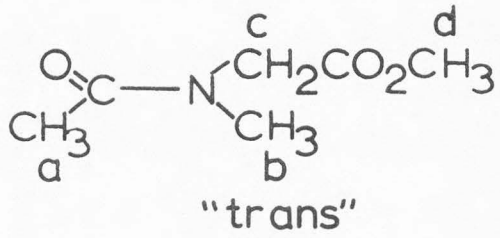
Barry and Marshall (70) have reported that N-methylation of glycine and other amino acids considerably reduces the number of stable conformations of the molecule by steric crowding.

Gutowsky and Holm (71) report the signal due to the acetyl group of dimethylacetamide and N-methylacetamide to be a singlet.




"cis"




"trans"

Figure 25. The NMR spectrum of methyl N-acetylsarcosinate (72).

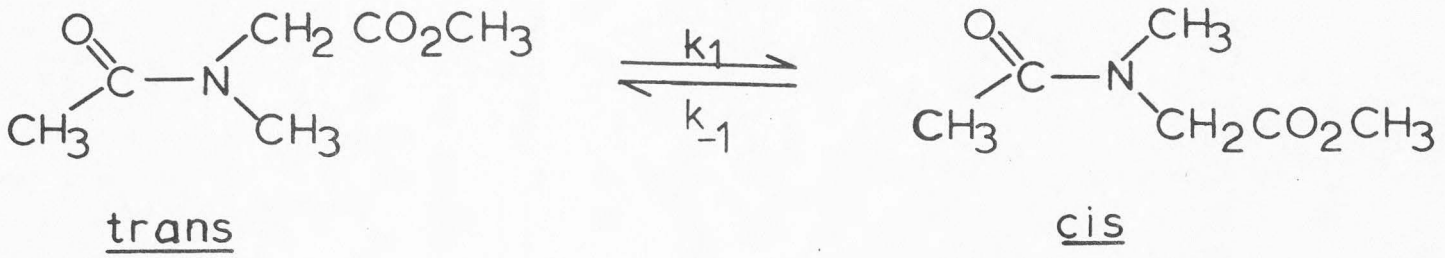
As N-methylacetamide is similar to methyl N-acetyl sarcosinate (72), there exists the possibility that the splitting of the a and d protons of 72 may not be due to a simple first-order rotation about the amide bond. Thus the need arises for a rate study, and it is proposed that this study be carried out on the a and b protons of 72 by a suitable total lineshape analysis to see whether the two exchanges occur at the same rate. This data would lead to conclusions about the nature of the conformational change responsible for the observed exchange, and the role of the open-extended form exchange which in methyl N-acetyl-sarcosinate is equivalent to rotation about the alpha methylene C-N bond (see Figure 26).

Lineshape calculations from the Bloch equations

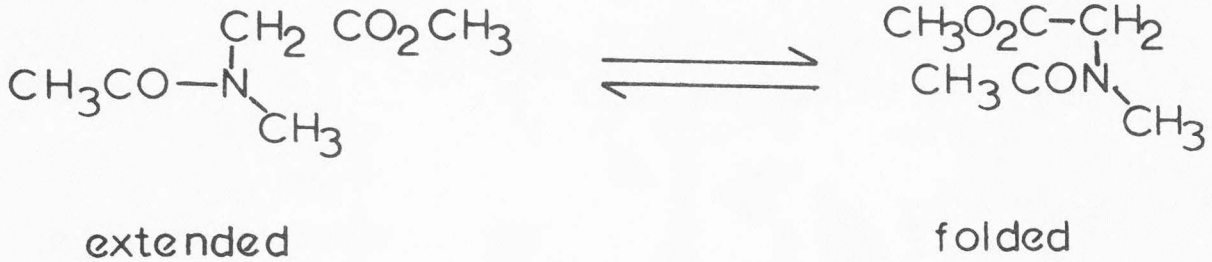
$$\frac{d M_+}{d t} = -\left[\frac{1}{T_z} + (w_o - w)\right] M_+ + i w_r M_z \qquad (2)$$

$$\frac{d M_z}{d t} = w_r M_y - \frac{(M_z - M_o)}{T_i} \qquad (3)$$

The Bloch equations in the above form describe the motion of the magnetic moment M in the presence of a static field $H_o$ in the z direction, and a much smaller field $H_i$, which rotates at an angular frequency w in a plane perpendicular to $H_o$. Since the coordinate system also rotates about the z axis with the angular frequency




a




b

Figure 26. Conformational changes in methyl N-acetylsarcosinate. (a) cis-trans isomerism, (b) extended-folded isomerism.

w, $H_i$ lies along the x axis (72). This describes the magnetization in a one-site case in the absence of exchange. The method used to derive an intensity function is to modify these equations to include the possibility of a nucleus being in one of several sites and then to add a perturbation term to account for the exchange of a nucleus between two or more sites as first reported by Gutowsky, McCall and Slichter (73) and summarized by Johnson (72).

The assumption is made that $H_i \ll H_o$ so that $M_z = M_o$ and the transverse relaxation, $1/T_2$, is the main contributor to line broadening in the absence of exchange. The modified equation then becomes:

$$\frac{d\,M_+^i}{d\,t} = -\left[\frac{1}{T_2} + i(w_i - w)\right] M_+^i + i\,w_r M_o P_i \qquad (4)$$

where $P_i$ is the mole fraction of the nuclei at site i at equilibrium. The solution of equation (4) is:

$$M_+^i(t) = \frac{i\,w_r M_o P_i}{\alpha_i}(i - e^{-\alpha_i t}) + M_+^i(o)e^{-\alpha_i t} \qquad (5)$$

where

$$\alpha_i = \frac{1}{T_2^i} + i(w_i - w)$$

In the absence of exchange $M_y$, which is directly proportional to the intensity of absorption, can be obtained directly by ignoring the transient terms in equation (5).

When exchange is occurring, two assumptions are made to simplify the solution. First, the average value of the magnetization at site i can be calculated by averaging $M_+^i(t)$ over the distribution of residence times of nuclei in site i. Thus,

$$\langle M_+^i \rangle = \frac{1}{\tau} \int_0^\infty e^{-t'/\tau} \cdot M_+^i(t')dt' = \frac{[+iw_r M_o P_i \tau + M_+^i(o)]}{1 + \alpha_i \tau} \tag{6}$$

where $\tau$ is the half life of nuclei in site i.

