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TAKUYA FURUTA for the degree of Doctor of Philosophy

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Title: APPROACHES TO THE SYNTHESIS OF PENICILLIN

Abstract approved: Redacted for Privacy

Dr. James D. White

Several approaches to the synthesis of penicillin from 2-iminothioazolidine 50, from 2-thiothiazolidine 66 and by photocyclization of 77 and 78 were investigated. 2-Iminothiazolidine 50 was prepared from dibromoester 45 by the action of benzylamine followed by treatment of aziridine 46 with potassium or ammonium thiocyanate. Attempted introduction of a two-carbon unit into 50 by decomposition of ethyl diazoacetate afforded 51 and 52. Similarly, acetyl derivative 53 gave a carbon-hydrogen insertion product 54 upon pyrolysis. The reaction of 53 with ethyl lithiodiazoacetate produced an unexpected product 55.

The synthesis of 2-thiothiazolidines by their reaction of aziridine 56 with carbon disulfide or potassium thiocyanate yielded only the undesired thiazolidines 57 and 60 respectively. However, the reaction of 66 with diethyl bromomalonate gave a 2-substituted thiazolidine 70. Reduction of 70 with sodium borohydride produced 71.

Compounds 77 and 78 were synthesized by the coupling of 76

and 66 with phthalimidoacetyl chloride respectively. Attempted β-lactam formation by photolysis of 77 or 78 yielded only Norrish type II cleavage and no cyclization product.

Biogenetically patterned approaches to the synthesis of 6-amino-penicillanic acid were also studied. Cysteine was protected at sulfur and nitrogen by the acetamidomethyl and tert-Boc groups respectively to give 86, which was condensed with aziridine 56 in the presence of DCC yielding 88. Photolysis of 88 followed by deprotection of sulfur gave the dimer 92. In another approach, a putative precursor of the thioaldehyde 89 was synthesized by a sequence in which cystine 93 was converted to N, N' -di-tert-Boc cystine 96 by treatment of tert-butoxycarbonylazide, the disulfide was cleaved by sodium metal in liquid ammonia, and the resulting thiol was immediately condensed with α-chloroacetophenone to give 97. Condensation of 97 with aziridine 56 in the presence of DCC produced 98 which upon photolysis afforded polymer.

Approaches to the Synthesis of Penicillin

by

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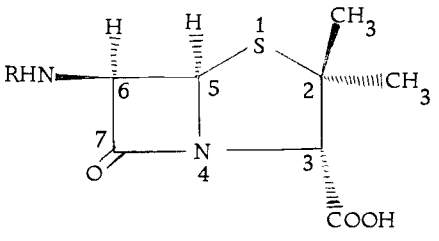
APPROACHES TO THE SYNTHESIS OF PENICILLIN

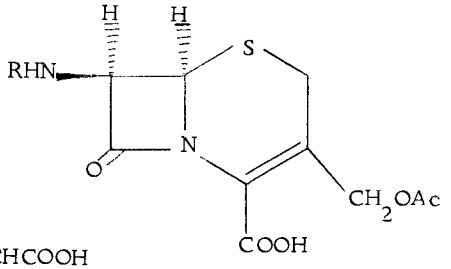
I. INTRODUCTION

The introduction of penicillin (1) to medicine marked the beginning of a new era in man's fight against disease. In spite of the discovery of other antibiotics, penicillin still continues to be the most commonly used drug against bacterial infection.

The antibiosis between a Penicillium mold and neighboring bacterial cultures was first observed in 1929 by Sir Alexander Fleming. Subsequently, a joint British and American program was set up during World War II to arrange for large-scale production of penicillin.[1] Recently, "semisynthetic penicillins" have been developed which can be taken orally and which are considerably more effective than the natural materials.[2] The semisynthetic penicillins are substances in which the natural aminoadipic side chain has been replaced by one of several synthetic appendages. However, biological synthesis by fermentation still plays the major role in the production of the bicyclic penicillin nucleus.



1



R=CO(CH$_2$)$_3$CHCOOH
NH$_2$

2

Two major problems arose after penicillin entered the market. The first of these, penicillin allergy, has been studied extensively and considerable evidence now suggests that the allergic response may be caused by a contaminant of higher molecular weight.[3] The second problem arises from resistance which many bacteria have developed towards penicillin. The presence of an enzyme (β-lactamase) in these bacteria, which renders the antibiotic ineffective by cleavage of its β-lactam, is generally accepted as a major factor in the resistance of many bacterial species to penicillins.

A solution to the second problem has been found in the introduction of a functional group (e. g. methoxy[4]) at C-6 of the penicillin nucleus. This structural modification prevents destruction of the antibiotic by β-lactamases. The use of cephalosporin C (2) represents an alternative solution, since this compound retains activity against bacteria which have built up resistance to penicillin. Cephalosporin C, unlike penicillin, is costly to produce by fermentation and, consequently, considerable effort has been expended in attempting synthesis of the cephem-type antibiotics from the more readily available penicillins.[4, 5]

The definitive structural assignment and stereochemistry of penicillin were obtained through X-ray crystallography by Crowfoot[6] in 1949. The three asymmetric centers of the penicillin nucleus have been shown to have the absolute configuration 3S, 5R, and 6R.[4]

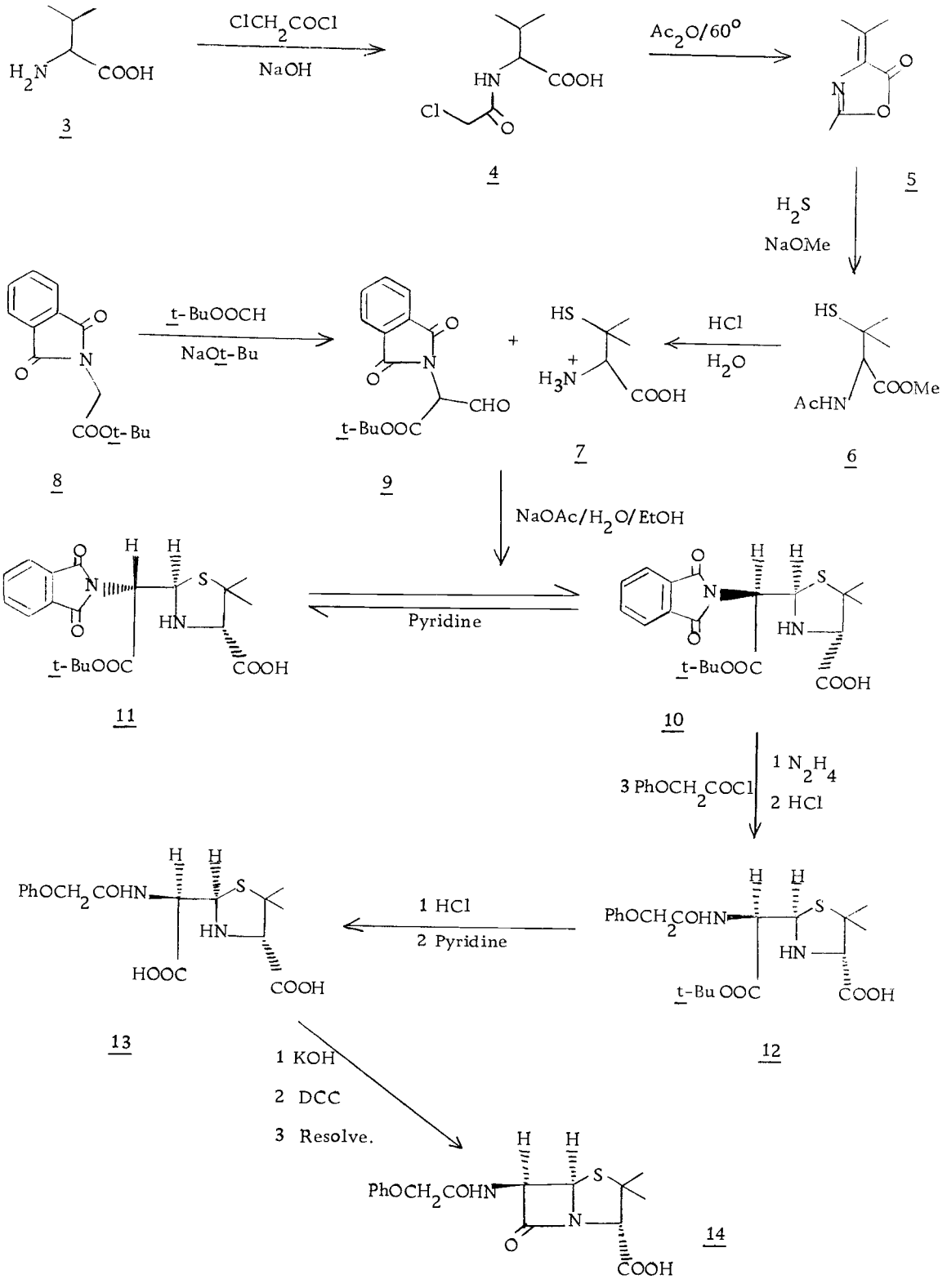

ClCH2COCl
NaOH
Ac2O/60°
H2S
NaOMe
t-BuOOCH
NaOt-Bu
HCl
H2O
NaOAc/H2O/EtOH
Pyridine
3 PhOCH2COCl
1 N2H4
2 HCl
1 HCl
2 Pyridine
1 KOH
2 DCC
3 Resolve.
3
4
5
6
7
8
9
10
11
12
13
14

Figure 1

The first total synthesis of penicillin V (14), in which the amino-adipic chain has been replaced by the phenoxymethylcarbonyl group, was reported by Sheehan and Henery-Logan.[7,8] The synthesis route adopted by these authors is outlined in Figure 1. In this route, only two of the four possible isomers were isolated after the condensation of penicillamine 7 with aldehyde 9. Cyclization to a β-lactam was carried out using dicyclohexylcarbodiimide and yielded 5.4% of penicillin after the phthalimide group was replaced with the phenoxy-methylcarbonyl chain. Later, this cyclization step was improved to 67% yield, using the N-tritylbenzyl ester 15 with diisopropylcarbo-diimide[8] (Figure 2).

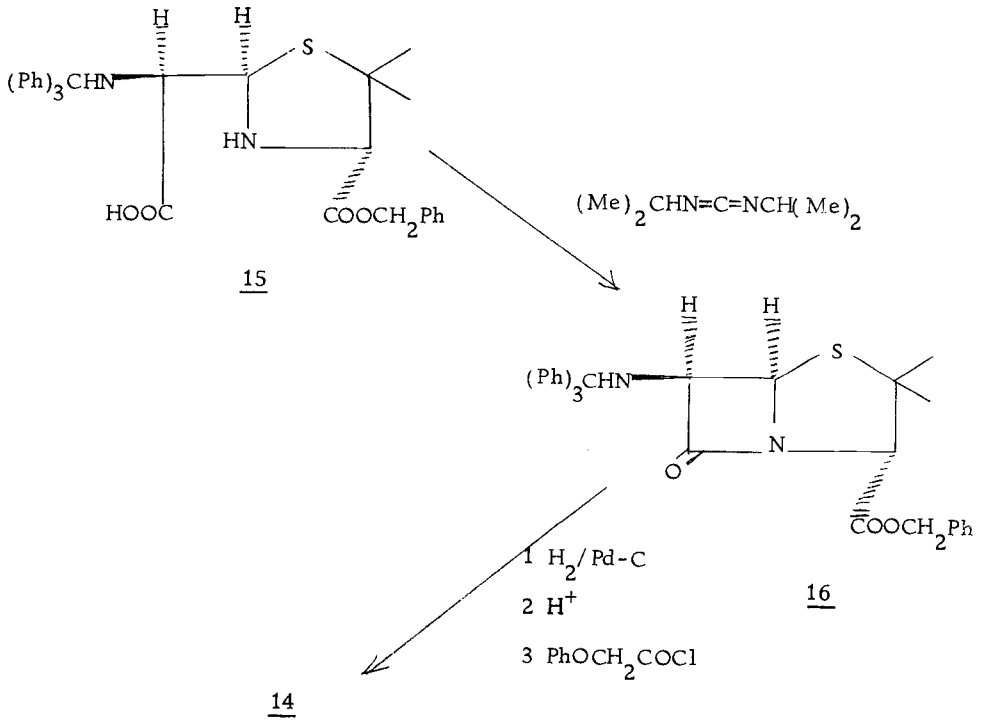


Figure 2

In a different approach, Bose and co-workers[9] used azidoacetyl chloride with triethylamine in a cycloaddition with a thiazoline derivative 18. This cycloaddition, however, gave only C-6 epipenicillin in low yield. 6-Epipenicillin was later converted to a penicillin of natural configuration by Firestone[10] (Figure 3). Very recently, an elegant total synthesis of C-6 blocked penicillins (6-methoxy[11] and 6-methyl[12]) has been published by Kishi. A stereocontrolled synthesis has also been reported by Baldwin,[13] which is outlined in Figure 4.

It is clear that the difficulty involved in the total synthesis of penicillins is not due primarily to the size of the molecule nor to its stereochemistry. Rather, the unusually high degree of substitution on a relatively few carbon atoms presents the major source of difficulty. Of the seven carbon atoms which constitute the penicillin nucleus, only the two carbon atoms of the methyl groups are not attached to hetero atoms. Another potential problem for the total synthesis of penicillin is the presence of several different carbonyl functions, all of which seem to be essential for biological activity. Added to this is the presence of a relatively strained, β-lactam ring in the penicillin nucleus. Total, stereocontrolled synthesis of penicillin, and especially of modified forms resistant to β-lactamase, therefore remains a substantial challenge to the organic chemist.

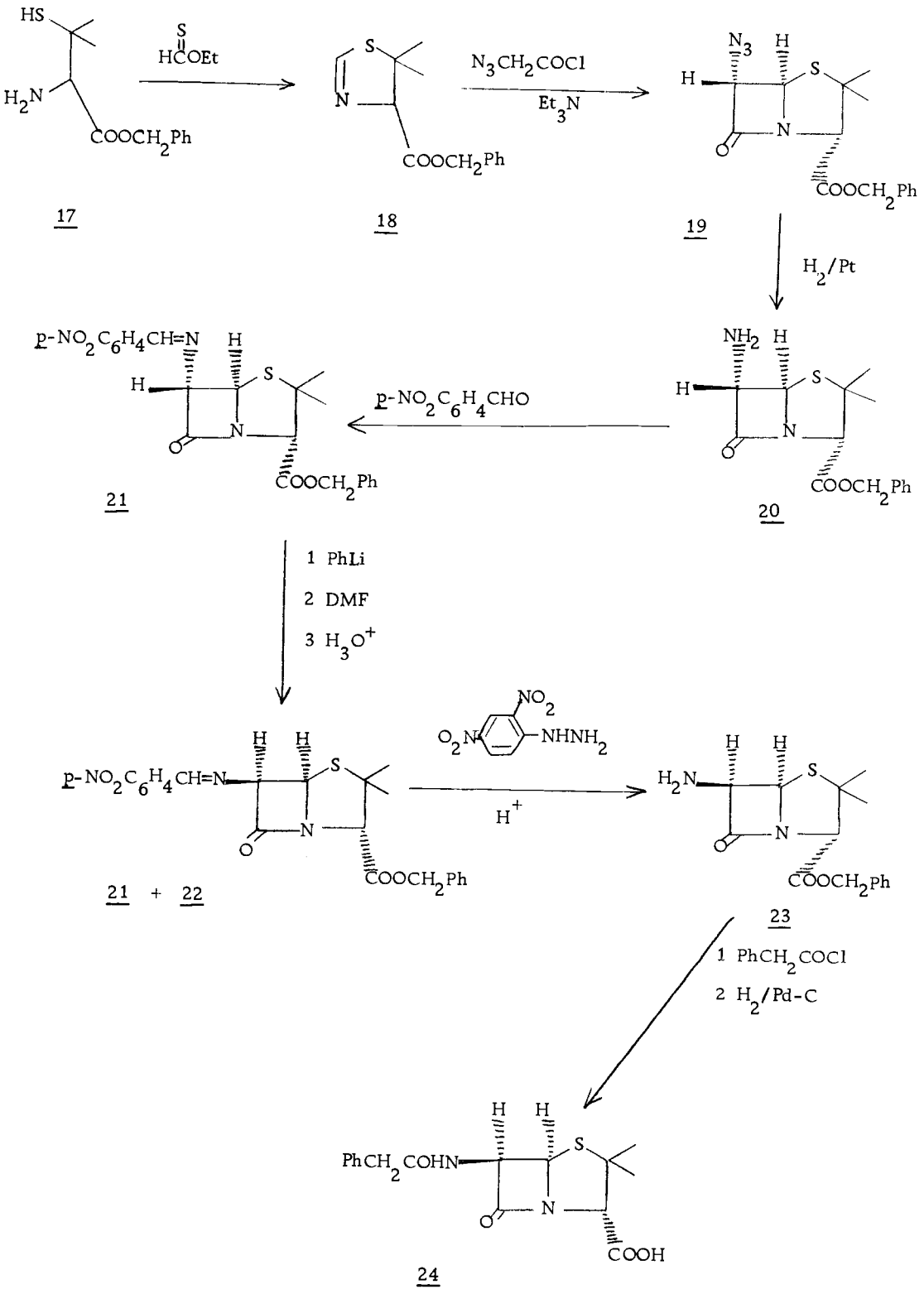

HS
H2N
COOCH2Ph
17
S
HCOEt
S
N
COOCH2Ph
18
N3CH2COCl
Et3N
N3
H
H
S
N
O
COOCH2Ph
19
H2/Pt
NH2
H
H
S
N
O
COOCH2Ph
20
p-NO2C6H4CHO
p-NO2C6H4CH=N
H
H
S
N
O
COOCH2Ph
21
1 PhLi
2 DMF
3 H3O+
p-NO2C6H4CH=N
H
H
S
N
O
COOCH2Ph
21 + 22
NO2
O2N
NHNH2
H+
H2N
H
H
S
N
O
COOCH2Ph
23
1 PhCH2COCl
2 H2/Pd-C
PhCH2COHN
H
H
S
N
O
COOH
24