The second assumption is to choose a boundary condition in which $M_+^i$ at time zero equals the transverse magnetization in site i immediately after all of the systems undergo simultaneous collisions. Thus the probability that a nucleus arriving in site i came from site j depends simply on $P_j$, obtaining $M_+^i(o) = P_i \sum_j \langle M_+^j \rangle$. The final expression is then:

$$M_+ = \sum_i \langle M_+^i \rangle = \frac{+iw_r M_o \sum_i P_i/(1+ \alpha_i \tau)}{\sum_i P_i \alpha_i /(1+ \alpha_i \tau)} \tag{7}$$

In the approximation of slow exchange, equation (7) gives

$$\pi (\Delta \nu)_{\frac{1}{2}} = \frac{1}{T_2^i} + \frac{(1-P_i)}{\tau} \qquad (8)$$

where $(\Delta \nu)_{\frac{1}{2}}$ is the observed line width and $\frac{1}{T_2}$ is the line width in the absence of exchange, and includes line broadening due to relaxation plus broadening due to field inhomogeneities and instrument peculiarities.

The modified Bloch equation in matrix form

When the Bloch equations are expanded to include more than two sites and written in matrix form, the result is given by (10) (72);

$$I_{(w)} = \frac{1}{\pi} \cdot \mathrm{Re}(-P \cdot [i(\Omega - W) + D]^{-1} \cdot \mathbf{1}) \qquad (10)$$

where:

I = intensity of absorption at frequency w

Re means the real part

$\Omega$ is a matrix from $\Omega_{ij} = \delta_{ij} w_i$
($\delta$ = Kronecker delta)

W = w times the unit matrix

D is a matrix containing the transition probabilities

P is a matrix containing relative populations

and $\mathbf{1}$ is the column vector.

P is a row matrix containing as many elements as magnetic sites, and the part in the square brackets of eq (10) can be expressed in terms of the square matrix A containing $i^2$ elements if there are i magnetic sites considered. For the simple two site case of methyl N-acetylsarcosinate, A is given by (11)

$$A = \begin{pmatrix} (\alpha_i - D_i) & D_4 \\ D_2 & (\alpha_2 - D_2) \end{pmatrix} \qquad (11)$$

where D is the relative transition probability, and contains the line widths and frequencies in the absence of exchange, and the rate constant for the exchange.

Sources of error in lineshape calculations

Allerhand, Gutowsky, Jonas and Meinzer (74) have discussed in detail the sources of error in rate calculations by total lineshape analysis. This section is a summary of that discussion.

The two major problems are accurate measurement of temperature and accurate measurement of line-widths.

The fluctuations in temperature are caused by variations in the gas flow. These fluctuations are short lived, but, while difficult to measure, they can be minimized by averaging several readings.

Short lived fluctuations in line width measurements are caused by instrument instabilities, such as temperature drifts, line voltage changes, frequency changes, magnetic field drifts, and changes in sample spinning rate. Again these errors are minimized by averaging several readings.

Systematic errors in temperature rise largely from calibration problems. If the temperature is measured by a thermocouple, the calibration may not be constant, and is subject to the same error as the actual temperature measurements. If temperature is measured by means of a standard with a temperature dependant chemical shift, such as methanol, the measurement is subject to the same errors as the measurement of line-widths.

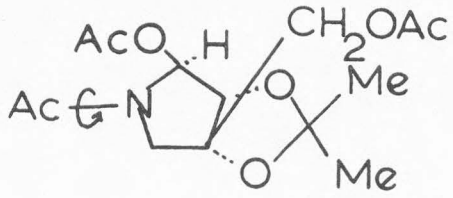
The systematic errors in line-width measurement arise from calibration of the sweep width, inhomogeneities in the magnetic field, and gradual deterioration of resolution due to uncontrollable factors. Another problem is the change in bulk magnetic susceptibility with temperature.

These errors are minimized by care to maintain the instrument in the best possible condition and "tune" throughout the experiment, and to obtain all data in as short a time span as possible.

The total lineshape method is less sensitive to these errors than approximate methods since the equation

includes a term which accounts for inhomogeneity broadening and also allows rates to be calculated over a larger temperature range.

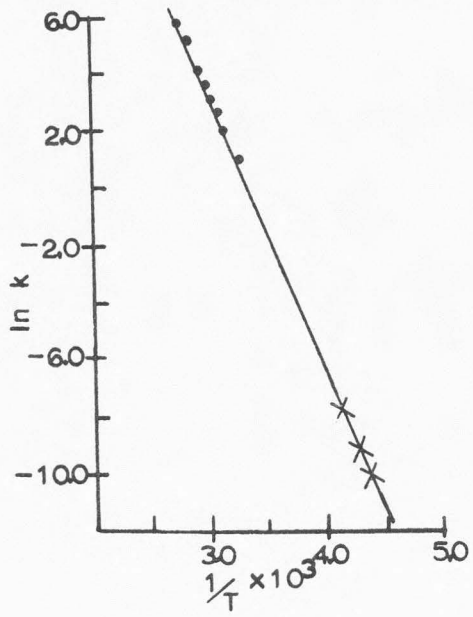
The validity of the total lineshape method has been demonstrated by Bushweller, O'Neil, Halford and Bissett (75). The hindered rotation about the amide bond of the N-acetylpyrrolidine 74 was studied by NMR lineshape, and since at -50°C the molecule is 100% in one conformation, the rate of thermal stereomutation was followed at lower temperatures directly by measuring NMR peak areas as a function of time. The resulting Arrhenious plot is shown in Figure 27.




74

Summary

The rates of exchange of a protons and b protons of methyl N-acetylsarcosinate were compared to determine whether or not both rates can be described by hindered rotation about the carbonyl-amide bond. The rates were determined by a total lineshape analysis based on the modified Bloch equations.




• rates from total lineshape

X rates from integrated peak intensities

Figure 27. Rates of exchange of the N-acetylpyrrolidine 74, the Arrhenius plot.

The results of this study will help to explain the splitting of the methyl ester proton peak in the NMR spectrum of N,N'-dimethylcarbobenzoxyalanylalanine methyl ester.

# RESULTS AND DISCUSSION

## The NMR spectrum of N,N'-dimethylcarbobenzoxyalanylalanine methyl ester (71)

At room temperature, the NMR signals arising from the N-methyl and methyl ester groups of 71 are each doublets. As the sample is heated, the doublets broaden and collapse to a singlet (see Figure 29).

The exchange of the methyl ester protons may be due to hindered rotation about the alanylalanine peptide bond,

$$71A \rightleftharpoons 71C$$

$$71B \rightleftharpoons 71D$$

or to a folded-form, extended form equilibrium, which is equivalent to rotation about the $C_3$-N bond, or to a

$$71A \rightleftharpoons 71B$$

$$71C \rightleftharpoons 71D$$

combination of the two motions (see Figure 28).

$$71A \rightleftharpoons 71D$$

$$71C \rightleftharpoons 71B$$

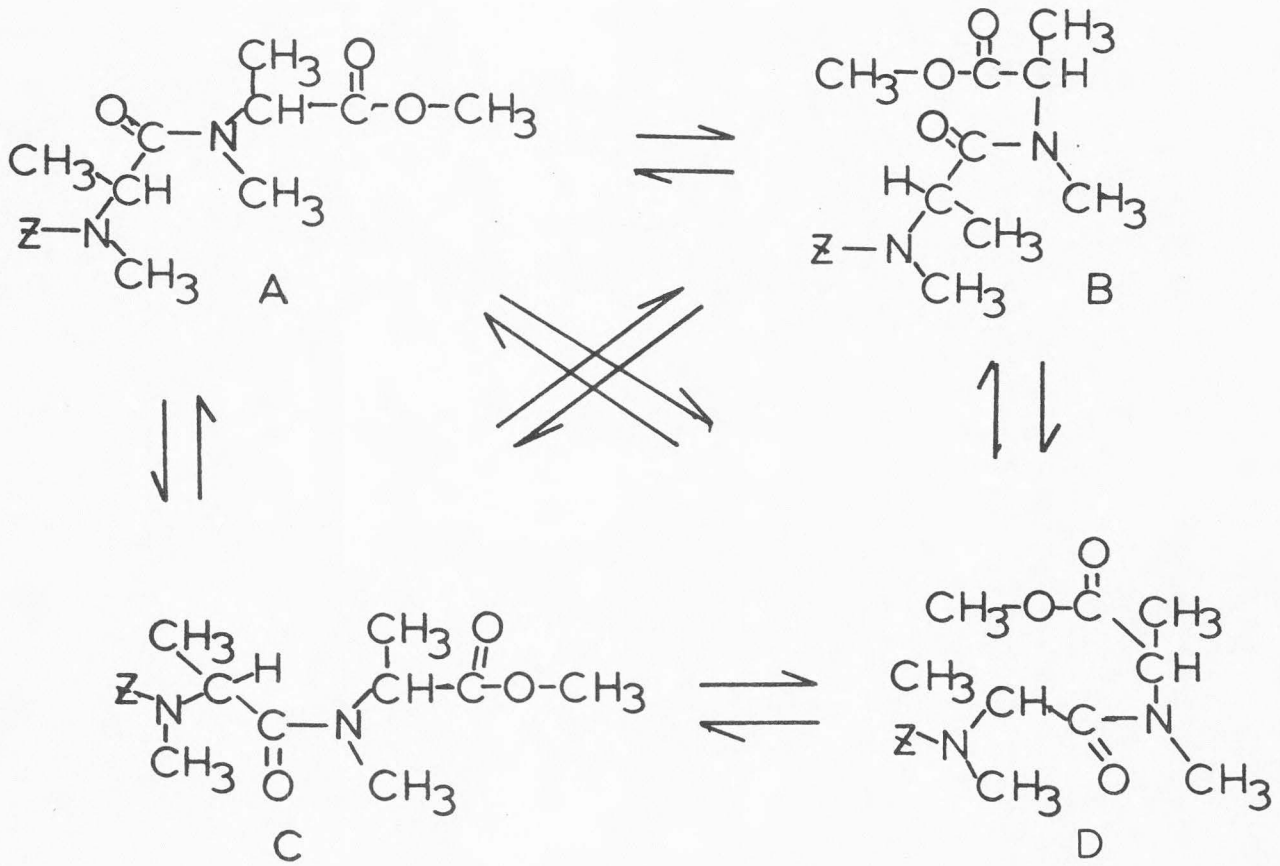



Figure 28. Conformational changes in N,N'-dimethylcarbobenzoxyalanylalanine methyl ester (71).