Figure 3

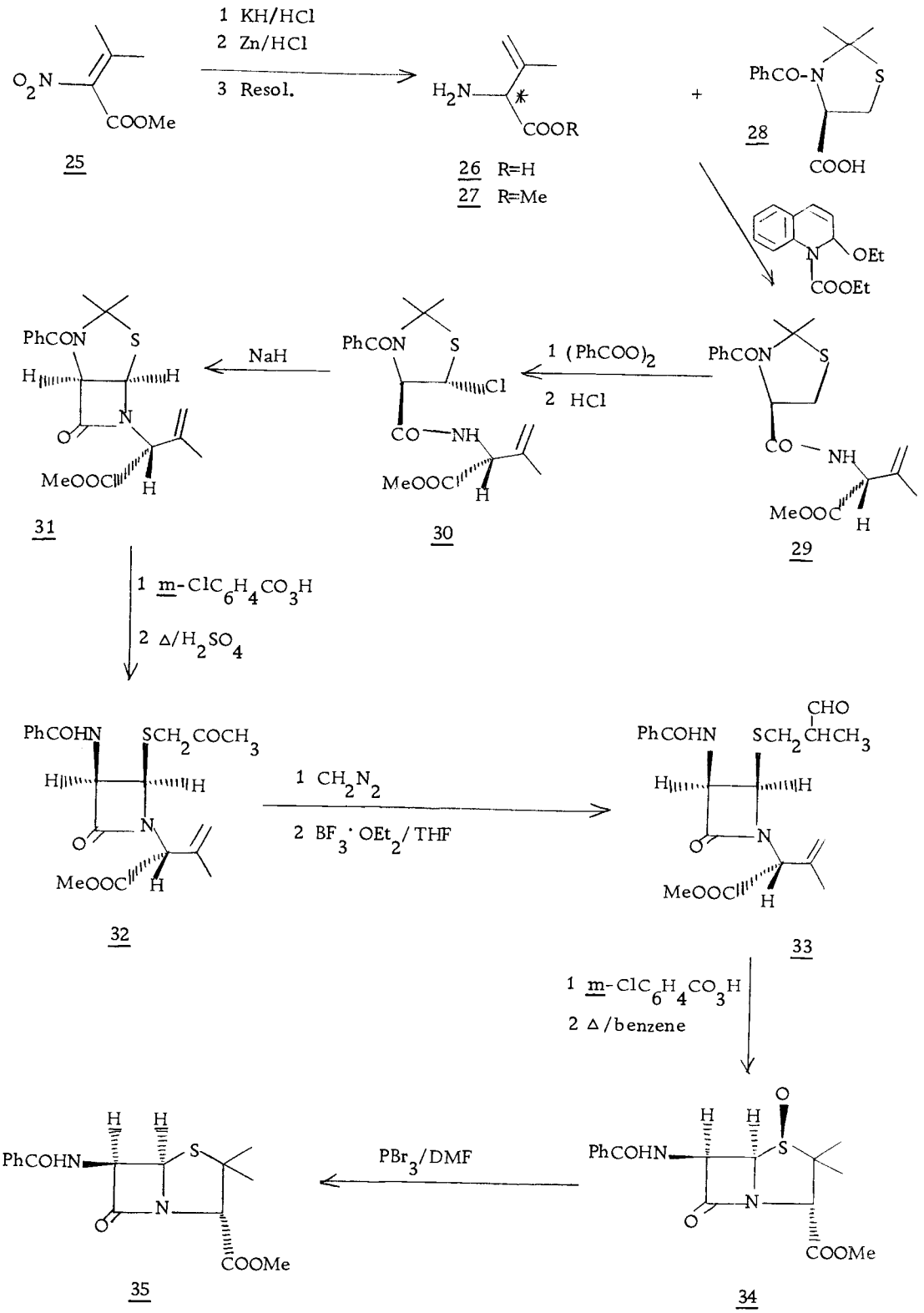

1 KH/HCl
2 Zn/HCl
3 Resol.
25
26 R=H
27 R=Me
28
1 (PhCOO)2
2 HCl
NaH
29
30
31
1 m-ClC6H4CO3H
2 Δ/H2SO4
1 CH2N2
2 BF3·OEt2/THF
32
33
1 m-ClC6H4CO3H
2 Δ/benzene
PBr3/DMF
34
35

Figure 4

II. APPROACHES FROM 2-IMINOTHIAZOLIDINES

There are many ways, in principle, by which the bicyclic ring system of penicillin can be constructed. Several possibilities are shown schematically below, the arrow(s) indicating bond(s) whose formation complete the synthesis of the bicyclic nucleus. The synthetic schemes A, B and E for the bicyclic ring system of penicillin

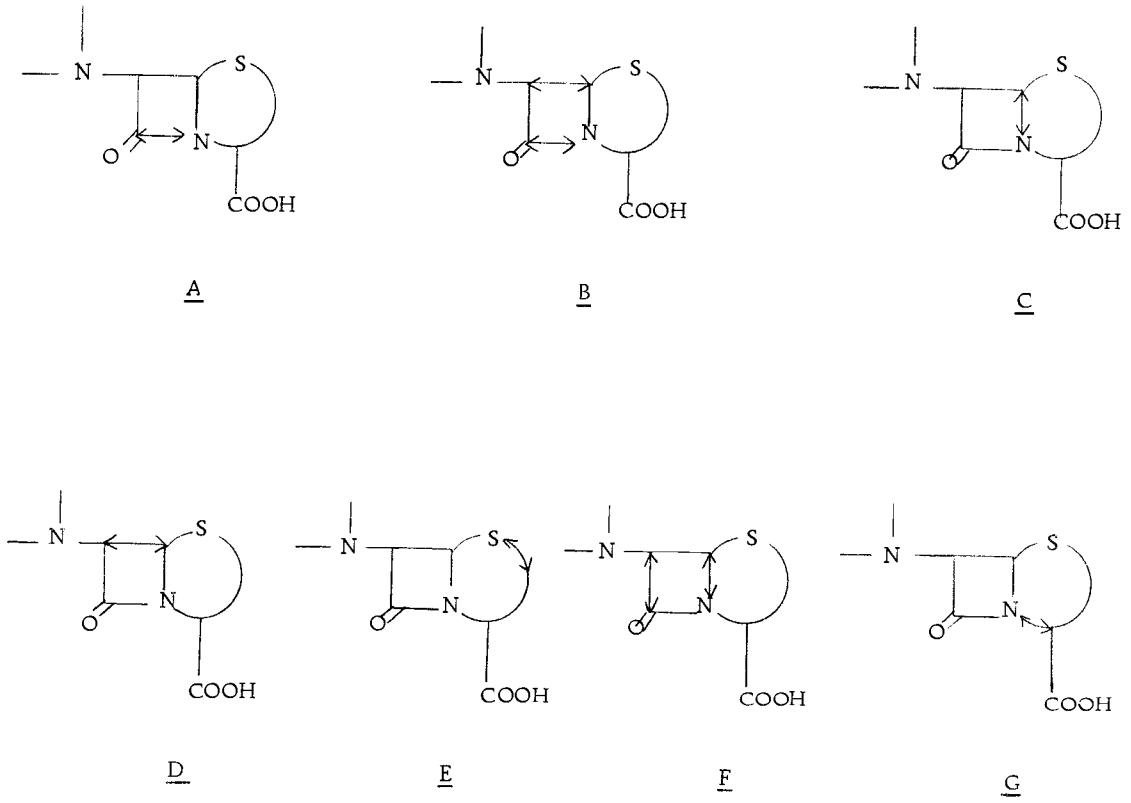
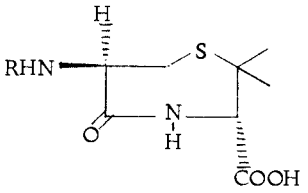


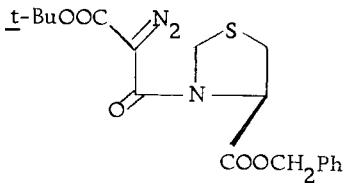
Figure 5

were realized by Sheehan,[7,8] Bose[9] and Baldwin[13] respectively, and are described in the previous section. The monocyclic analogs of benzylpenicillin 36 and 6-aminopenicillanic acid 37, corresponding at

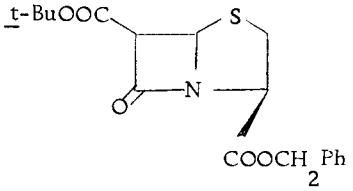
both chiral centers to the natural penicillin, were synthesized by Leonard and Ning.[14] However, experiments intended to effect transannular cyclization *in vitro* or *in vivo* have so far been unsuccessful. No synthesis of penicillin using the type D scheme has yet been published. However, several useful methods for generating the four-membered ring in model penicillins, by an intramolecular cyclization process, have been reported. Lowe showed that α-diazomalonyl derivative 38, on photolysis, generates a carbene which can insert into a hydrogen-carbon bond to form stereoisomers of 39.[15] The



36 R=$PhCH_2CO$
37 R=H

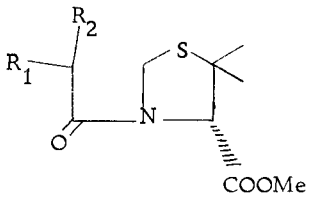


38

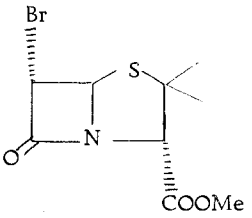


39

dibromide 40, after conversion to the masked carbene 41 followed by thermolysis, yielded 42 in low yield.[16,17]



40 R_1=R_2=Br
41 R_1=Br, R_2=HgBr

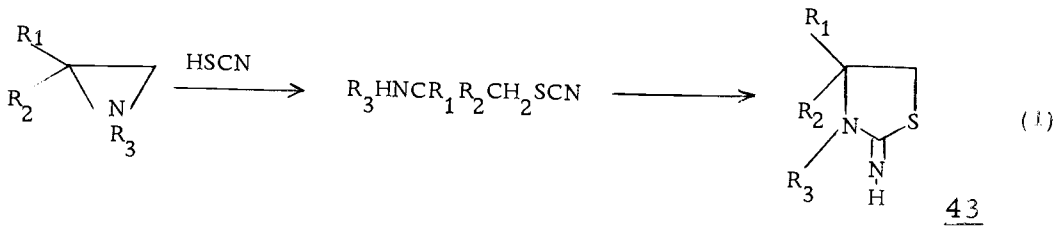


42

We have chosen a route utilizing ring closure A for the following reasons: (a) since Sheehan's[7,8] earlier synthesis of penicillin V using this approach, no attempts have been made to synthesize penicillin along these lines in spite of the fact that many new methods for β-lactam synthesis have been developed and conventional methods have also been improved[18,19,20,21] (b) the properties of thiazolidines and thiazolines, although studied extensively during the World War II penicillin program, have received little attention[22] subsequently.

Our initial scheme for synthesis of penicillin was through the thiazolidine derivative 49, followed by extension of the side chain at C-2 and formation of the β-lactam (Figure 6). The dibromo ester 45, which was made by esterification of β-methylcrotonic acid followed by treatment with bromine,[23] was allowed to react with benzylamine in benzene[24] to give aziridine 46 in 83% yield.

It is known that thiocyanic acid, which yields a very nucleophilic anion, reacts with aziridines to produce either a ring opened product or a product (e. g. 43) resulting from subsequent ring closure (eq. 1).[25]



(1)

43

Ring opening of ethylenimine with isothiocyanate occurs only when ethylenimine is completely in the form of an aziridinium ion, and

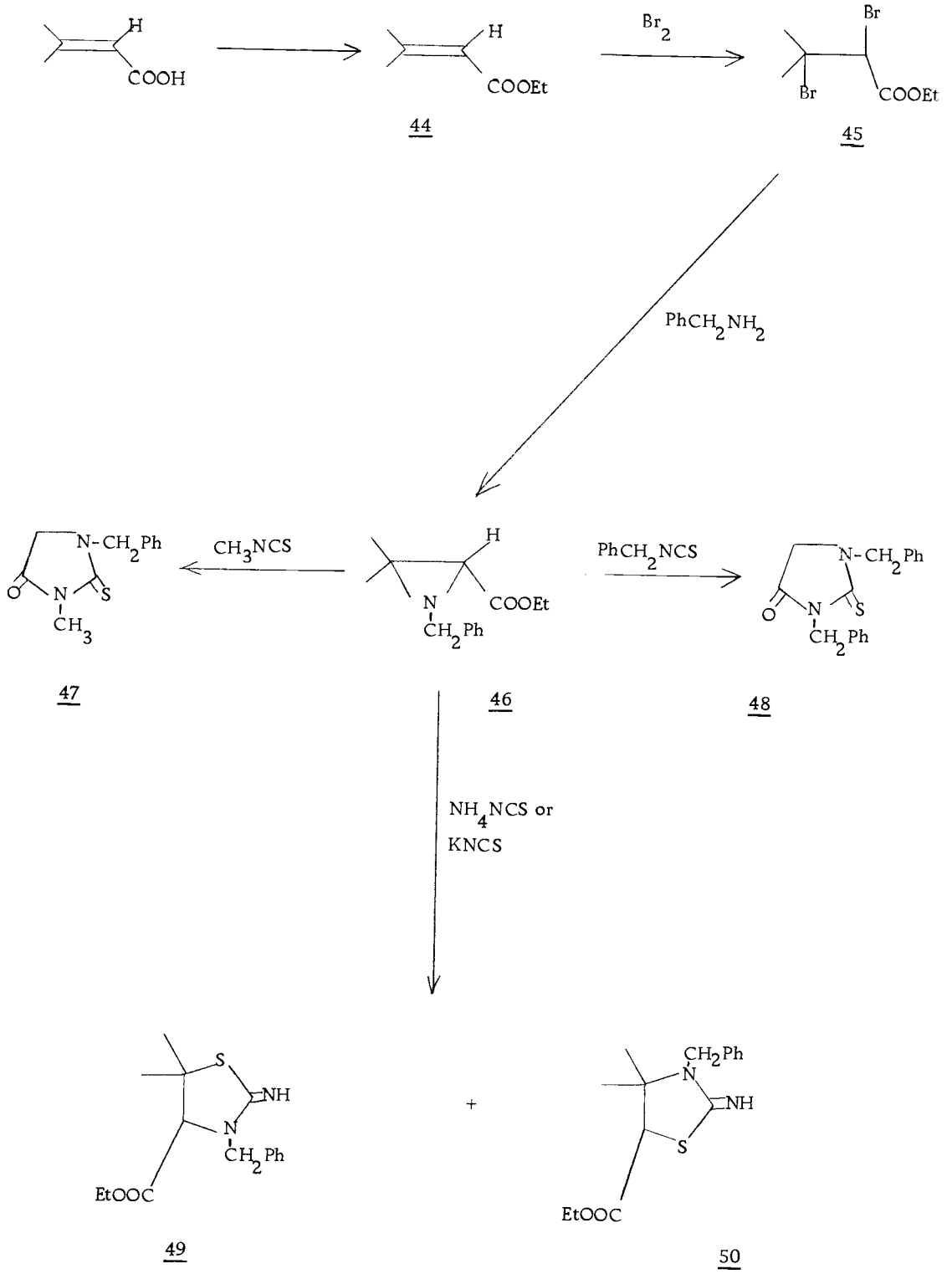
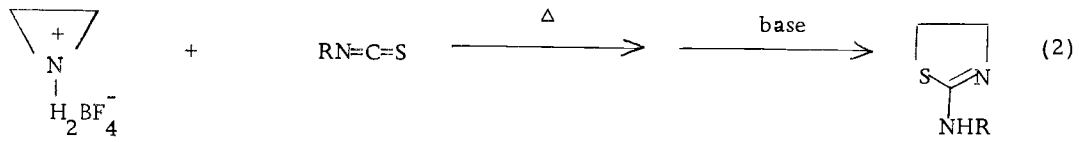

COOH
COOEt
Br2
Br
Br
COOEt
44
45
PhCH2NH2
N-CH2Ph
O
N
S
CH3
CH3NCS
H
N
COOEt
CH2Ph
PhCH2NCS
N-CH2Ph
O
N
S
CH2Ph
47
46
48
NH4NCS or
KNCS
S
NH
N
CH2Ph
EtOOC
+
CH2Ph
N
NH
S
EtOOC
49
50

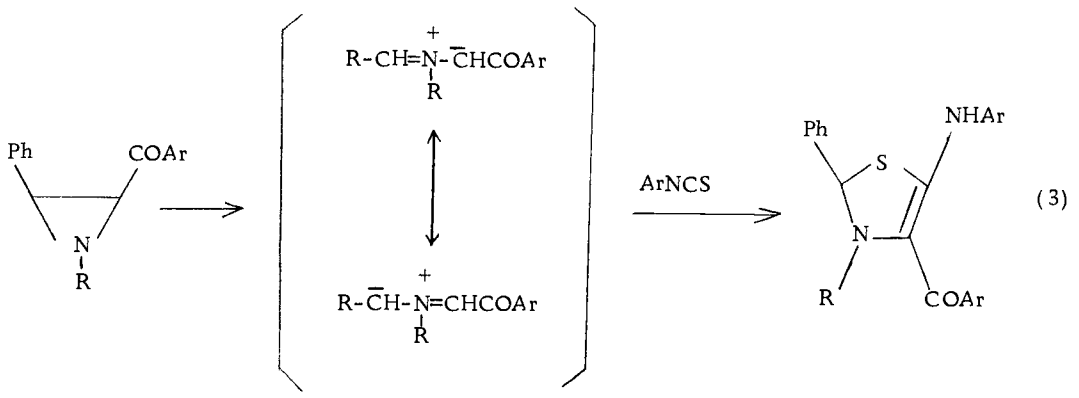
Figure 6

the product from this reaction is a 2-amino-2-thiazoline (eq. 2).[25]



(2)

Under neutral conditions, it has been shown that 2-aroylaziridines undergo cleavage of the 2-3 bond to an azomethine ylid, with subsequent [2+3] cycloaddition to aryl isothiocyanates (eq. 3).[26]



(3)

The reactivity of 46 with several isothiocyanates and thiocyanic acid was studied in the hope of producing a suitably functionalized thiazolidine. The reaction of 46 with ammonium thiocyanate in dry THF at 55° C led to a mixture of 4-carbethoxy and 5-carbethoxy derivatives (49 and 50). Nmr evidence revealed that the ratio of 49 (gem. CH_3, singlets, at δ 1.41 and 1.58; CH-4, singlet, at δ 3.75; $PhCH_2$, doublets, at δ 3.96 and 5.25, J=14.4 Hz) to 50 (gem. CH_3, singlets, at δ 1.26 and 1.44; C-4, singlet, at δ 4.06; $PhCH_2$, singlet, at δ 4.56)[27] was 3:22. Thus, almost 90% of reaction took place by

S_N2 attack to give the undesired regioisomer. In an attempt to promote S_N1 attack on 46, the latter was allowed to react in the form of an aziridinium ion.[25] Thus, the use of acetic acid as solvent enhanced the amount of 49 vs. 50 (26:74), and when formic acid was employed as solvent, the ratio of 49 to 50 was 46:54. The use of very strongly acidic media (e. g. trifluoroacetic acid or mineral or Lewis acids in organic solvents) gave impure products.