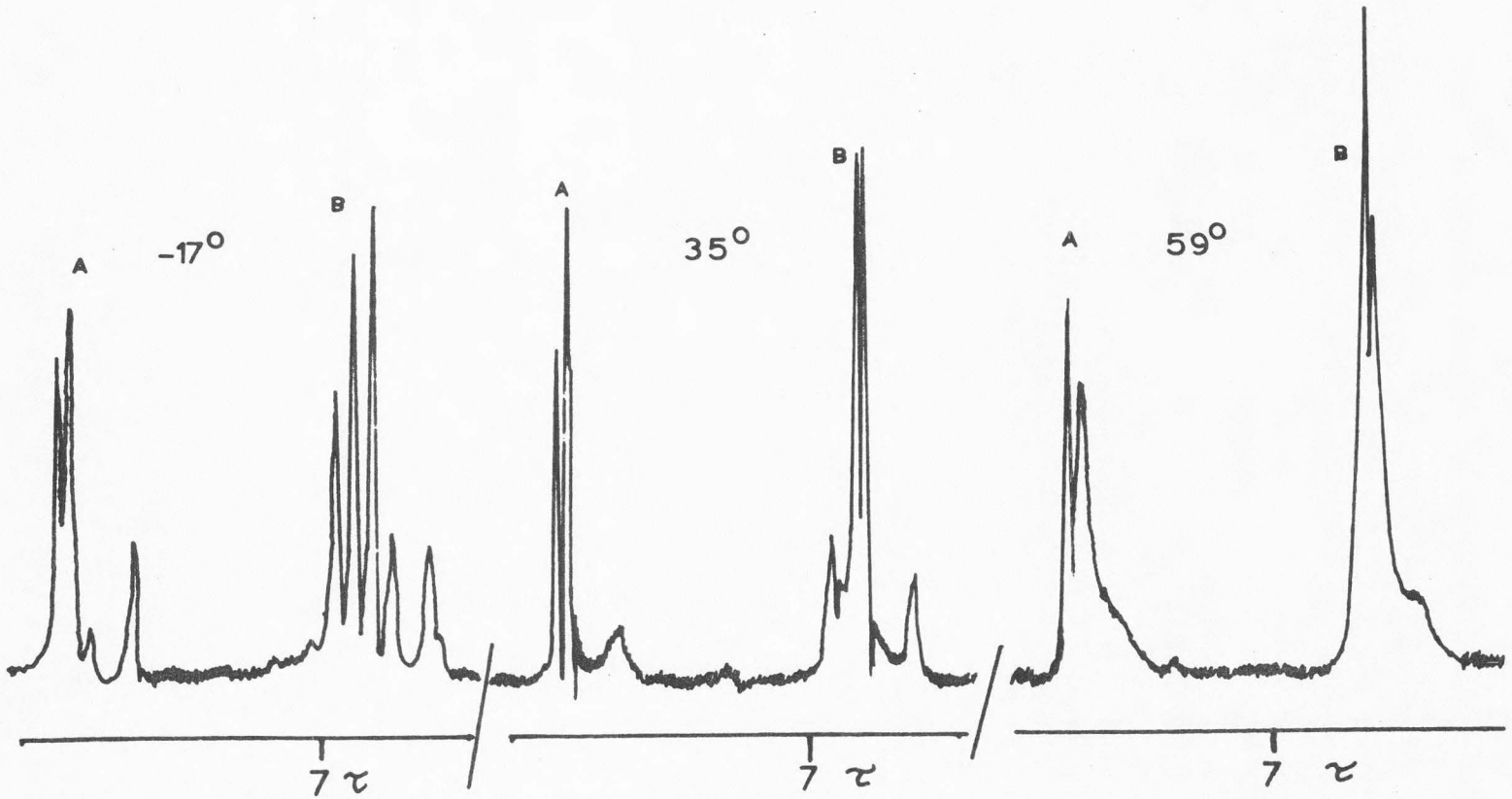



Figure 29. The temperature dependent NMR spectra of N,N'-dimethylcarbobenzoxyalanyl-alanine methyl ester (71) (A) methyl ester protons, (B) N-methyl protons.

The NMR spectrum of methyl N-acetylsarcosinate (72)

The NMR spectrum of 72 containing 1% deuterochloroform at room temperature consists of four sets of doublets, all of which broaden and collapse to singlets with increasing temperature (see Figure 30). The rates of exchange of the acetyl protons (a) and the N-methyl protons (b) are studied and compared.

The method

The effect of exchange of nuclei between two non-equivalent sites is to broaden and coalesce the peaks in the NMR spectrum. This operation is approximated in the model based on the modified Bloch equations by inverting the "A" matrix and multiplying it by the "P" matrix and the unit vector (Eq 10 and 11). The various values contained in the "A" and "P" matrices then are those values which would exist if there were no exchange.

To obtain these values at temperatures where exchange is occurring, the measurements are taken at low temperatures where the spectrometer detects no exchange, and a temperature dependant graph of the quantity is extrapolated into the region of exchange.

One of the quantities measured is the width of the signal at half-maximum intensity ($\Delta\nu$). Plots of $\Delta\nu$ versus $1/T$ measured over the range of $-25^{\circ}C$ to $+30^{\circ}C$ gave straight lines which were extrapolated into the region of exchange (see Figure 31).