The reaction of aziridine 46 with methylisothiocyanate or benzylisothiocyanate in benzene yielded, in both cases, a hydantoin derivative (47 and 48 respectively). Thus, in contrast to the reaction of 46 with salts of thiocyanic acid, the initial step of this latter reaction takes place at the thiocarbonyl group by attack of the lone pair electrons of the aziridine nitrogen.

Since 50 contains all of the functionality present in the thiazolidine ring of penicillin (but with a reversed substitution pattern), several attempts were made to extend the synthesis from 50 towards a structure which conceivably could serve as an analog of the natural antibiotic. These efforts were directed principally toward attachment of a functionalized, two-carbon chain to C-2 of the thiazolidine nucleus. The pyrolysis of ethyl diazoacetate in the presence of 50 was carried out in octane solvent and afforded 51 together with thiocyanate 52. There was no carbon-nitrogen double bond addition product present. Acetylation of 50 with acetic anhydride gave acetylthiazolidine 53 in

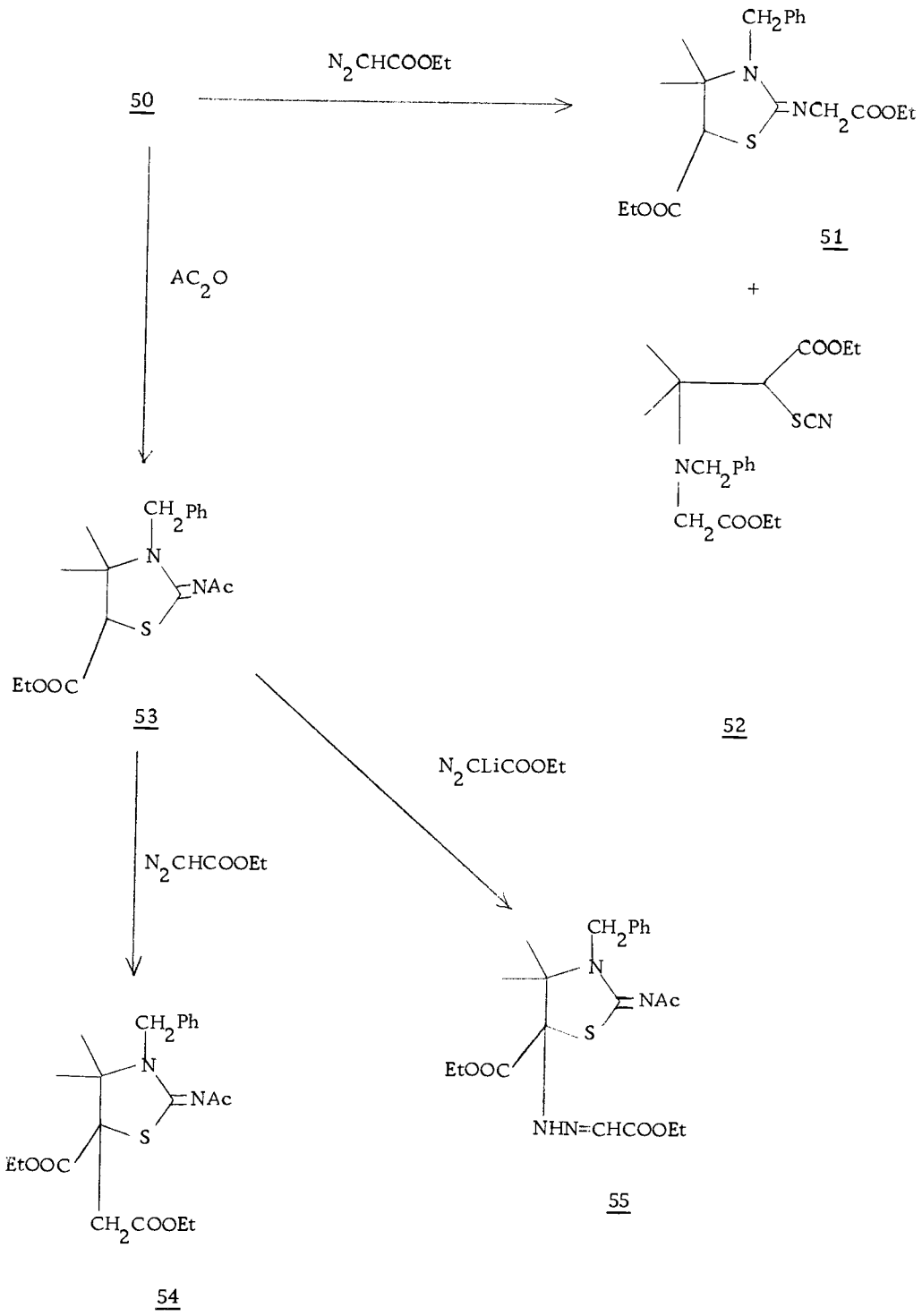

50
$N_2CHCOOEt$
CH_2Ph
N
NCH_2COOEt
S
EtOOC
51
+
COOEt
SCN
NCH_2Ph
CH_2COOEt
52
AC_2O
CH_2Ph
N
NAc
S
EtOOC
53
$N_2CLiCOOEt$
$N_2CHCOOEt$
CH_2Ph
N
NAc
S
EtOOC
CH_2COOEt
54
CH_2Ph
N
NAc
S
EtOOC
NHN=CHCOOEt
55

Figure 7

98% yield. Pyrolysis of ethyl diazoacetate in the presence of 53 gave about 45% of the carbon-hydrogen insertion product 54. It is known that carbenes which are generated by thermal means are reluctant to insert into carbon-hydrogen bond.[28] Hence, it seems surprising that such a high proportion of product resulting from this mode was observed. This may be due to the hydrogen at C-4 having a relatively high acidity, since it is α to both an ester carbonyl and a sulfur atom.

In another approach aimed towards attachment of a two carbon unit at C-2, the reaction of 53 with ethyl lithiodiazoacetate[29] was investigated. Unexpectedly, this reaction gave a quantitative yield of 55. Compound 55 was fully identified by ir (NH absorption at 3200 cm^{-1} and C=O absorptions at 1735 and 1698 cm^{-1}), nmr ($2CH_3$-C-O, triplets at δ 1.26 and 1.28; gem. CH_3, singlets, at δ 1.23 and 1.49; CH_3CO, singlet, at δ 2.16; 2C-CH_2-O, quartets, at δ 4.21 and 4.30; CH_2, singlet, at δ 4.88; vinyl CH, singlet, at δ 7.02), and mass spectra (at m/e 448 for the molecular ion).

III. APPROACHES FROM A 2-THIOTHIAZOLIDINE

It is apparent from the foregoing results that a major obstacle to synthesis of penicillin and its analogs from a 2-iminothiazolidine is the introduction of a two-carbon unit into compound 50. Consequently, an alternative approach was developed, utilizing the 2-thiothiazolidine 57 (Figure 8). This compound was prepared from dibromide 45 by treatment with a saturated ammonia solution of ethanol[30] followed by carbon disulfide.[31] The S-methyl derivative 58 was obtained by methylation of 57 with iodomethane and triethylamine.[32] Its ir spectrum showed absorption at 1575 cm^{-1} for C=N, and the nmr spectrum displayed peaks at δ 2.53 for the S-methyl group and at δ 4.34 for the C-5 hydrogen. The mass spectrum of

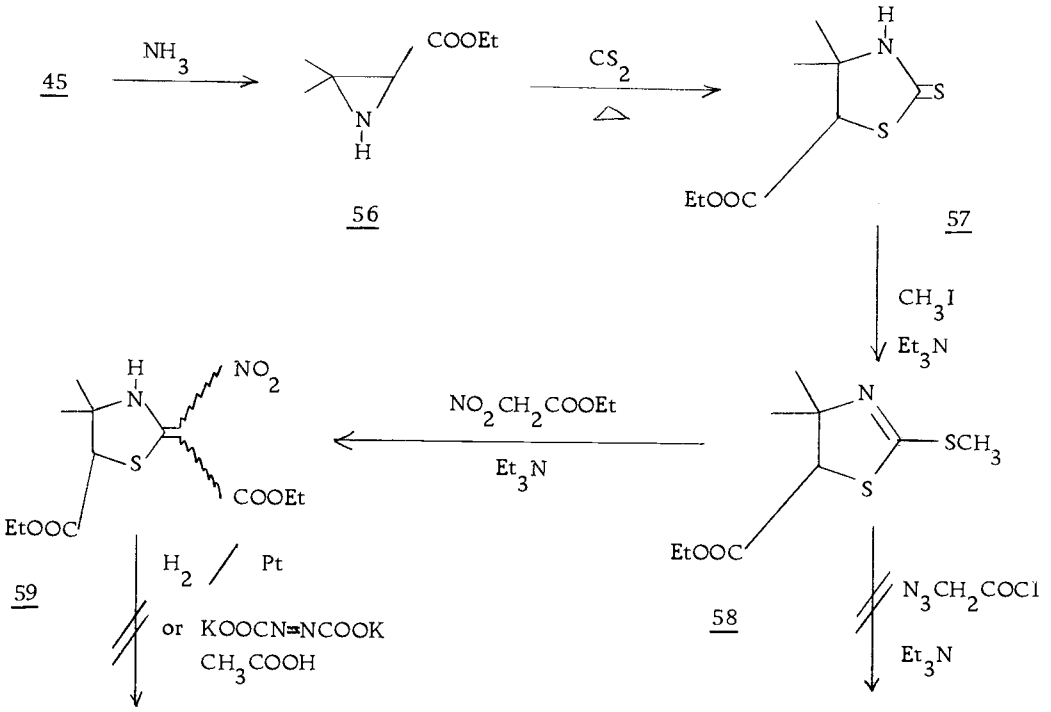


Figure 8

58 showed a parent peak at m/e 233, with m/e 115 and 100 as other major peaks. The peaks of mass 115 and 100 can be explained by the fragmentations shown in Figure 9. The ion of m/e 115 is due to the

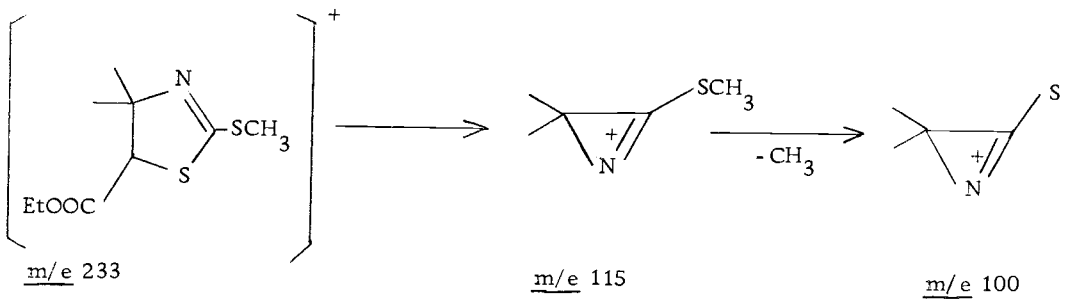


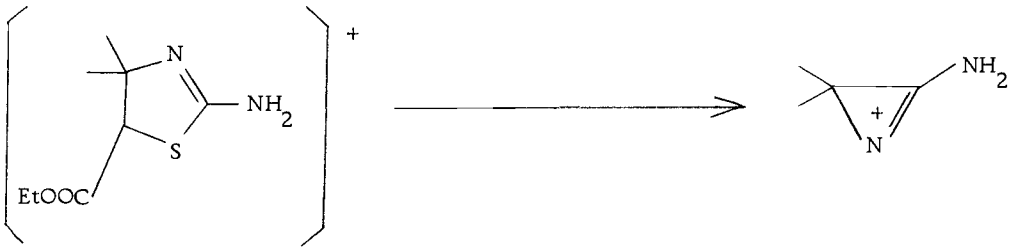
Figure 9

loss of EtOOCCHS from the parent ion and is followed by the loss of a methyl group to produce the base peak at m/e 100.

The reaction of 58 with azidoacetyl chloride and triethylamine[33] yielded only a small amount of an unidentified product. However, the condensation of 58 with ethyl nitroacetate and triethylamine[34] afforded a single product in 54% yield. Its ir spectrum showed absorptions at 3310 (NH), 1740 and 1685 cm^{-1}, and its nmr spectrum revealed the presence of two ethyl groups. Its structure was therefore tentatively assigned as 59. However, the mass spectrum showed no parent peak at m/e 318. Attempted reduction of 59 by catalytic hydrogenation or with potassium azodicarboxylate[35] in acetic acid gave only the starting material.

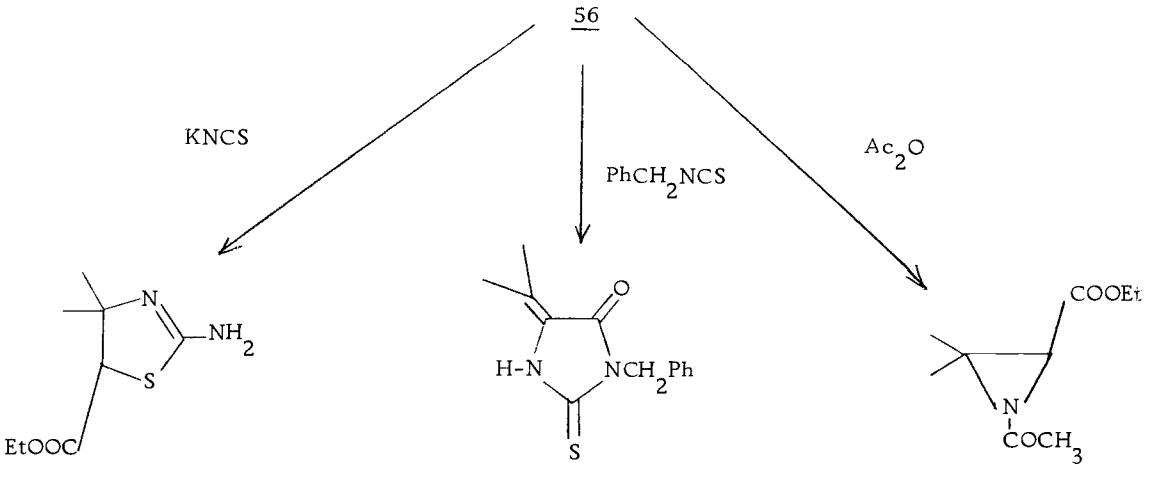
Although the reaction of 56 with several thiocyanates was studied, none gave the desired 5,5-dimethylthiazolidine derivative

(Figure 10). Thus, treatment of 56 with potassium thiocyanate yielded 94% of crystalline 2-aminothiazoline 60, again resulting from the unwanted orientation in cycloaddition. The regiochemistry of 60 was determined by the mass spectrum which displayed a parent peak at m/e 202 with m/e 84 for a base peak. The peak of mass 84 can be



m/e 202 m/e 84

explained by the loss of EtOOCCHS from the parent ion. The reaction of benzylisothiocyanate with 56 provided the very stable hydantoin derivative 61. Acetylation of 56 with acetic anhydride was carried out to confirm the structure of aziridine 56 and pure N-acetylaziridine 62 was obtained in 79% yield after vacuum distillation.