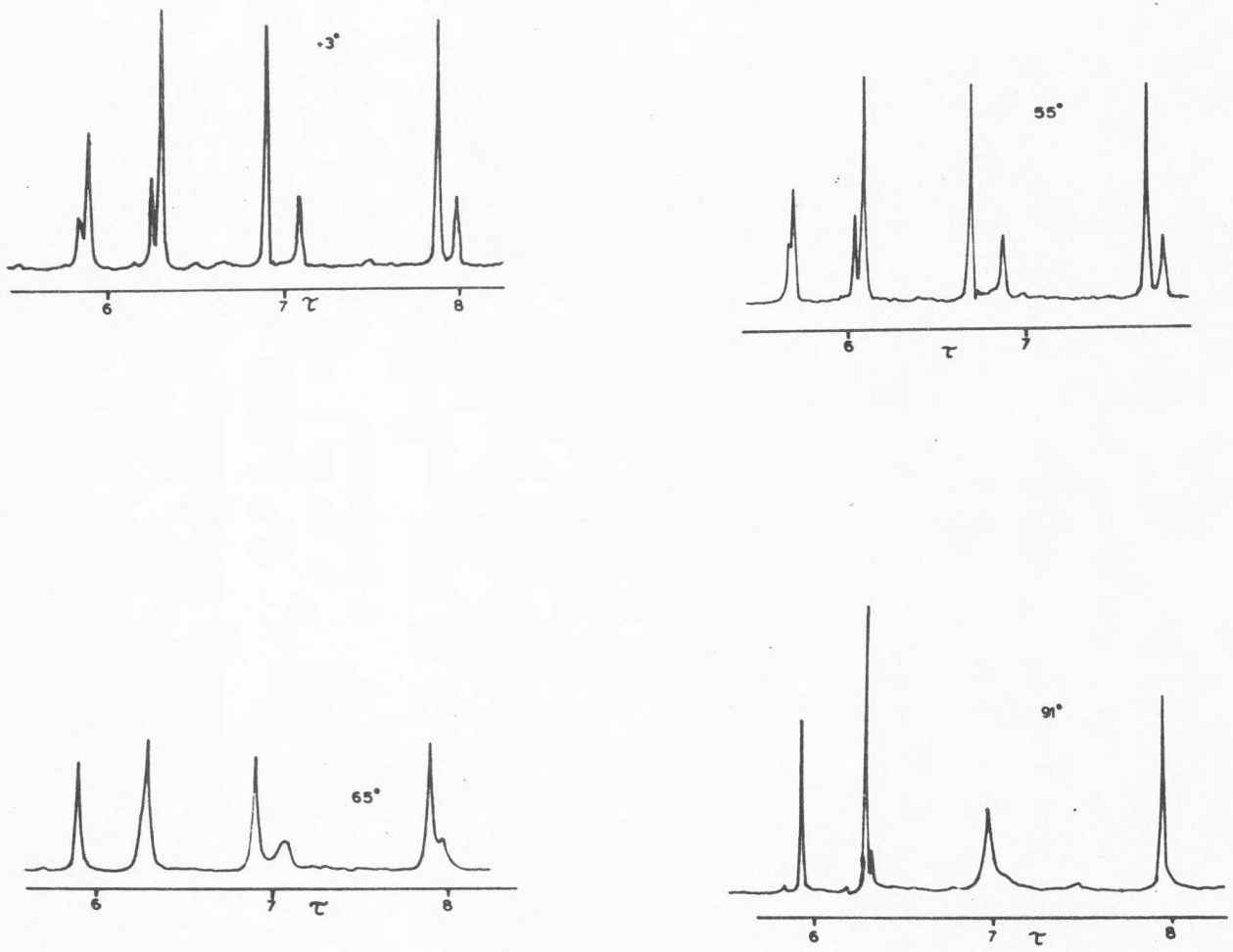



Figure 30. The temperature dependent NMR spectra of methyl N-acetylsarcosinate.

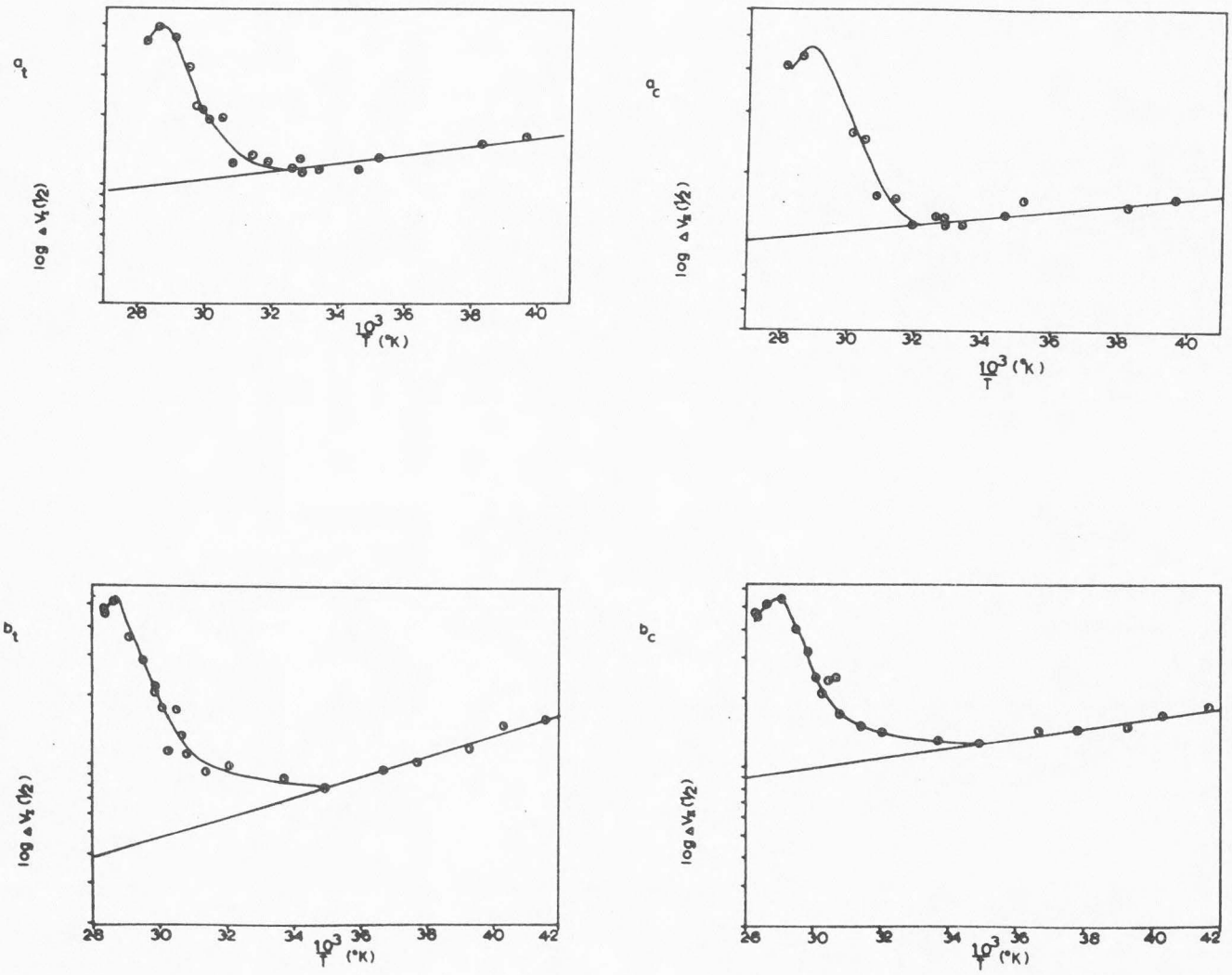



Figure 31. Plots of log $\Delta$ v vs. 1/T for methyl N-acetylsarcosinate.

Plots of the log of the populations (P) versus 1/T also gave straight lines, which were extrapolated into the exchange region (Figure 32). In the simple two site case, the transition probability is related directly to the population of the site into which the transition is occurring. The relative transition probabilities are then the ratio of the populations.

The third quantity required is the difference in chemical shift ($\Delta w$) between the two peaks. It was found that a plot of $\Delta w$ versus T was a straight line, which was also extrapolated into the exchange region (see Figure 33).

In this experiment, it is desirable to define two rate constants, $k_1$ and $\underline{k}_1$, where $k_1$ represents the transition from the trans to the cis isomer and $\underline{k}_1$ the transition from the cis to the trans isomer (see Figure 26). Thus, if the relative transition probability from cis to trans is defined as 1, the relative transition probability from trans to cis is equal to the population of the cis isomer divided by the population of the trans isomer.

The rate constant used in calculation of the theoretical spectra at various temperatures was $\underline{k}_1$. Values of $\underline{k}_1$ were supplied at each temperature and the spectra calculated and compared with the experimental data. The correct rate constant would produce a calculated spectrum ideally superimposable on the experimental spectrum.