60 61 62

Figure 10

Since previous efforts failed to provide a suitably substituted thiazolidine, an alternative approach to preparation of this heterocycle was pursued based on a method described by Cook et al.[36] (Figure 11). Glycinamide hydrochloride 63,[37] prepared in 76% from ethyl chloroacetate, was allowed to react with carbon disulfide in ethanol[38] giving thiazolidone 64 (54% yield). Condensation of 64 with

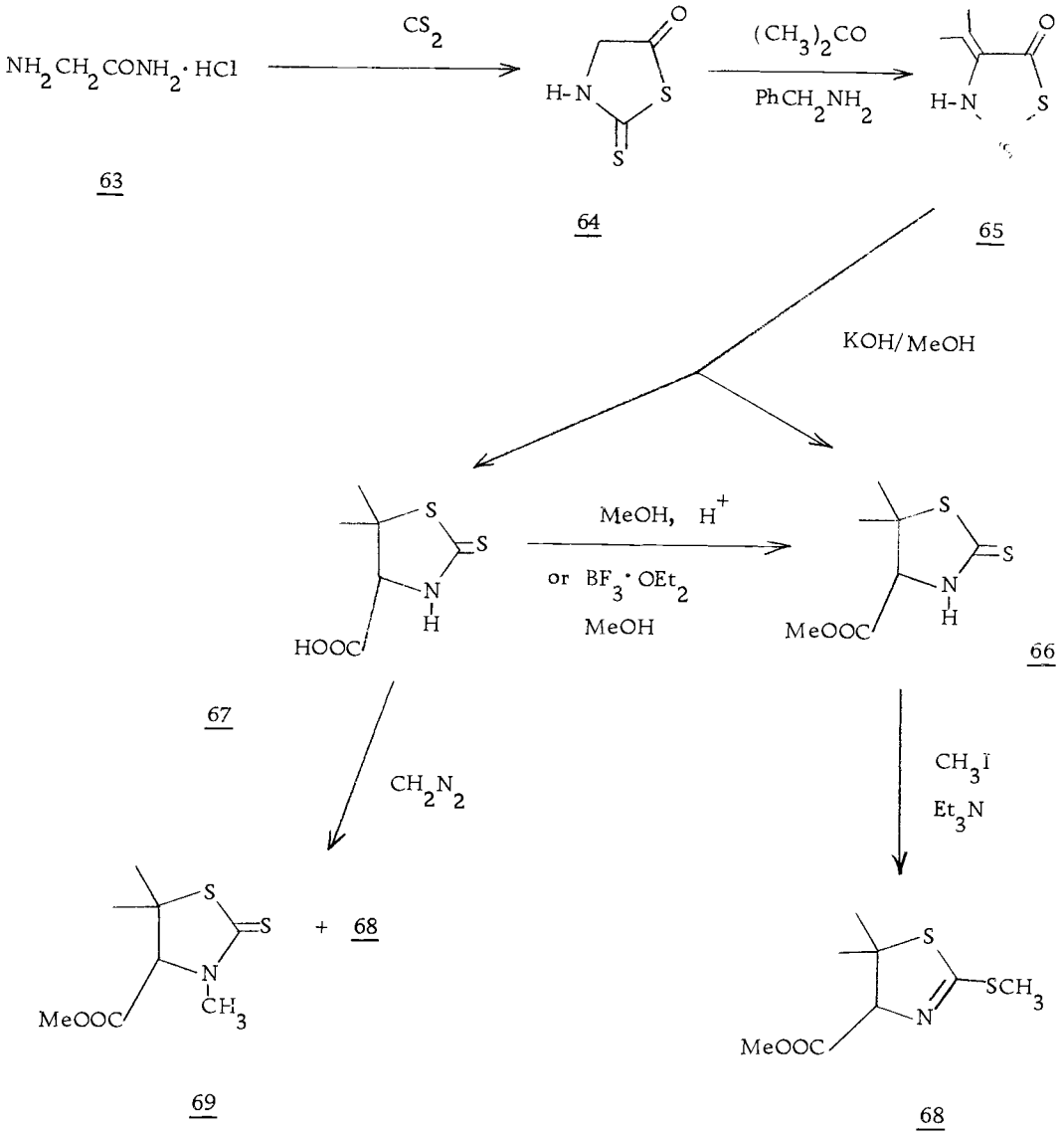
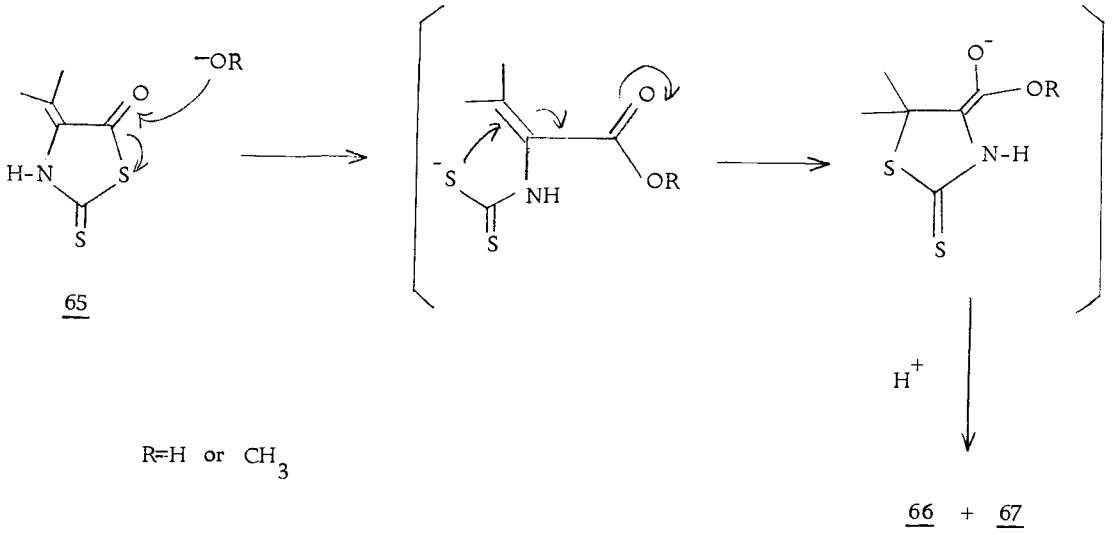


Figure 11

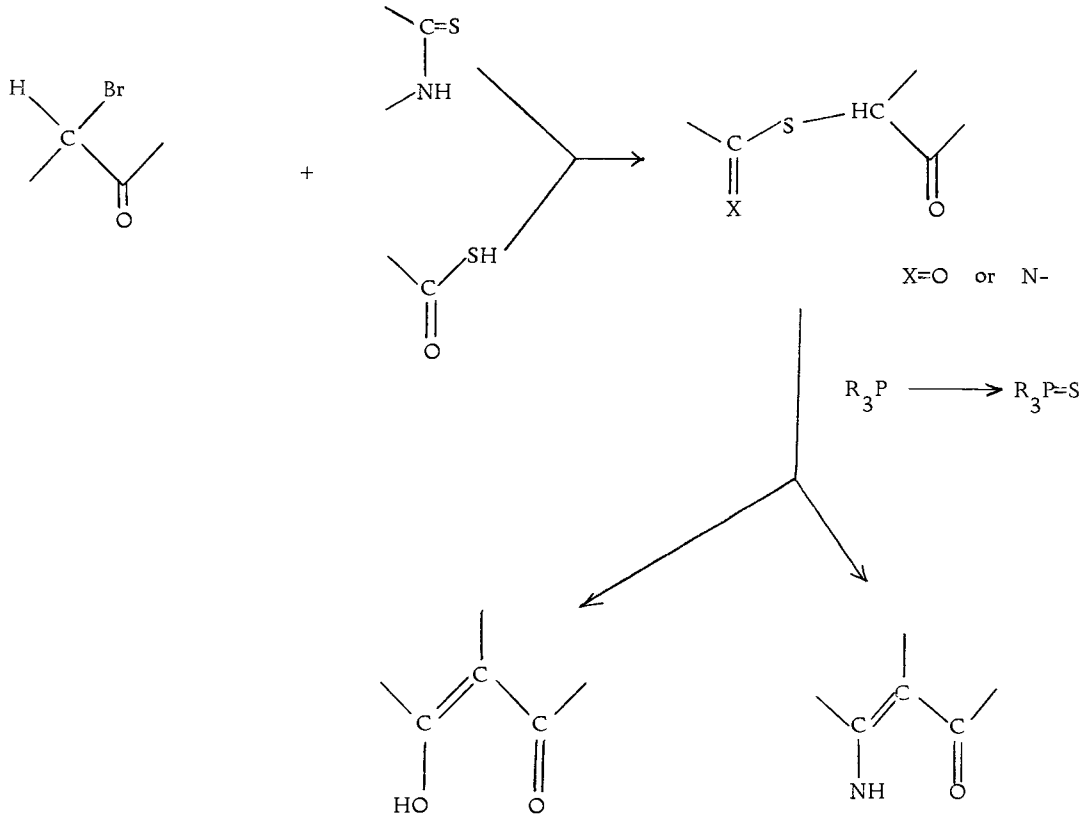
acetone in the presence of benzylamine gave 65 as yellow crystals in 81% yield.[39,40] Treatment of 65 with potassium hydroxide in methanol provided the neutral ester 66 accompanied by acid 67, in 27% and 72% yield respectively.[36] The probable mechanism of this reaction is shown below.



When the acid 67 was treated with methanol in the presence of sulfuric acid and the product recrystallized from chloroform-hexane, the crystalline ester 66 (prisms) was obtained which melted at 105.5-107° C (lit.[36,41] 106-107° C). In contrast, when 67 was treated with boron trifluoride etherate in methanol,[42] followed by a recrystallization from ether-hexane, plate-type crystals of the same ester 66, which had melting point at 92-93° C, were obtained. Although the ir spectra of these products were different, the nmr and mass spectra were identical, confirming the existence of two distinct crystalline modifications. Ester 66 was treated with iodomethane in the presence

of triethylamine to yield S-methylthiazoline 68.[41] When acid 67 was allowed to react with diazomethane, N-methyl ester 69 (CH_3N, singlet, at δ 3.38) was formed, accompanied by 68 (CH_3S, singlet at δ 2.55) which was shown to be identical with material prepared as described above. Nmr evidence revealed the ratio of 68 to 69 as 9:2.

Recently, Eschenmoser has published a novel method for alkylative coupling via sulfur extrusion,[43] a concept which was used effectively in the total synthesis of Vitamin B_{12}.[44] This method seemed well suited to preparation of 70 (Figure 12). Treatment of 66 with



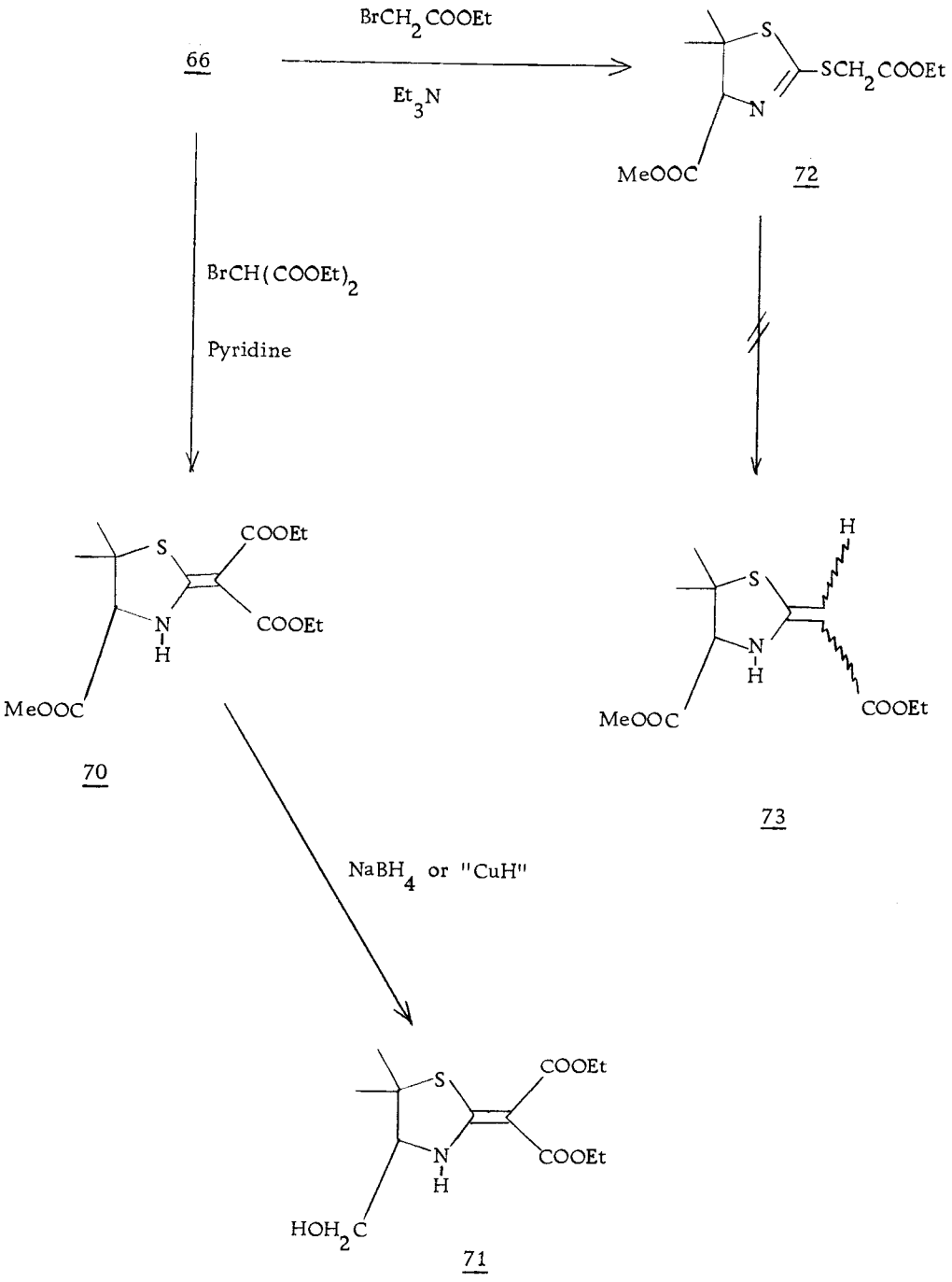
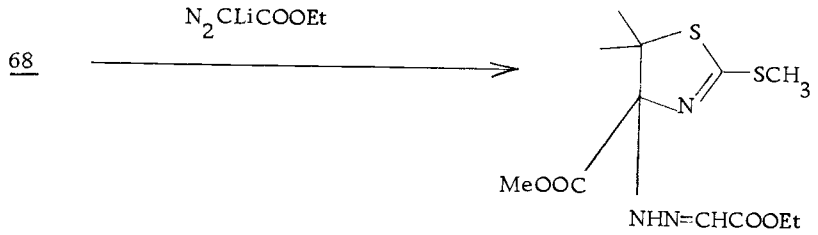

BrCH2COOEt
66
Et3N
SCH2COOEt
MeOOC
72
BrCH(COOEt)2
Pyridine
COOEt
COOEt
MeOOC
70
H
COOEt
73
NaBH4 or "CuH"
COOEt
COOEt
HOH2C
71

Figure 12

diethyl bromomalonate and pyridine in chloroform gave 70 in 96% yield after purification by column chromatography. Reduction of the carbon-carbon double bond in 70 was attempted with a variety of reducing agents,[45-48] but without success. When 70 was allowed to react with sodium borohydride in ethanol,[45] reduction took place at the methoxycarbonyl group giving 71 in 72% yield. Reduction with Cu(I)H complex, which was generated from the action of cuprous bromide and Vitride in THF at -78° C,[46] also gave 71 but in low yield.

The lack of reactivity of the double bond in 70 prompted a search for a functional group at C-2 of 66 which would be less resistant to reduction. When ethyl bromoacetate was allowed to react with 66 in the presence of triethylamine, the product was thiazoline 72 in 81% yield. However, this compound failed to produce the α,β-unsaturated ester 73 under a variety of conditions.[43] Instead, only ring opening occurred, as judged by nmr ($2CH_3$, singlets, at δ 1.75 and 2.41).

In the hope of preparing a useful 2-substituted thiazolidine, 68 was treated with ethyl lithiodiazoacetate in a THF-ether mixture at -110° C. Careful purification by preparative layer chromatography led to the crystalline thiazoline 74 (NH absorption, at 3310 cm^{-1}; C=O absorption at 1735 and 1685 cm^{-1}; vinyl CH, singlet, at δ 7.06) in 65% yield (Figure 13). Neither condensation of 68 with ethyl nitroacetate nor lithio-2-phenyl-5-oxazolone yielded any product.

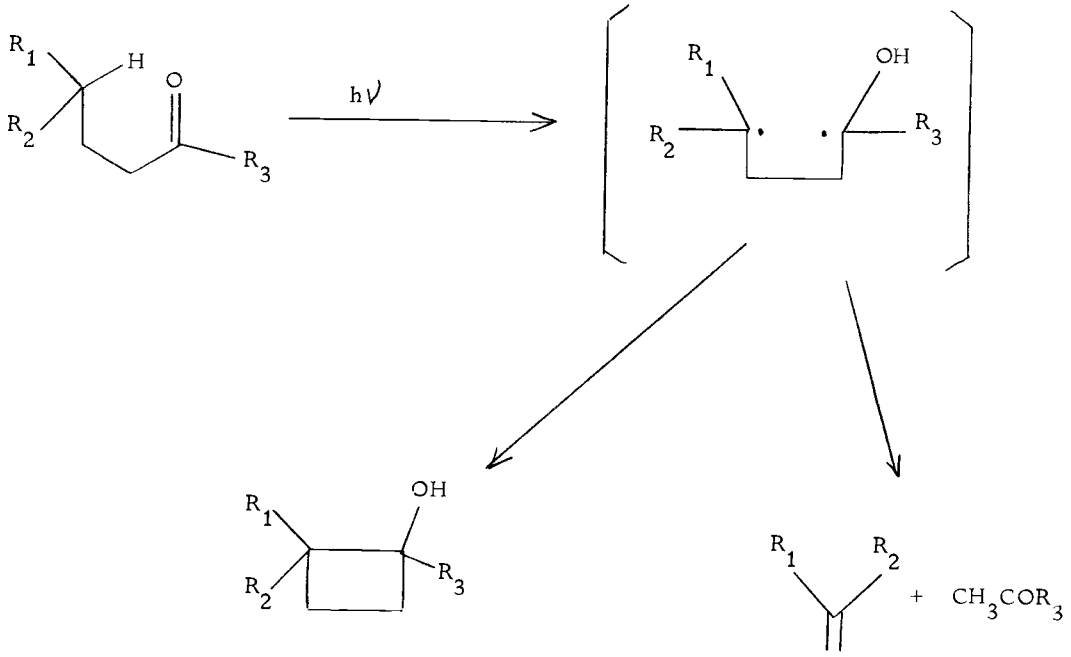


74

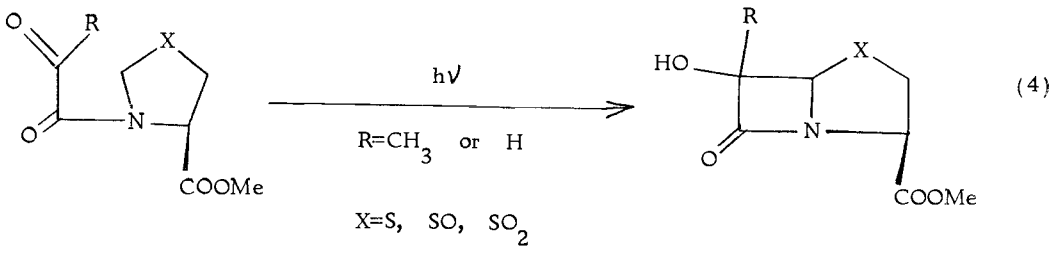
Figure 13

IV. PHOTOCHEMICAL APPROACHES

Carbonyl compounds containing γ C-H bonds undergo, upon irradiation, characteristic 1, 5-hydrogen shifts to yield both cleavage and cyclization products.[49] These reactions have been studied most



extensively with ketones. The cleavage reaction is commonly called Norrish type II photoelimination, after its discoverer.[50] Cyclobutanol formation, which almost always accompanies cleavage, was first reported by Yang in 1958.[51] Recently, Henery-Logan and Chen[52] used this transformation and have achieved the synthesis of model, penam-type compounds from 3-pyruvoyl-4-carbomethoxythiazolidine and its sufloxide and sulfone derivatives (eq. 4).



(4)

In the course of our search for a synthetic route to β-lactams, we have investigated the photochemical behavior of 77 (Figure 14). The C-2 thione function in 67 was exchanged for an oxo substituent with 3% hydrogen peroxide and 1 N potassium hydroxide,[53] yielding 2-thiazolidone 75. This was immediately esterified with excess diazomethane to give the crystalline methyl ester 76 in 55% yield based on 67. Coupling of phthalimidoacetyl chloride with the sodium salt of 76 led to a quantitative yield of crystalline 77. Irradiation of 77

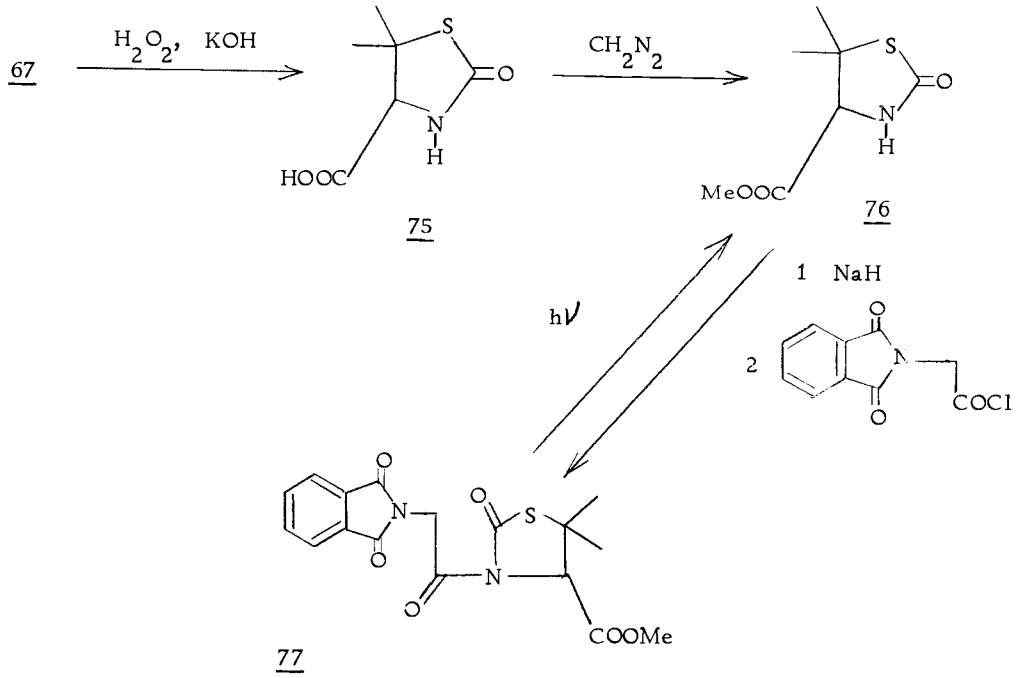
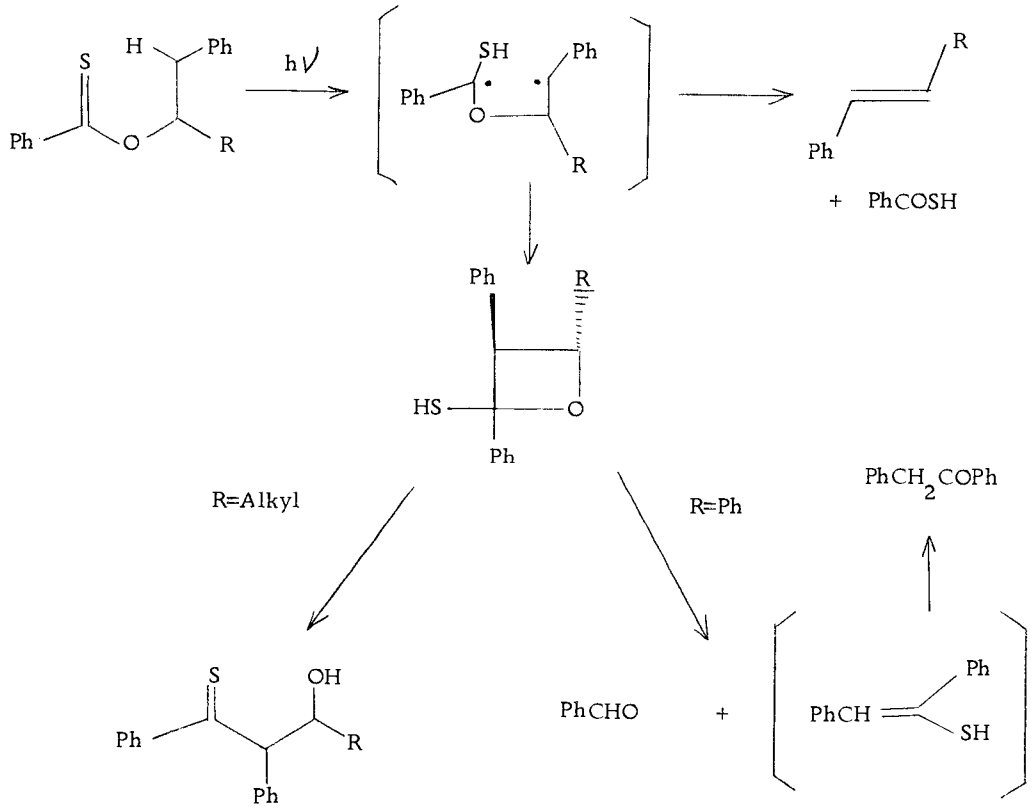


Figure 14

with a Hanovia 450-W lamp, through a Pyrex filter at 5-8° C in a dry tert-butanol-benzene mixture under nitrogen yielded a large amount of 76, but no β-lactam could be detected (by infrared).

It has also been shown that thiocarbonyl systems participate readily in photochemical reactions and produce thiol analogs of cyclobutanol as well as the type-II cleavage products.[54-59] In particular, Barton and co-workers have exploited this reaction, using O-1-alkyl-2-phenylethyl thiobenzoates, and they have postulated a cyclobutanethiol as an intermediate.[58] 2-Thiothiazolidine derivative 78 was



synthesized from the reaction of the sodium salt of 66 and phthalimidoacetyl chloride (Figure 15). Irradiation of 78 and separation of products by preparative-layer chromatography gave 2-thiazolidone 76, 77 and N-methylphthalimide (79) as the major products. Again, no β-lactam was apparently formed.

These results indicate that the preferred photochemical pathway from 77 and 78 involves Norrish type II elimination rather than cyclobutanol formation. Formation of 76 and 77 is apparently the result of exchange of the C-2 thione function with oxygen, present in nitrogen as an impurity.

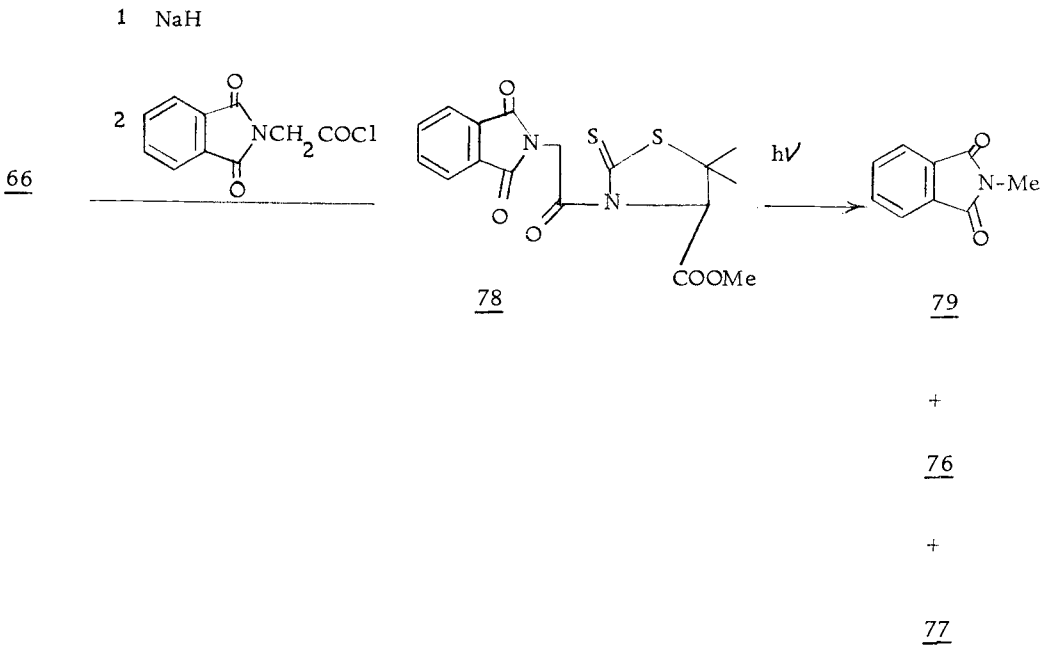


Figure 15

V. BIOGENETICALLY PATTERNED APPROACHES

It has been suggested that penicillin (1) is synthesized in nature by oxidation of a cysteinyldehydrovaline dipeptide (80) to a thioaldehyde 81, followed by cyclization (Figure 16).[60] Recently, Baldwin

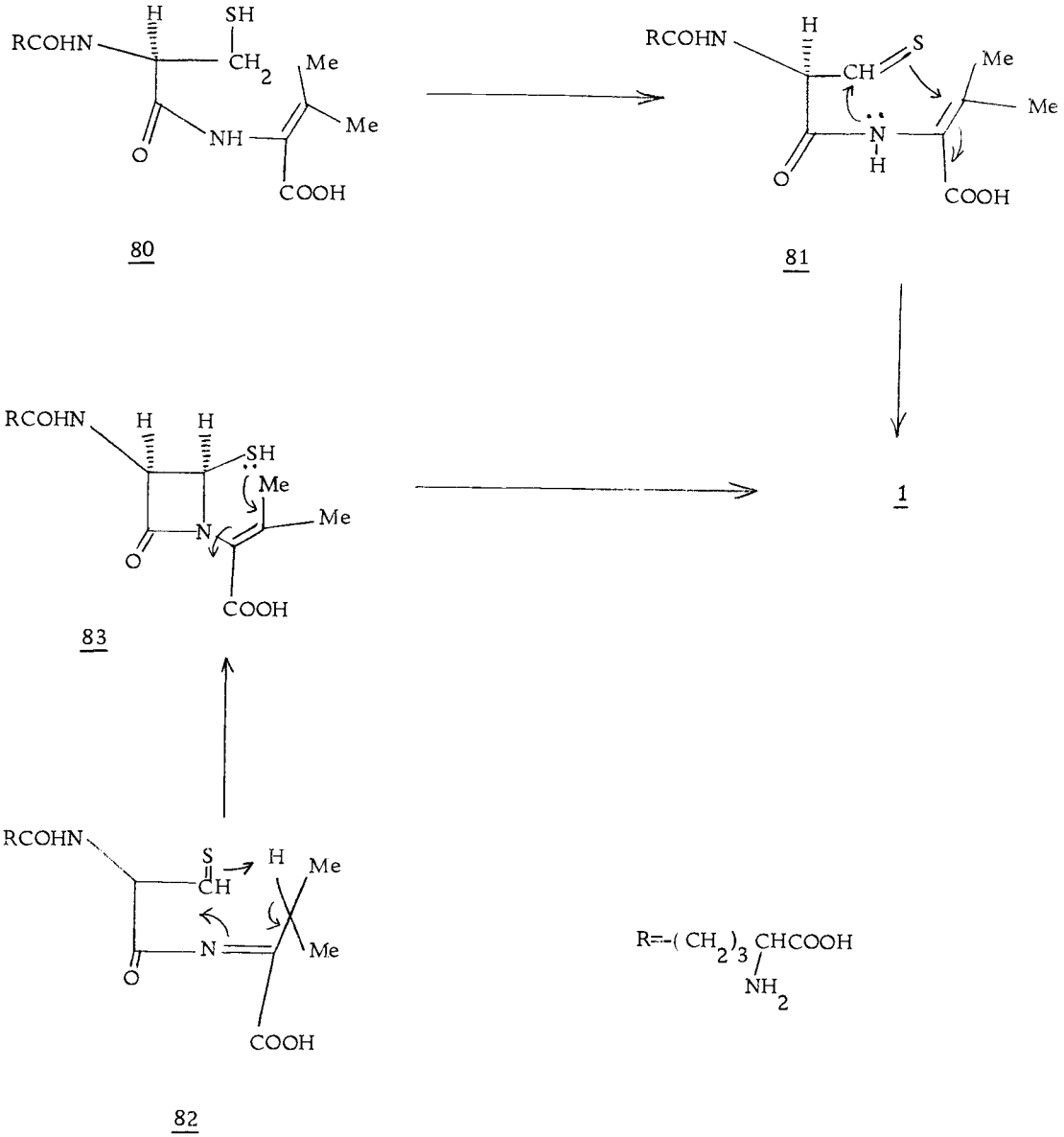


Figure 16

has suggested an interesting modification of Arnstein's mechanism, in which the β-lactam of penicillin is formed by an "ene" reaction of 82.[61] This suggestion has stimulated efforts towards synthesis of thioaldehydes (e. g. 81 and 82) by chemical oxidation of cysteinyl-valine derivative.

Our initial approach to synthesis of a suitable thioaldehyde derivative is shown in Figure 17. The acetamidomethyl group was chosen for protection of the thiol of cysteine because this protecting chain is stable under strongly acidic and basic conditions but is easily removed upon treatment with mercuric acetate to give free thiol.[62] The S-protected cysteine 85 was prepared from condensation of cysteine hydrochloride monohydrate with N-hydroxymethylacetamide (84). Protection of the amino group in 85 was carried out with tert-butoxycarbonylazide and tetramethylguanidine in THF to give the N-tert-Boc cysteine derivative 86 in 46% yield.[62] This compound could not be obtained in crystalline form and for characterization purposes, 86 was converted to its ester 87 by treatment with N-hydroxysuccinimide and dicyclohexylcarbodiimide.

Condensation of 86 with aziridine 56 was carried out with dicyclohexylcarbodiimide in THF at 0° C to give a 66% yield of 88 after purification by column chromatography. The structure of 88 was confirmed by its ir (NH absorption at 3360; C=O absorption at 1750-1650 cm^{-1}) and nmr spectra (CH_3-C-O, triplet, at δ 1.31;

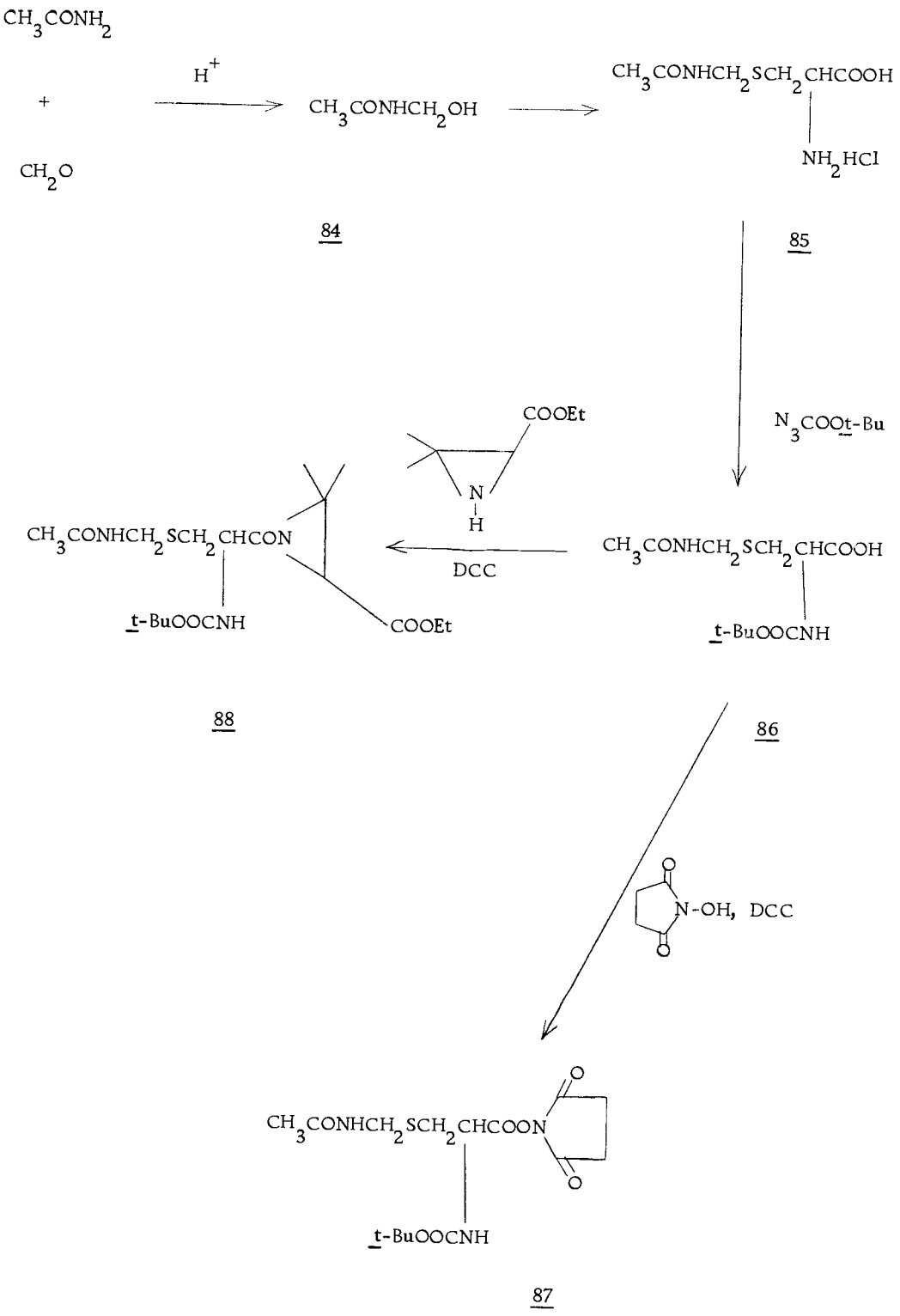
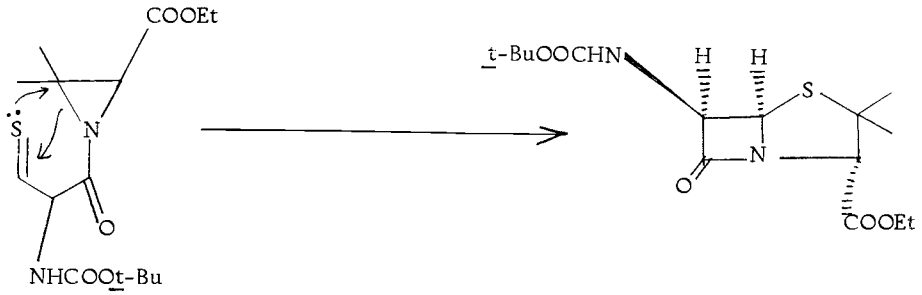

CH3CONH2
+
CH2O
H+
CH3CONHCH2OH
CH3CONHCH2SCH2CHCOOH
NH2HCl
84
85
N3COOt-Bu
COOEt
N
H
DCC
CH3CONHCH2SCH2CHCON
t-BuOOCNH
COOEt
CH3CONHCH2SCH2CHCOOH
t-BuOOCNH
88
86
N-OH, DCC
CH3CONHCH2SCH2CHCOON
t-BuOOCNH
87

Figure 17

$5CH_3$, singlet, at δ 1.44; CH_3CO, singlet, at δ 2.01) as well as a parent ion in its mass spectrum at m/e 417.