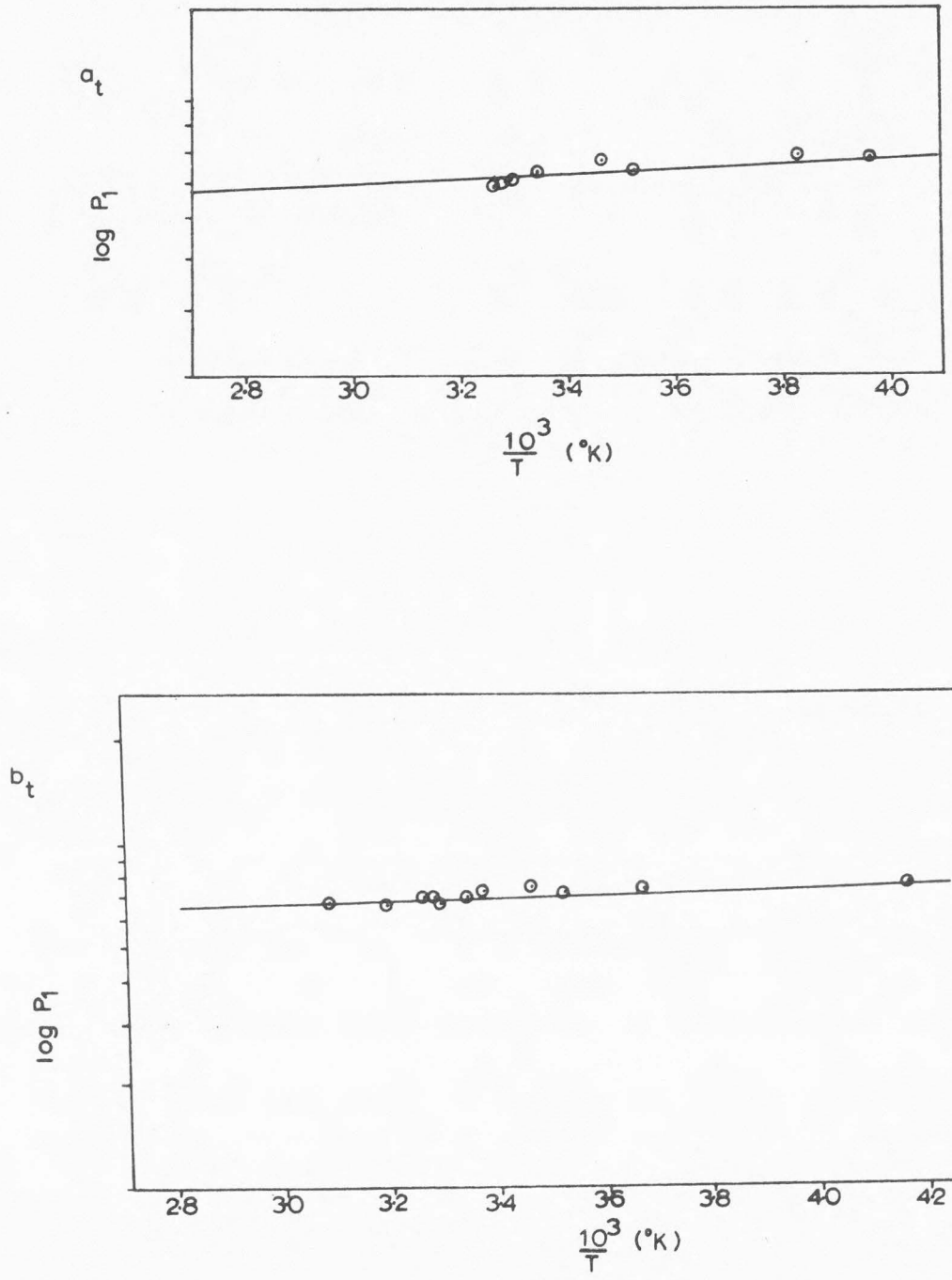
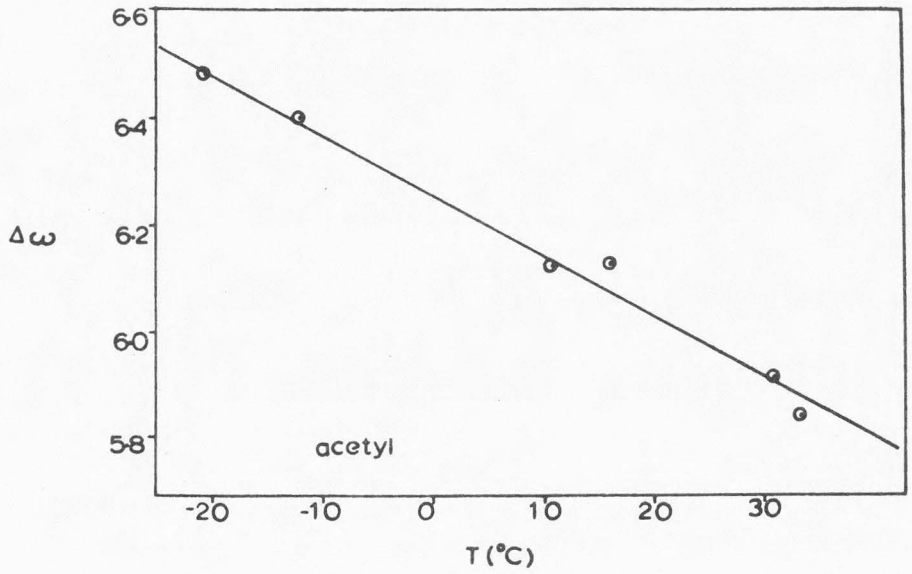



Figure 32. Plots of log P vs. 1/T for trans acetyl peak and trans N-methyl peak of methyl N-acetyl-sarcosinate.



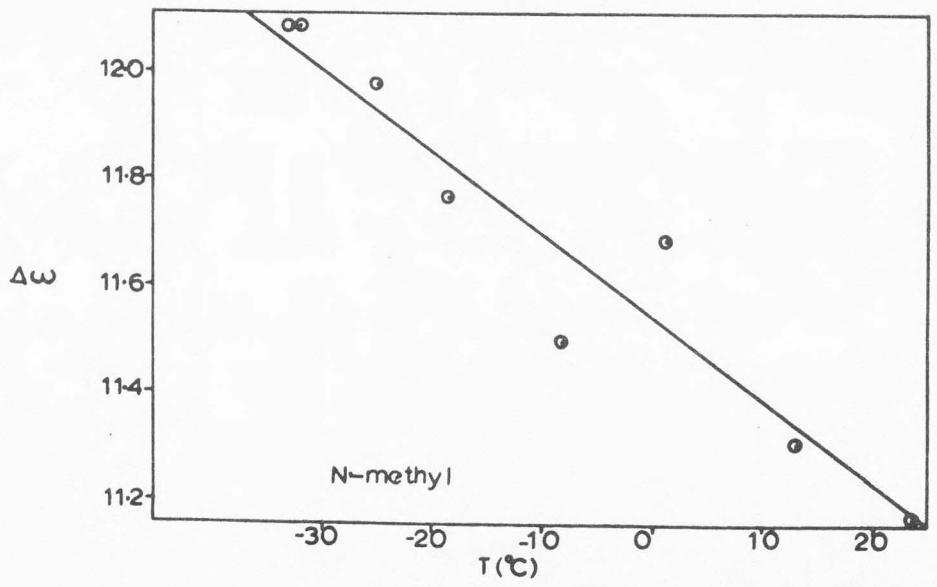




Figure 33. Plots of $\Delta\omega$ vs. T for methyl N-acetylsarcosinate.

The criteria chosen for comparison were signal width at half-maximum intensity, $\Delta\omega$, and general shape. The signal width was heavily weighted since it is the most accurately measured quantity.

The kinetic data and activation parameters

The rate constants were determined from 40°C to 80°C and are summarized in Table 4. From the Arrhenius plots (Figure 34) were obtained energy of activation (Ea), enthalpy of activation, ($\Delta H^*$), entropy of activation, ($\Delta S^*$), and the free energy of activation, ($\Delta F^*$), according to the following formulae;

$$Ea = 2.303 \cdot R \cdot (\text{Slope of the Arrhenius plot})$$

$$\Delta H^*(T) = Ea - RT$$

$$\Delta F^*(T) = 2.303\ RT \log \frac{k_b T}{k_{-1} h}$$ (from Siddall, Stewart, and Knight, (66))

$$\Delta S^*(T) = 2.303 \cdot R \left[ \log k_{-1} - \log \frac{K_b T}{h} \right] + \frac{\Delta H^*}{T}$$

where

$k_b$ = Boltzmann's constant

$k_{-1}$ = the rate constant from least squares line

$h$ = Planck's constant

$R$ = gas constant in cal $deg^{-1}$ $mole^{-1}$

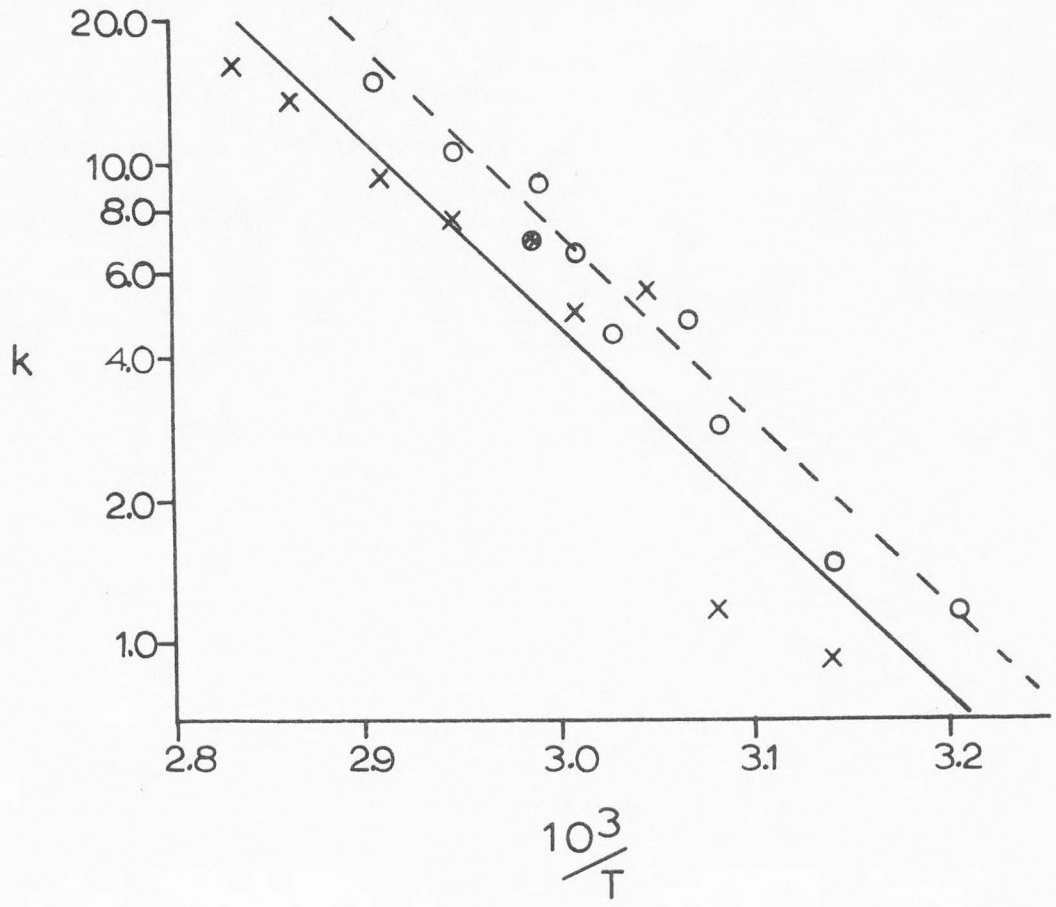
The data are summarized in Table 5.