Synthesis of a penicillin by a biogenetically patterned approach depends upon formation of thioaldehyde 89 after deprotection of the sulfur atom followed by oxidation. Attack by the thioaldehyde on the aziridine ring in the manner shown below would lead to β-lactam



89 90

formation and give 90. However, it was found that the N-acylaziridine system 88 undergoes a rapid Norrish type II aziridine cleavage, in which the amino carbonyl and a methyl hydrogen participate to give 91. Thus, when 88 was irradiated in dry benzene at room temperature, using a Hanovia 450-W medium-pressure mercury lamp and a Pyrex filter, two compounds were formed in good yield, as judged by thin-layer chromatography (Figure 18). Isolation of each compound gave 91a and 91b, the nmr spectra of which showed a peak for a methyl group at δ 1.85 for 91a and δ 1.78 for 91b with vinyl methylene peaks at δ 5.07 for 91a and δ 5.06 for 91b. The mass spectrum of each compound showed a molecular ion at m/e 417. Consequently,

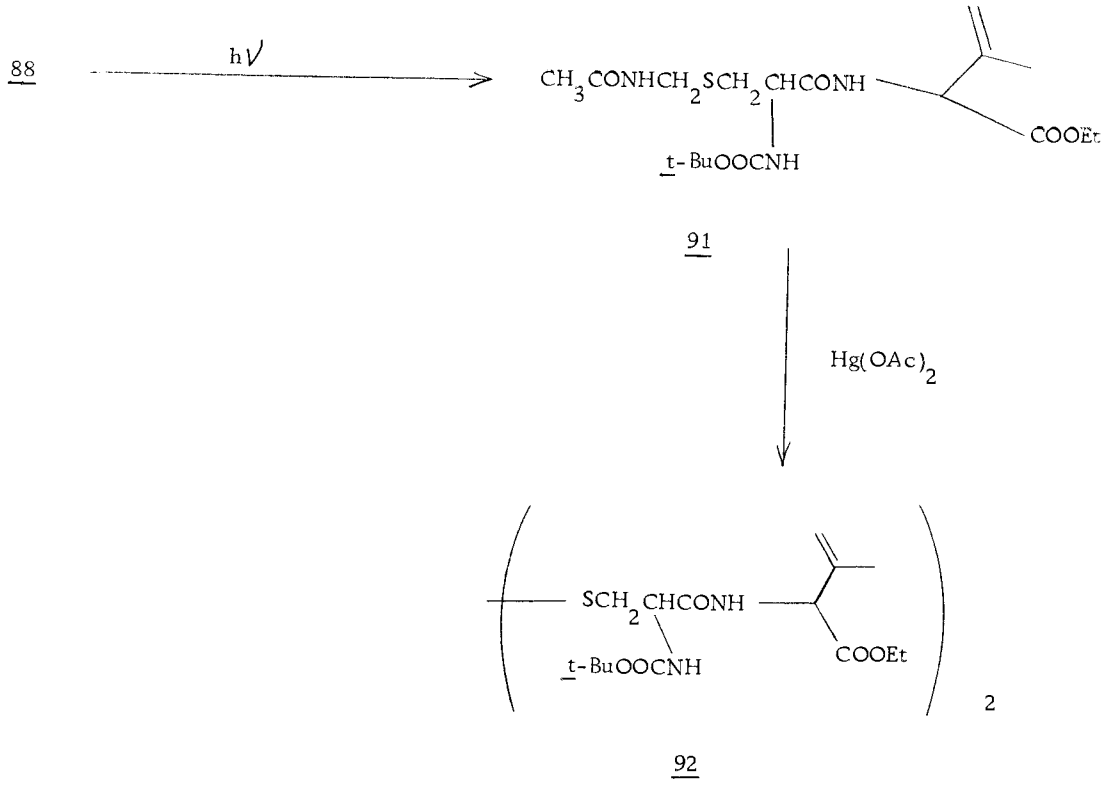


Figure 18

91a and 91b are diastereomers. Treatment of the mixture of 91a and 91b with mercuric acetate in a pH 4 buffer solution of aqueous THF gave a product which retained the vinylic methylene protons at δ 5.08, but from which peaks for the acetamidomethyl group at δ 1.9-2.1 and 4.4-4.8 had disappeared. The ir spectrum of this product showed absorptions at 3400 (NH) and 1740-1650 cm^{-1} for carbonyls, and the absence of a peak in the 2600 cm^{-1} region for a thiol. The nmr spectrum also exhibited a broad peak at δ 1.1-1.6 for the saturated methyl groups, a broad singlet at δ 1.74 for two methyl groups,

substituted on a carbon-carbon double bond, a multiplet at δ 3.3-3.6 for methylene protons, a multiplet at δ 4.6 for a methine protons which is attached to carbonyl and amino groups, a multiplet at δ 6.00 for a methine proton, and a broad peak at δ 7.56 for NH. A plausible structure for this compound is disulfide 92.

In parallel with this approach, a second scheme based on work carried out by Scott,[63] was explored, using the benzoylmethylene protecting group for the sulfur of cysteine in the hope that this could be removed without cleavage of the aziridine. This protecting group is stable under conventional reaction conditions but, upon irradiation oxidative cleavage takes place in this chain to give a thioaldehyde. L-Cystine (93) was converted to N,N'-diphenylacetylcystine (94) in 74% yield by the action of α-phenylacetyl chloride in aqueous base.[64] The disulfide was cleaved by sodium metal in liquid ammonia and the resulting thiol was immediately condensed with α-chloroacetophenone to yield the diprotected cysteine 95[63] in 67% yield (from 94). Attempted condensation of 95 with aziridine 56 in the presence of dicyclohexylcarbodiimide, however, gave no tractable product.

Suspecting that difficulties in this condensation might arise from the N-phenylacetyl protecting group, cystine (93) was converted to its tert-Boc derivative 96 by treatment with tert-butoxycarbonyl-azide and sodium hydroxide in aqueous dioxane.[65] Reductive cleavage of 96 with sodium in liquid ammonia, followed by protection with

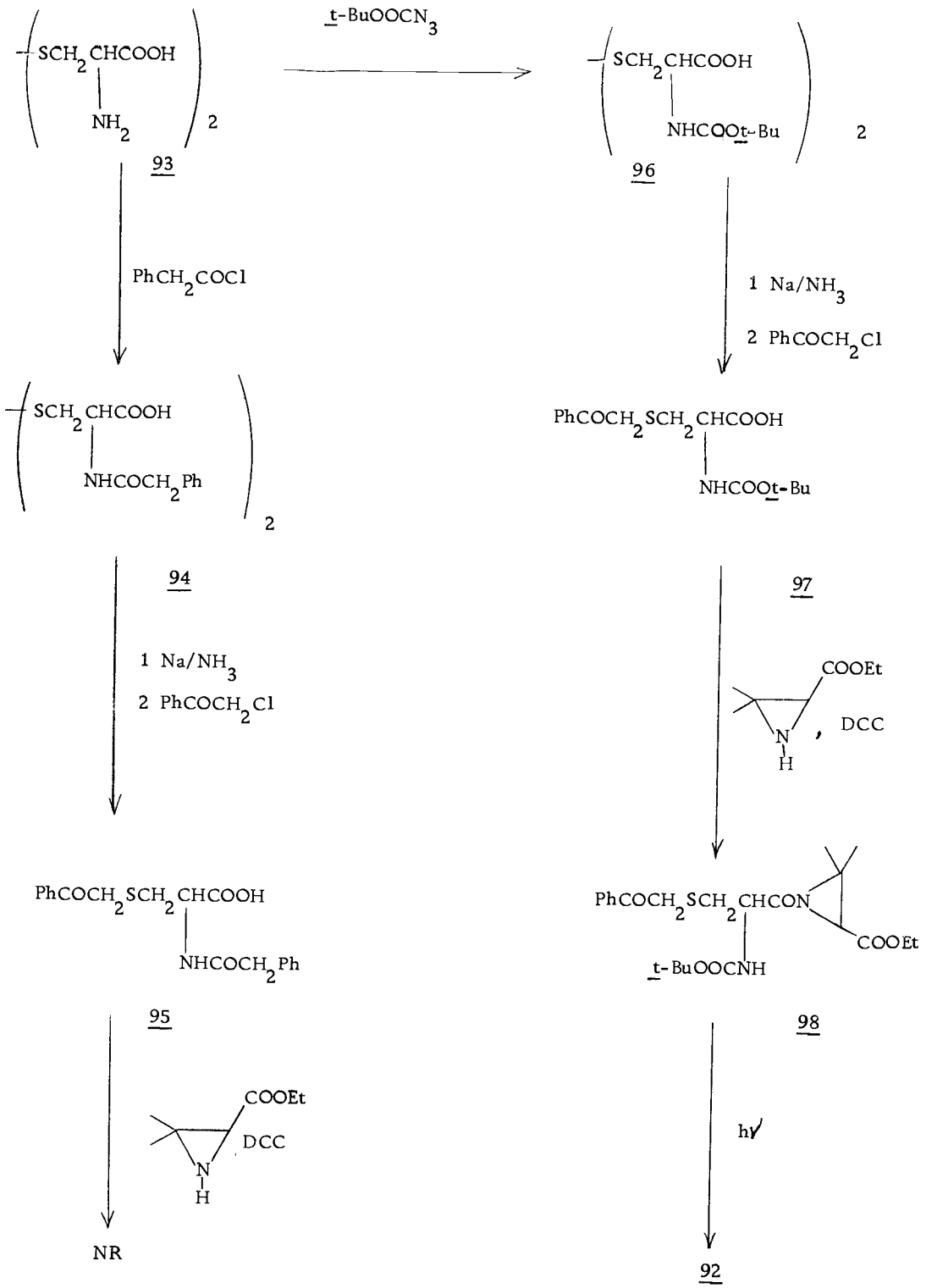

t-BuOOCN3
SCH2CHCOOH
NH2
2
93
PhCH2COCl
SCH2CHCOOH
NHCOCH2Ph
2
94
1 Na/NH3
2 PhCOCH2Cl
PhCOCH2SCH2CHCOOH
NHCOCH2Ph
95
COOEt
DCC
N
H
NR
SCH2CHCOOH
NHCOOt-Bu
2
96
1 Na/NH3
2 PhCOCH2Cl
PhCOCH2SCH2CHCOOH
NHCOOt-Bu
97
COOEt
DCC
N
H
PhCOCH2SCH2CHCON
COOEt
t-BuOOCNH
98
hν
92

Figure 19

α-chloroacetophenone gave 97 in 42% yield. Reaction of 97 with aziridine 56 in the presence of dicyclohexylcarbodiimide in THF led to 98 in 24% yield. The structure of 98 was confirmed by ir (NH absorption at 3410 cm^{-1}, C=O absorption at 1740, 1710, and 1680 cm^{-1}) and nmr (CH_3-C-O, triplet, at δ 1.29; $5CH_3$, singlet, at δ 1.50; $COCH_2S$, singlet, at δ 4.02) and mass spectra (m/e 464 for molecular ion). Photolysis of 98 in benzene at 6° C for 2 hours (Hanovia 450-W medium-pressure mercury lamp with a Pyrex filter) gave a product which exhibited absorptions at 3400 (NH) and 1700 (braod C=O) cm^{-1} in its ir spectrum. The nmr spectrum showed two triplets at δ 1.26 and 1.28, a singlet at δ 1.43 for six methyl groups, a singlet at δ 1.78 for two methyl groups, and a broad peak at δ 5.03 for vinyl methlene protons. Resonances due to the phenacyl group were absent. The product appears to be a disulfide, but a detailed structure analysis is lacking.

The fact that no β-lactam has been isolated in Baldwin's,[61] Scott's,[63] or this study raises concern regarding the proposed biogenesis of penicillin.

In summary, this work has not achieved its admittedly ambitious goal. However, it does lay the foundation for several, independent approaches which could conceivably be extended to a synthesis of the original target.

VI. EXPERIMENTAL

General

Melting points were determined on a Kofler hot stage microscope and are corrected; boiling points are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 137 or 727B infrared spectrophotometer. Ultraviolet (UV) spectra were obtained using a Cary Model 15 ultraviolet spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined on a Varian Associates Model EM-360 or HA-100 spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in δ units. Mass spectra and exact mass determinations were obtained using a CEC-103B spectrometer at an ionizing potential of 70 eV. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Illinois and by Dr. Susan Rottschaefer, Department of Chemistry, University of Oregon. Analytical thin-layer and preparative-layer chromatograms were made with Merck silica gel GF-254.

N-Benzyl-2-carbethoxy-3, 3-dimethylaziridine (46)

To a solution of 16.0 g (55.6 mmol) of ethyl 2, 3-dibromo-3-methylbutanoate (45)[23] in 120 ml of dry benzene was added 19.0 g (177 mmol) of dry benzylamine at room temperature over a period of 30 min.[24] After addition was complete, a white precipitate

appeared and the mixture was refluxed at 80-85° C for 40 hr. An additional 3 ml of benzylamine was added to above mixture and further refluxing was performed for 20 hr. The white precipitate was removed by filtration and the solvent was evaporated in vacuo. Ether (80 ml) was added to the residue in order to remove the remaining benzylamine hydrochloride. This procedure was repeated until no more precipitate appeared after addition of ether. The solvent was evaporated in vacuo and the residual oil was twice distilled under reduced pressure to give 10.7 g (83% based on dibromide 45) of N-benzyl-2-carbethoxy-3,3-dimethylaziridine (46): bp 109-115° C (0.25 mm); ir (film) 1745 (C=O), 1720, 1496 cm^{-1}; nmr ($CDCl_3$) δ 1.25 (3H, t), 1.32 (6H, s), 2.12 (1H, s), 3.78 (2H, s), 4.17 (2H, q), 7.1-7.4 (5H, m).

1-Benzyl-3-methylhydantoin-2-thione (47)

A mixture of 500 mg (2.14 mmol) of aziridine 46 and 204 mg (2.80 mmol) of methylisothiocyanate in 5 ml of dry benzene was refluxed for 7 hr. The reaction mixture was cooled to room temperature and the solvent was evaporated in vacuo to give 450 mg of a brown oil, the tlc of which showed three major spots at R_f values 0.40, 0.60 and 0.67 (ether-hexane). Two spots of R_f values 0.60 and 0.67 corresponded to those of aziridine 46 and methylisothiocyanate respectively. Preparative-layer chromatography of the crude product (100 mg) gave

75 mg (66.8%) of 1-benzyl-3-methylhydantoin-2-thione (47). This oil crystallized on standing and was recrystallized from an ether-hexane mixture: mp 74-75° C; ir (Nujol) 1755 (C=O), 1600, 1500 cm^{-1}; nmr ($CDCl_3$) δ 3.29 (3H, s), 3.86 (2H, s), 5.04 (2H, s), 7.35 (5H, s); mass spectrum m/e 220 (M^+).

Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.98; H, 5.49; N, 12.72. Found: C, 60.13; H, 5.75; N, 12.51.

1,3-Dibenzylhydantoin-2-thione (48)

A mixture of 200 mg (0.86 mmol) of aziridine 46 and 128 mg (0.86 mmol) of benzylisothiocyanate in 4 ml of dry xylene was refluxed at 120-130° C for 4 hr. After the reaction mixture had cooled, the solvent was removed in vacuo, yielding approximately 150 mg of a dark brown oil, the tlc of which showed two major spots at R_f values 0.20 and 0.26 (benzene). The product, R_f 0.26, was separated and purified by two-fold preparative-layer chromatography giving 30 mg (11.4%) of 1,3-dibenzylhydantoin-2-thione (48). This compound showed instability at room temperature: ir (film) 1752 (C=O), 1605, 1495 cm^{-1}; nmr ($CDCl_3$) δ 3.84 (2H, s), 5.02 (2H, s), 5.07 (2H, s), 7.2-7.6 (10H, m); mass spectrum m/e 296 (M^+).

3-Benzyl-4-carbethoxy-5, 5-dimethyl-2-iminothiazolidine (49) and 3-Benzyl-5-carbethoxy-4, 4-dimethyl-2-iminothiazolidine (50)

A. From Potassium Thiocyanate

A mixture of 3.0 g (12.9 mmol) of aziridine 46 in 30 ml of formic acid was stirred at 50° C for 1 hr and 1.37 g (14.9 mmol) of potassium thiocyanate was added all at once. The mixture was warmed to 80° C and stirred for 10 hr. The solvent was evaporated in vacuo and 50 ml of ice-water, followed by solid sodium bicarbonate, were added to the acidic residue until pH 8 was reached. The organic layer was extracted twice with ether and the ether solutions were washed with brine and dried over sodium sulfate. After combination of the ether solutions, evaporation of solvent gave 3.38 g of oily product, the nmr of which showed that there was 46% of 3-benzyl-4-carbethoxy-5, 5-dimethyl-2-iminothiazolidine (49) and 54% of 3-benzyl-5-carbethoxy-4, 4-dimethyl-2-iminothiazolidine (50) present. These two isomers were separated and purified by preparative-layer chromatography using an ether-hexane mixture as solvent. Compound 49 crystallized upon scratching and was recrystallized from a hexane-ether mixture. Compound 49: mp 94-94.5° C; ir (Nujol) 3400 (NH), 1735 (C=O), 1605 (C=N) cm^{-1}; nmr ($CDCl_3$) δ 1.29 (3H, t), 1.41 (3H, s), 1.58 (3H, s), 3.75 (1H, s), 3.96 (1H, d, J=14.4 Hz), 4.21 (2H, q), 5.25 (1H, d, J=14.4 Hz), 5.66 (1H, broad), 7.32 (5H, m); mass

spectrum m/e 292 (M^+). Compound 50: ir (film) 3370 (NH), 1730 (C=O), 1605 (C=N) cm^{-1}; nmr ($CDCl_3$) δ 1.26 (3H, s), 1.29 (3H,t), 1.44 (3H, s), 4.06 (1H, s), 4.22 (2H, q), 4.56 (2H, s), 5.54 (1H, broad), 7.1-7.4 (5H, m); mass spectrum m/e 292 (M^+).