Table 4. Rate constants for the cis to trans Transition* of methyl N-acetylsarcosinate

| T(°C) | $k_{-1}$(a)($sec^{-1}$) | $k_{-1}$(b)($sec^{-1}$) |
|---|---|---|
| 38.6 | --- | 1.2 |
| 45.1 | --- | 1.5 |
| 45.9 | .95 | --- |
| 51.3 | 1.2 | 2.9 |
| 52.9 | --- | 4.8 |
| 55.0 | 5.5 | 6.3 |
| 57.6 | --- | 4.5 |
| 59.6 | 5.1 | 6.7 |
| 61.6 | 7.2 | 9.4 |
| 61.8 | 7.1 | 7.4 |
| 66.4 | 7.8 | 11.0 |
| 71.4 | 9.5 | 15.0 |
| 76.5 | 13.5 | ---- |
| 80.2 | 16.0 | ---- |

*S,($k_{-1}$a); = ± 40%** S,($k_{-1}$b) = ± 16%**

**relative to the least squares value.




× $k_{-1}$ for acetyl protons

o $k_{-1}$ for N methyl protons

—— least squares line for acetyl peak

– – least squares line for N methyl

Figure 34. Arrhenius plot for cis to trans exchange of acetyl (a) and N-methyl (b) protons of methyl N-acetylsarcosinate.

Table 5. Activation parameters for the cis to trans transition of methyl N-acetylsarcosinate (72)

| | acetyl (a) | N-methyl (b) |
|---|---|---|
| Ea (Kcal/mole) | 17.7 ± 3.3 | 17.8 ± 1.2 |
| $\Delta H^*(61.8^\circ)$(Kcal/mole) | 16.9 ± 3.2 | 17.0 ± 1.1 |
| $\Delta F^*(61.8^\circ)$(Kcal/mole) | 18.2 ± 0.28 | 18.8 ± 0.1 |
| $\Delta S^*(61.8^\circ)$(e.u.) | -4.9 ±11.4 | -4.1 ± 3.8 |
| $k_{-1}$ $(61.8^\circ)(sec^{-1})$ | 5.2 ± 2.3 | 8.1 ± 1.2 |

Estimation of errors

A standard deviation for the rate constants was calculated from the equation:

$$S = \sqrt{\frac{\left[(k'-k_{-1})/k'\right]^2}{n-2}}$$

where

$k_{-1}$ = experimental rate constant

$k'$ = the least squares value at the same temperature

The denominator is n - 2 since in a graph two degrees of freedom are taken in the axes. The magnitudes of the standard relative deviations thus obtained, (16% for the $N-CH_3$ peak and 40% for the acetyl peak), are as expected from the 10 to 15% error in measurement of the line-widths. The sources of this error were previously discussed.

The values of the free energy of activation agrees well with values reported for similar systems (66) (see Table 3). The large error in the entropies of activation indicates that this value is small but negative, as reported by Siddall, Stewart, and Knight (66).

The interpretation

Since the rate constants and activation parameters for the exchange of the N-methyl group were the same within experimental error as for the exchange of the acetyl group and since both exchanges gave first-order Arrhenius plots, it is concluded that the splittings of all the peaks in the NMR spectrum of methyl N-acetylsarcosinate (72) is due solely to hindered rotation about the amide bond as shown in Figure 26, and that rotation about the alpha methylene carbon-nitrogen bond is very fast.

It is proposed also that the splitting of the NMR signal arising from the methyl ester protons of N,N'-dimethylcarbobenzoxyalanylalanine methyl ester (71) can be explained solely by hindered rotation about the alanylalanine peptide bond, and that the folded-extended form equilibrium as postulated by Marraud, Neel, Avignon, and Hyong (63) is not contributing to the splitting of this peak.

# EXPERIMENTAL

## The synthesis of methyl N-acetylsarcosinate (72)

Following the method of Olsen (76) to a solution of 5.0 g N-acetylglycine (.043 mol) in 70 ml of anhydrous dimethylformamide were added 40 g of silver oxide (0.2 mol) and 28 ml of methyl iodide (0.43 mol). The mixture was stirred for 3 days at room temperature and filtered. The filtrate was poured into chloroform. The chloroform solution was washed with 2 x 100 ml of 5.0% aqueous potassium cyanide and 3 x 100 ml of water, dried over magnesium sulfate, and evaporated to leave a yellow liquid. This liquid was distilled and the fraction boiling at 85°C (0.7 torr) was collected to give 1.6 g of 71 (26%); (Lit. bp 61°, 0.11 torr) (77).

NMR ($CDCl_3$) $\tau$ 5.88 (D,2H); 6.27 (D,3H); 7.00 (D,3H); 7.95 (D,3H).

## Measurement of spectra

The methyl N-acetylsarcosinate was sealed in an NMR sample tube. All spectra were recorded with a Varian A-60 Analytical NMR Spectrometer equipped with a V-6040 NMR Variable Temperature Controller.

The signals were recorded at a sweep width of 50 cps, a sweep time of 500 sec, (0.10 cps/sec), while maintaining a constant setting on all other controls with the exception of the y-gradient which was adjusted to maximum peak height

at each temperature. Each peak was recorded three times and the average values were used.

The relative integral intensities were obtained by measuring the areas under the peaks with a Gelman Planimeter. The temperatures were measured by means of a methanol sample in a sealed tube purchased from Varian Associates in terms of the difference in chemical shift ($\Delta w$) between the hydroxyl proton and the methyl protons according to the empirically derived equation:

$$T\ (^{o}K) = 406.0 - 0.551 \cdot \Delta w - 63.4 \cdot (\Delta w)^{2} \cdot 10^{-4}$$

The theoretical curves were calculated on a Univac 1108 Computer at the University of Utah, Salt Lake City, through a remote control unit, on a Fortran program made available by Professor M. Saunders, Yale University.

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# VITA

Alan LeRoy Love

Candidate for the Degree of

Doctor of Philosophy

Dissertation: I. Studies toward the Synthesis of Echinodithianic Acid and II. The Temperature Dependant NMR Spectrum of Methyl N-Acetylsarcosinate

Major Field: Organic Chemistry

Biographical Information:

Personal Data: Born at Seattle, Washington, November 26, 1941, son of Lewis C. and Irene Z.; married Lesley D. Clarke, June 10, 1968; one child--Naomi Christine.

Education: Graduated from Juneau--Douglas High School, Juneau, Alaska, 1960; received the Bachelor of Science degree from Wheaton College, Wheaton, Illinois, 1966; completed requirements for Doctor of Philosophy degree at Utah State University, 1971.