B. From Ammonium Thiocyanate

A mixture of 1.0 g (4.29 mmol) of 46 and 392 mg (5.16 mmol) of ammonium thiocyanate in 25 ml of dry tetrahydrofuran was stirred at 55° C for 24 hr. The solvent was removed in vacuo and the residue was taken up into ether. The ether solution was washed with brine and dried over sodium sulfate. Removal of solvent, followed by column chromatography with aluminum oxide and ether-hexane as solvent, yielded 1.06 g of a mixture of compounds 49 and 50. Its nmr spectrum showed that it contained less than 12% of 49 and more than 88% of 50.

2-Acetimino-3-benzyl-5-carbethoxy-4,4-dimethylthiazolidine (53)

A mixture of 3.21 g (11.0 mmol) of imino compound 50 in 15 ml of acetic anhydride was stirred at room temperature overnight. During this time, a precipitate appeared. The precipitate was collected by filtration and washed with hexane to give 1.95 g of 2-acetimino-3-benzyl-5-carbethoxy-4,4-dimethylthiazolidine (53). The excess acetic anhydride was evaporated from the filtrate and the residue was taken up into dichloromethane. The dichloromethane solution was washed with aqueous sodium bicarbonate and brine and dried over sodium sulfate. Removal of solvent gave 1.65 g of 53. This material

was recrystallized from a benzene-hexane (1:2) mixture to yield 3.60 g (98%) of 53: mp 130-131° C; ir (Nujol) 1738 (C=O), 1620 (C=O), 1512 cm^{-1}; nmr ($CDCl_3$) δ 1.23 (3H, t), 1.27 (3H, s), 1.39 (3H, s), 2.17 (3H, s), 3.86 (1H, s), 4.17 (2H, q), 4.80 (2H, s), 7.30 (5H, m); mass spectrum m/e 334 (M^+).

Anal. Calcd for $C_{17}H_{22}N_2O_3S$: C, 61.05; H, 6.63; N, 8.38. Found: C, 61.09; H, 6.73; N, 8.26.

2-Acetimino-3-benzyl-5-carbethoxy-5-carbethoxymethyl-4,4-dimethylthiazolidine (54)

A suspension of 100 mg (0.299 mmol) of 53 and 20 mg of copper powder in 2 ml of dry benzene was refluxed and a solution of 350 mg (3.07 mmol) of ethyl diazoacetate in 1 ml of dry benzene was added dropwise over a period of 15 min. After addition was complete, the reaction mixture was allowed to reflux for an additional 30 min. The copper powder was filtered off and washed with a small amount of ether. The filtrate was washed with aqueous sodium bicarbonate and brine and dried over sodium sulfate. Evaporation of solvent afforded 350 mg of crude, dark-brown oil, the tlc of which showed three main spots at R_f values 0.27, 0.32, and 0.59. Three compounds were separated by column chromatography, using aluminum oxide and ether-hexane as eluent. Diethyl maleate, R_f 0.59, and 102 mg of a mixture, R_f 0.27 and 0.32 were obtained. The nmr of the mixture showed that

it contained approximately 45% of 2-acetimino-3-benzyl-5-carbethoxy-5-carbethoxymethyl-4, 4-dimethylthiazolidine (54). A sample of pure 54 crystallized when the fraction from column chromatography was allowed to stand overnight without evaporation of solvent. It was recrystallized from ether-hexane: mp 142.5-143.5° C; ir (Nujol) 1727 (C=O), 1625 (C=O), 1505 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (3H, s), 1.24 (3H, t), 1.28 (3H, t), 1.35 (3H, s), 2.21 (3H, s), 2.70 (1H, d, J=16 Hz), 3.22 (1H, d, J=16 Hz), 4.15 (2H, q), 4.23 (2H, q), 4.63 (1H, d, J=16 Hz), 4.97 (1H, d, J=16 Hz), 7.33 (5H, m); mass spectrum m/e 420 (M^+).

Anal. Calcd for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66. Found: C, 59.88; H, 6.81; N, 6.41.

3-Benzyl-5-carbethoxy-2-carbethoxymethylimino-4, 4-dimethylthiazolidine (51) and Ethyl 3-(N-Benzyl-N-carbethoxymethyl)amino-3-methyl-2-thiocyanobutanoate (52)

A suspension of 80 mg (0.274 mmol) of 50 and 11 mg of copper powder in 0.5 ml of octane was refluxed under nitrogen. A solution of 42 mg (0.368 mmol) of ethyl diazoacetate in 0.5 ml of dry benzene was added dropwise for 30 min under continuous stirring; evolution of nitrogen ensued. After addition was complete, the suspension was stirred for further 30 min, the copper powder was filtered off and washed with a small amount of ether. The filtrate was washed with

aqueous sodium bicarbonate and brine and dried over sodium sulfate. Removal of solvent afforded 100 mg of crude product. Its tlc showed five spots at R_f value 0.15, 0.27, 0.32, 0.45, and 0.52, with the spot at R_f 0.15 corresponding to 50. Separation and purification by two-fold preparative-layer chromatography, with ether-hexane as solvent, gave 15 mg of 3-benzyl-5-carbethoxy-2-carbethoxymethylimino-4, 4-dimethylthiazolidine (51): ir (film) 1735 (C=O), 1630 (C=N) cm^{-1}; nmr ($CDCl_3$) δ 1.17 (3H, s), 1.24 (6H, t), 1.37 (3H, s), 4.05 (1H, s), 4.08 (2H, s), 4.19 (2H, q), 4.25 (2H, q), 4.57, 4.59 (2H, each d, J=16 Hz), 7.1-7.5 (5H, m); mass spectrum m/e 378 (M^+) and 10 mg of ethyl 3-(N-benzyl-N-carbethoxymethyl)amino-3-methyl-2-thiocyanobutanoate (52): ir (film) 2215 (C≡N), 1735 (C=O), cm^{-1}; nmr ($CDCl_3$) δ 1.29 (3H, t), 1.32 (3H, t), 1.53 (3H, s), 1.56 (3H, s), 3.36 (2H, s), 3.90 (1H, s), 4.22 (2H, q), 4.27 (2H, q), 4.30 (2H, s), 7.36 (5H, m); mass spectrum m/e 246 (M^+).

Preparation of Compound 55

According to the procedure of Schöllkopf et al.,[29] 0.14 ml of 2.35 M n-butyllithium in hexane was added to a solution of 33.8 mg (0.296 mmol) of ethyl diazoacetate in 2.5 ml of a dry ether-tetrahydrofuran mixture (2:3) at -110° C over a period of 30 min. After stirring for 30 min, 90 mg (0.269 mmol) of 53 in 3 ml of dry tetrahydrofuran was added dropwise to the solution over 40 min. The

resulting mixture was allowed to warm to -30° C slowly and then cooled to -70° C to add 20 mg (0.326 mmol) of acetic acid in 1 ml of tetrahydrofuran during 20 min. After the reaction mixture had warmed to room temperature, the solvent was removed in vacuo (below 30° C). The residue was extracted with dichloromethane and the dichloromethane solution was washed with aqueous bicarbonate and brine and dried over sodium sulfate. After evaporation of solvent in vacuo, the tlc of the residue showed two main spots at R_f values 0.09 and 0.28. These two compounds were separated and purified by preparative-layer chromatography with ether-hexane as solvent, to give 38.7 mg of 53 (R_f 0.28) and 71.4 mg of 55. Compound 55 crystallized on standing and was recrystallized from a dichloromethane-hexane mixture: mp 120.5-122° C (decomp.); ir (Nujol) 3200 (NH), 1735, 1698 (C=O), 1630, 1570, 1515, 1500 cm^{-1}, nmr ($CDCl_3$) δ 1.23 (3H, s), 1.26 (3H, t), 1.28 (3H, t), 1.49 (3H, s), 2.16 (3H, s), 4.21 (2H, q), 4.30 (2H, q), 4.88 (2H, s), 7.02 (1H, s), 7.2-7.5 (6H, m, includes NH); mass spectrum m/e 448 (M^+).

Anal. Calcd for $C_{21}H_{28}N_4O_5S$: C, 56.23; H, 6.29; N, 12.49. Found: C, 56.35; H, 6.29; N, 12.52.

2-Carbethoxy-3,3-dimethylaziridine (56)

A solution of 10 g of dibromide 45 in 100 ml of dry ethanol was saturated with dry liquid ammonia under cooling.[30] The solution

was allowed to stand at room temperature for 14 days in the dark. During this period, a further quantity of dry liquid ammonia was added to the mixture. Dry ether (ca. 50 ml) was added to the reaction mixture and the resulting white precipitate was filtered. The filtrate was evaporated in vacuo below 45° C and another 50 ml of dry ether was added to the residue. The precipitate was filtered and the filtrate was evaporated under reduced pressure. This process was repeated 2-3 times. This material was used for next reaction without purification after it was checked for purity: ir (film) 3300 (NH), 1730 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.28 (3H, t), 1.28 (3H, s), 1.30 (3H, s), 1.50 (1H, broad), 2.43 (1H, s), 4.23 (2H, q).

5-Carbethoxy-4, 4-dimethylthiazolidine-2-thione (57)

A mixture of 196 mg (1.37 mmol) of aziridine 56 and an excess of carbon disulfide was sealed in a 2 ml vial and heated at 100° C for 5 hr in an oil bath,[31] with occasional shaking. After the mixture was cooled, the vial was opened and the contents were poured into 50 ml of water. The organic layer was extracted twice with ether and the extracts were washed with brine and dried over sodium sulfate. Evaporation of solvent in vacuo gave 203 mg of a brown oil. This was purified by column chromatography, using Florisil with hexane-ether mixture (1:1) as eluent to give 175 mg (58.7%) of pure 5-carbethoxy-4, 4-dimethylthioazolidine-2-thione (57). This material was

allowed to stand for a few days at room temperature to crystallize and could be recrystallized from an ether-hexane mixture: mp 99.0-99.5° C; ir (Nujol) 3200 (NH), 1735 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.30 (3H, t, J=7 Hz), 1.43 (3H, s), 1.64 (3H, s), 4.24 (2H, q), 4.47 (1H, s), 8.7 (1H, broad); mass spectrum m/e 219 (M^+).

Anal. Calcd for $C_8H_{13}NO_2S_2$: C, 43.81; H, 5.97; N, 6.39. Found: C, 44.06; H, 6.14; N, 6.12.

5-Carbethoxy-4,4-dimethyl-2-methylthio-2-thiazoline (58)

To a solution of 525 mg (2.39 mmol) of thiazolidine 57 and 340 mg (2.39 mmol) of iodomethane in 4 ml of dry tetrahydrofuran, was added 242 mg (2.39 mmol) of triethylamine dropwise during 15 min at room temperature and the resulting mixture was warmed at 40° C under stirring for 4 hr.[32] During the reaction period, an additional 340 mg of iodomethane was added. The reaction mixture was filtered and the precipitate was washed with a small portion of ether. The combined filtrate was evaporated in vacuo and 20 ml of water was added to the residue. The organic layer was extracted twice with ethyl acetate and the combined extract was washed with saturated cupric sulfate solution and brine. After drying the ethyl acetate solution over sodium sulfate, evaporation of solvent in vacuo gave a yellow oil which was purified by column chromatography, using silica gel and ether-hexane (1:2) as eluent, to give 385 mg (69.0%) of

5-carbethoxy-4, 4-dimethyl-2-methylthio-2-thiazoline (58). A pure sample was obtained by distillation: bp 110° C (2 mm); ir (film) 1740 (C=O), 1575 (C=N) cm^{-1}; nmr ($CDCl_3$) δ 1.29 (3H, t, J=7 Hz), 1.32 (3H, s), 1.53 (3H, s), 2.53 (3H, s), 4.23 (2H, q), 4.34 (1H, s); mass spectrum m/e 233 (M^+).

Anal. Calcd for $C_9H_{15}NO_2S_2$: C, 46.32; H, 6.48; N, 6.00. Found: C, 46.47; H, 6.60; N, 6.15.

5-Carbethoxy-2-carbethoxynitromethlidene-4, 4-dimethylthiazolidine (59)

According to the procedure of Hirai,[34] a mixture of 190 mg (0.815 mmol) of 2-methylthiothiazoline 58, 163 mg (1.22 mmol) of ethyl nitroacetate[66] and a catalytic amount of zinc chloride was stirred for 8 hr at 110° C under nitrogen. The reaction mixture was cooled to room temperature and 5 ml of water was added to it. The organic layer was extracted with ether and the ethereal solution was washed with brine and dried over sodium sulfate. Evaporation of solvent in vacuo gave a brown mixture which was separated and purified by preparative-layer chromatography, using ether-hexane (1:1) as solvent, to give 75 mg (53.8%) of 2-carbethoxynitromethylidene-5-carbethoxy-4, 4-dimethylthiazolidine (59): ir (film) 3310 (NH), 1740 (C=O), 1685 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.30 (6H, t, J=7 Hz), 1.38 (3H, s), 1.57 (3H, s), 4.25 (4H, q), 4.33 (1H, s), 6.95 (1H, broad).

2-Amino-5-carbethoxy-4, 4-dimethyl-2-thiazoline (60)

A solution of 385 mg (2. 69 mmol) of 2-carbethoxy-3, 3-dimethylaziridine (56) in 8 ml of formic acid was stirred at 60° C for 30 min and 407 mg of potassium thiocyanate was added at once. The mixture was warmed to 80° C and stirred overnight. After the reaction mixture was cooled to room temperature, 10 ml of water was added and solid sodium bicarbonate was added until the pH reached 8. The organic layer was extracted with ether and the extract was washed with sodium bicarbonate solution and brine and dried over sodium sulfate. Evaporation of solvent in vacuo gave a brown oil that crystallized on standing. Pure 2-amino-5-carbethoxy-4, 4-dimethyl-2-thiazoline (60) was obtained by recrystallization from hexane-ether, (510 mg, 93. 5%): mp 103-104° C; ir (Nujol) 3510 (NH), 1730 (C=O), 1670, 1615 cm^{-1}; nmr ($CDCl_3$) δ 1. 26 (3H, s), 1. 29 (3H, t, J=7 Hz), 1. 47 (3H, s), 4. 20 (2H, q), 4. 30 (1H, s), 5. 31 (2H, broad s); mass spectrum m/e 202 (M^+).

Anal. Calcd for $C_8H_{14}N_2O_2S$: C, 47. 50; H, 6. 98; N, 13. 85. Found: C, 47. 34; H, 7. 06; N, 13. 89.

3-Benzyl-5-isopropylidenehydantoin-2-thione (61)

A solution of 385 mg (2. 69 mmol) of 2-carbethoxy-3, 3-dimethylaziridine (56) and 626 mg of benzylisothiocyanate in 10 ml of dry

benzene was refluxed overnight. After the reaction mixture was cooled to room temperature, the white precipitate was filtered and washed with a small amount of ether to give 294 mg of colorless crystalline material. The combined filtrate was washed with aqueous sodium bicarbonate and brine and dried over sodium sulfate. Removal of solvent in vacuo gave colorless crystals, which were combined with the first crop and recrystallized from a chloroform-hexane mixture to give 579 mg (87.5%) of 3-benzyl-5-isopropylidene-hydantoin-2-thione (61): mp 202.5-203° C; ir (Nujol) 3195 (NH), 1730 (C=O), 1665 (C=C), 1498 (NH) cm^{-1}; nmr (d_6-DMSO) δ 2.00 (3H, s), 2.22 (3H, s), 4.97 (2H, s), 7.32 (5H, m), 11.92 (1H, broad s); mass spectrum m/e 246 (M^+).

Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.38; H, 5.73; N, 11.37. Found: C, 63.20; H, 5.69; N, 11.47.

N-Acetyl-2-carbethoxy-3,3-dimethylaziridine (62)

A solution of 1.54 g (10.8 mmol) of 2-carbethoxy-3,3-dimethylaziridine (56) and 0.9 ml of pyridine in 4 ml of acetic anhydride was stirred at room temperature for 8 hr. The resulting solution was poured into 30 ml of ice-water. The aqueous mixture was neutralized by solid sodium bicarbonate and the organic layer was extracted twice with ether. The ether extracts were washed with brine and dried over sodium sulfate. Removal of solvent in vacuo gave 1.77 g of yellow oil

which was distilled under reduced pressure to give 1.57 g (78.8%) of pure N-acetyl-2-carbethoxy-3,3-dimethylaziridine (62): bp 120° C (0.6 mm); ir (film) 1750, 1700 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.28 (3H, t, J=7 Hz), 1.42 (6H, s), 2.13 (3H, s), 3.02 (1H, s), 4.24 (2H, q); mass spectrum m/e 185 (M^+).

Glycinamide Hydrochloride (63)[37]

To a saturated aqueous ammonia solution (1 ℓ), 122.56 g (1 mol) of ethyl chloroacetate was added dropwise under cooling with an ice-water bath. During the addition of ethyl chloroacetate, ammonia gas was bubbled into the mixture until the organic phase disappeared. The resulting mixture was further stirred at room temperature for three days. The solution was saturated with ammonia gas once each day while stirring. The reaction mixture was evaporated in vacuo to remove excess ammonia and then dried under high vacuum below 40°C, yielding colorless crystals. The solid was filtered and washed with a small portion of methanol and dried over phosphorus pentoxide to give 83.5 g (75.5%) of glycinamide hydrochloride (63). This material was used for the next step without further purification: mp > 250° C; ir (Nujol) 3500-2500, 1700 (C=O) cm^{-1}.

2-Thioxo-5-thiazolidone (64)[38]

To a solution of 50 g (0.452 mol) of glycinamide hydrochloride

(63) in 170 ml of aqueous saturated ammonia solution was added a solution of 50 ml of carbon disulfide in 100 ml of 100% ethanol at room temperature. The mixture was initially a yellow-orange color and changed to a deep orange color upon further stirring. The mixture was stirred overnight at room temperature and was concentrated in vacuo to ca. 100 ml. The mixture was acidified with dilute hydrochloric acid and the precipitate was filtered and washed with water. The filtrate was further concentrated in vacuo to give a second crop. This process was repeated two more times and the combined yellow crystals were dried over phosphorus pentoxide under reduced pressure to yield 32.6 g (54.1%) of 2-thioxo-5-thiazolidone (64): mp 163-165° C (transition point) and > 270° C (lit.[67] mp > 300° C); ir (Nujol) 3260 (NH), 1700 (broad C=O), 1510 cm^{-1}; nmr ($CDCl_3$ and d_6-DMSO) δ 4.57 (2H, s), ca. 11.05 (1H, broad).

4-Isopropylidene-2-thioxo-5-thiazolidone (65)

According to the method of Miller et al.,[40] a suspension of 10 g (75.1 mmol) of 2-thioxo-5-thiazolidone (64) in 103 ml of dry acetone was prepared and 0.6 ml of benzylamine was added. After addition of benzylamine was complete, the mixture had a red color. Ca. 20 minutes later the suspension had dissolved to a deep purple solution, after which a precipitate appeared. The precipitate was filtered and washed with ether. The filtrate was concentrated and cooled to give

a second crop, which was collected by filtration and washed with ether. This procedure was repeated three more times to afford 10.5 g (81%) of yellow 4-isopropylidene-2-thioxo-5-thiazolidone (65): mp 202-203.5° C (lit.[36] mp 211° C); ir (Nujol) 3290 (NH), 1680 (C=O), 1600 (C=C) cm^{-1}; nmr (d_6-DMSO) δ 2.11 (3H, s), 2.17 (3H, s), 12.6 (1H, broad).

4-Carbethoxy-5, 5-dimethylthiazolidine-2-thione (66)

A. From 65[41]

To a warm solution of 2.0 g of potassium hydroxide in 35 ml of methanol was added 2.47 g (14.25 mmol) of 4-isopropylidene-2-thioxo-5-thiazolidone (65) at once. The resulting mixture was stirred for 24 hr at room temperature. The solution, after filtration, was evaporated in vacuo to a syrup which was dissolved in 20 ml of water and acidified with dilute hydrochloric acid. The organic layer was extracted twice with ethyl acetate. The extracts were washed with aqueous sodium bicarbonate and brine and dried over sodium sulfate. Evaporation of solvent in vacuo gave 820 mg of a neutral compound which was recrystallized from chloroform-hexane to yield 750 mg (26.6%) of 4-carbomethoxy-5, 5-dimethyl-thiazolidine-2-thione (66): mp 105.5-107° C (lit.[41] mp 106-107° C); ir (Nujol) 3380 (NH), 1738 (C=O), 1480 cm^{-1}; nmr ($CDCl_3$) δ 1.50 (3H, s), 1.72 (3H, s), 3.88

(3H, s), 4.68 (1H, s), 8.16 (1H, broad); mass spectrum m/e 205 (M^+).

The alkaline extract was acidified with dilute hydrochloric acid and the organic layer was extracted twice with ethyl acetate. The extracts were washed with aqueous sodium chloride and dried over sodium sulfate. Removal of solvent in vacuo afforded 1.97 g (72.2%) of 4-carboxy-5,5-dimethylthiazolidine-2-thione (67) which was recrystallized from a chloroform-hexane mixture; mp 148-149° C (lit.[41] mp 148° C); ir (Nujol) 3380 (NH), 1740 (C=O), 1470 cm^{-1}; nmr ($CDCl_3$ and d_6-DMSO) δ 1.52 (3H, s), 1.70 (3H, s), 4.57 (1H, s), 8.99 (1H, broad), 10.81 (1H, broad).

B. From 67

1. A mixture of 3.0 g (15.7 mmol) of 67, 30 ml of dry benzene, 20 ml of dry methanol, and 0.3 ml of concentrated sulfuric acid was refluxed for 24 hr. The reaction mixture was concentrated in vacuo and 20 ml of aqueous sodium bicarbonate was added to the cold residue (0-5° C). The organic phase was extracted twice with ethyl acetate and the extracts were washed with aqueous sodium bicarbonate and brine and dried over sodium sulfate. Evaporation of solvent in vacuo afforded 3.17 g (98.3%) of crystalline methyl ester 66 which was recrystallized from a chloroform-hexane mixture. The ir and nmr spectra of this material were identical with those of material prepared as described in method A above.

2. According to Marshall et al., [42] a cold solution of (0-4° C) of 1.04 g (5.44 mmol) of 67 in 10 ml of dry methanol was prepared and 0.81 ml (6.31 mmol) of boron trifluoride etherate was added with stirring. The resulting mixture was refluxed for 20 hr. The reaction mixture was concentrated to ca. 3 ml in vacuo at room temperature and the residue was poured into 20 ml of ice-water. The organic layer was extracted twice with ether and the extracts were washed with aqueous sodium bicarbonate and brine and dried over sodium sulfate. Evaporation of the solvent in vacuo gave 1.11 g of partially solidified material which was recrystallized from an ether-hexane mixture to afford 747 mg (66.9%) of methyl ester 66, identical with material prepared as described above.

4-Carbethoxy-5, 5-dimethyl-2-methylthio-2-thiazoline (68)

A. With Diazomethane

To a cold solution of 2.0 g (10.4 mmol) of 2-thiothiazolidine 67 in 8 ml of ether was added a large excess of a cold ether solution of diazomethane. The resulting solution was allowed to stand several hours at room temperature and the ether solution was washed with brine and dried over sodium sulfate. Removal of solvent in vacuo followed by vacuum distillation (110-120° C/0.2 mm) gave 2.28 g of light yellow oil. The nmr spectrum of this oil showed that there were

4-carbomethoxy-5, 5-dimethyl-2-methylthio-2-thiazoline (68) and 4-carbomethoxy-5, 5-dimethyl-N-methylthiazolidine-2-thione (69) with the ratio of 68:69 as 82:18 by integration. The two products were separated by preparative-layer chromatography or column chromatography with ether-hexane as solvent to give 68: (lit.[41] bp 82-83° C/0.15 mm); ir (film) 1755 (C=O), 1730, 1555 (C=N) cm^{-1}; nmr ($CDCl_3$) δ 1.40 (3H, s), 1.70 (3H, s), 2.55 (3H, s), 3.82 (3H, s), 4.66 (1H, s) and 69: ir (film) 1750 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.43 (3H, s), 1.70 (3H, s), 3.38 (3H, s), 3.88 (3H, s), 4.45 (1H, s).

B. With Iodomethane

To a solution of 100 mg (0.487 mmol) of 66 and 69 mg (0.487 mmol) of iodomethane in 3 ml of dry tetrahydrofuran was added 54 mg (75 µl) of dry triethylamine dropwise at room temperature with stirring. The resulting solution was heated at 44° C and stirred overnight. A further 19 mg of iodomethane was added with stirring. Ca. 20 ml of water was added to the reaction mixture and the organic phase was extracted twice with ether. The extracts were washed with saturated cupric sulfate solution and brine and dried over sodium sulfate. Removal of solvent in vacuo gave 165 mg of oil which was distilled at 105° C (0.2 mm) to yield 100 mg (93.6%) of 68. The ir and nmr spectra of this compound were identical with those of material prepared by method A.

4-Carbomethoxy-2-dicarbethoxymethylidene-5,5-dimethylthiazolidine (70)

To a solution of 1.384 g (6.74 mmol) of 66 in 45 ml of dry chloroform was added 1.93 g (8.09 mmol) of diethyl bromomalonate followed by 0.64 g (8.09 mmol) of dry pyridine dropwise at room temperature. The resulting solution was stirred for 24 hr at 60-61° C and a further 0.49 g of diethyl bromomalonate was added.[43] The mixture was stirred for 24 hr. After cooling to room temperature, the solvent was evaporated *in vacuo* and 50 ml of ether was added. The precipitated sulfur was filtered off and the filtrate was washed with saturated cupric sulfate solution and brine and dried over sodium sulfate. Evaporation of the solvent *in vacuo*, followed by column chromatography on Kieselgel Woelm (activity 3, with ether-hexane 1:1 as eluent) gave 2.13 g (95.4%) of 4-carbomethoxy-2-dicarbethoxymethylidene-5,5-dimethylthiazolidine (70): ir (film) 3245 (NH), 1750, 1710, 1668, 1640, 1530 cm^{-1}; nmr ($CDCl_3$) δ 1.31 (6H, t, J=7 Hz), 1.38 (3H, s), 1.68 (3H, s), 3.85 (3H, s), 4.23 (2H, q), 4.48 (1H, s), 10.01 (1H, broad); mass spectrum m/e 331.108; calcd for $C_{14}H_{21}NO_6S$: 331.109.

2-Carbethoxymethylthio-4-carbomethoxy-5,5-dimethyl-2-thiazoline (72)

A solution of 200 mg (0.974 mmol) of 66 and 244 mg (1.46 mmol)

of ethyl α-bromoacetate in 8 ml of dry dichloromethane was stirred at 30° C for 24 hr. A further 122 mg of ethyl α-bromoacetate was added and the resulting mixture was stirred for 48 hr (addition of an equivalent amount of triethylamine reduced the reaction time).[43] Ca. 20 ml of ether and 10 ml of aqueous sodium bicarbonate were added to the reaction mixture and the organic phase was separated, washed with brine and dried over sodium sulfate. Removal of solvent in vacuo, followed by column chromatography with Florisil and ether-hexane (1:1) as eluent, gave 230 mg (81%) of 2-carbethoxymethylthio-4-carbomethoxy-5, 5-dimethyl-2-thiazoline (72): ir (film) 1762, 1740, 1558 cm^{-1}; nmr ($CDCl_3$) δ 1.26 (3H, t), 1.38 (3H, s), 1.69 (3H, s), 3.79 (3H, s), 3.95 (2H, s), 4.22 (2H, q), 4.61 (1H, s); mass spectrum m/e 291.061; calcd for $C_{11}H_{17}NO_4S_2$: 291.060.

2-Dicarbethoxymethylidene-5, 5-dimethyl-4-hydroxymethylthiazolidine (71)

A. By Reduction of 70 with Sodium Borohydride

A mixture of 56 mg (0.169 mmol) of 70 and 6.4 mg of sodium borohydride in 4 ml of 100% ethanol was stirred at room temperature for 24 hr.[45] The solvent was removed at room temperature under reduced pressure and 10 ml of water and 15 ml of ether were added. The ether extract was washed with brine and dried over sodium sulfate. Removal of solvent in vacuo gave 49 mg of an oil, the tlc

of which showed two spots at R_f values 0.26 and 0.53. The compound (R_f 0.26, 37 mg, 72.2%) was identified to 2-dicarbethoxymethylidene-5,5-dimethyl-4-hydroxymethylthiazolidine (71): ir (film) 3500 (OH), 3310 (NH), 1670, 1635, 1530 cm^{-1}; nmr ($CDCl_3$) δ 1.29 (6H, t, J=7 Hz), 1.36 (3H, s), 1.52 (3H, s), 3.09 (1H, broad), 3.81 (3H, s), 4.22 (4H, q), 9.96 (1H, broad); mass spectrum m/e 303.114; calcd for $C_{13}H_{21}NO_5S$: 303.114. The compound with R_f value 0.53 was not identified.

B. By Reduction of 70 with "Copper Hydride" Complex

According to the method of Semmelhack,[46] a suspension of 137 mg (0.954 mmol) of cuprous bromide in 1.8 ml of dry tetrahydrofuran was prepared and 620 μl of 60% Vitride (1.91 mmol) was added dropwise at -10° to 0° C with stirring. The mixture was stirred for 30 min, cooled to -60° C, and a solution of 39.5 mg (0.119 mmol) of 70 in 0.5 ml of dry tetrahydrofuran was added dropwise. The resulting dark colored suspension was stirred at -30° to -20° C for 1 hr and quenched with 0.5 ml of water followed by 0.5 ml of acetic acid. The reaction mixture was concentrated in vacuo at 0° C and the organic layer was extracted twice with ether. The extracts were washed with aqueous sodium bicarbonate and brine and dried over sodium sulfate. After evaporation of the solvent in vacuo, the tlc of this sample showed spots at R_f values 0.75, 0.69, 0.62, and 0.24. The material

with R_f value 0.24 was isolated and purified by preparative-layer chromatography to afford 15 mg (41.5%) of 2-dicarbethoxymethylidene-5,5-dimethyl-4-hydroxymethylthiazolidine (71). The ir and nmr spectra of this compound were identical with those of material prepared as described in method A.

Preparation of Compound 74

A solution of 0.29 ml of 2.6 M butyllithium in hexane, precooled to -70° C, was added dropwise at -110° C to a solution of 86.2 mg (0.755 mmol) of ethyl diazoacetate in 3.2 ml of ether-tetrahydrofuran mixture (3:1) over a period of 30 min. The resulting solution was stirred an additional 20 min at -110° C.[29] A solution of 150 mg (0.684 mmol) of 2-methylthiothiazoline 68 in 1 ml of dry tetrahydrofuran, precooled to -70° C, was added dropwise to the above solution at -110° C over 35 min. The mixture was allowed to warm to -25° C slowly (3 hr). The solution was cooled to -50° C again and a solution of 46 mg (0.755 mmol) of acetic acid in 1 ml of dry tetrahydrofuran was added slowly, after which the mixture was allowed to warm to room temperature. The solution was concentrated in vacuo below 40° C and the residue was taken up twice into ether. The ether solutions were washed with aqueous sodium bicarbonate and brine and dried over sodium sulfate. Removal of solvent in vacuo gave 212 mg of brown oil which was purified by preparative-layer chromatography, using an ether-hexane (1:1)

mixture as solvent, to give 60 mg of 68 and 89.2 mg (39.1%; 65.3% based on consumed starting material) of 74. This product crystallized on standing and was recrystallized from an ether-hexane mixture; mp 96.5-97.5° C; ir (Nujol) 3310 (NH), 1735 and 1685 (C=O), 1555, 1525 cm^{-1}; nmr ($CDCl_3$) δ 1.27 (3H, t, J=7 Hz), 1.48 (3H, s), 1.63 (3H, s), 2.54 (3H, s), 3.85 (3H, s), 4.22 (2H, q), 7.06 (1H, s), 7.33 (1H, broad s); mass spectrum m/e 333 (M^+).

Anal. Calcd for $C_{12}H_{19}N_3O_4S_2$: C, 43.22; H, 5.74; N, 12.60. Found: C, 43.30; H, 5.75; N, 12.84.

4-Carbomethoxy-5,5-dimethyl-2-thiazolidone (76)

Following a procedure of Cook et al.,[53] 63 ml of 3% hydrogen peroxide was added dropwise to a solution of 2.279 g (11.92 mmol) of 67 in 54 ml of 1 N potassium hydroxide at room temperature with stirring. During the addition, the temperature rose to 41° C and began to drop after 20 min. After stirring for 5 hr, the mixture was concentrated in vacuo and the residue was acidified with dilute hydrochloric acid at 0-5° C. The organic layer was extracted four times with ethyl acetate and the extracts were washed with brine and the combined extract was dried over sodium sulfate. Removal of solvent in vacuo gave 1.139 g of a crystalline solid. This material was used for esterification without further purification. A mixture of 980 mg of 75 in ether was treated with an excess of ethereal diazomethane,

and the resulting yellow solution was allowed to stand for 10 hr at room temperature. The usual work up yielded 1.23 g (54.6% based on 67) of crystalline 4-carbomethoxy-5, 5-dimethyl-2-thiazolidone (76) which was recrystallized from an ether-hexane mixture: mp 82-82.5° C (lit.[53] mp 82-83° C); ir (Nujol) 3250 (NH), 1745 (C=O), 1680 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.47 (3H, s), 1.71 (3H, s), 3.83 (3H, s), 4.32 (1H, s), 6.92 (1H, broad).

4-Carbomethoxy-5, 5-dimethyl-N-phthalimidoacetyl-2-thiazolidone (77)

Thiazolidine 76 (100 mg, 0.528 mmol) was stirred with 25.7 mg of 57% sodium hydride dispersion in 3.5 ml of dry benzene at room temperature until evolution of hydrogen ceased. A solution of 124 mg (0.555 mmol) of phthalimidoacetyl chloride in 1.2 ml of dry benzene was added dropwise at room temperature with stirring and the resulting mixture was stirred for 24 hr at room temperature.[40] Ca. 10 ml of water was added to the reaction mixture, the organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The extracts were washed with aqueous sodium bicarbonate and brine, and dried over sodium sulfate. The combined extract was concentrated in vacuo to yield 203 mg (102%) of crystalline 4-carbomethoxy-5, 5-dimethyl-N-phthalimidoacetyl-2-thiazolidone (77) which was recrystallized from a chloroform-hexane mixture: mp 200-201° C;

UV λ_{max}^{EtOH} 296 (ε 2090), 242 (ε 17850) nm; ir (Nujol) 1778, 1745, 1730, 1693 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.50 (3H, s), 1.76 (3H, s), 3.77 (3H, s), 4.70 (1H, s), 4.95 (1H, d, J=18 Hz), 5.04 (1H, d, J=18 Hz), 7.81 (4H, m); mass spectrum m/e 376 (M^+).

Anal. Calcd for $C_{17}H_{16}N_2O_6S$: C, 54.24; H, 4.29; N, 7.44. Found: C, 54.03; H, 4.33; N, 7.33.

4-Carbomethoxy-5, 5-dimethyl-N-phthalimidoacetyl-2-thioxothiazolidine (78)

A mixture of 108.5 mg (0.528 mmol) of 66 and 25.7 mg (0.610 mmol) of 57% sodium hydride dispersion in 2.5 ml of dry benzene was stirred until evolution of hydrogen ceased. A solution of 124 mg (0.555 mmol) of phthalimidoacetyl chloride in 1 ml of dry benzene was added dropwise at room temperature under stirring.[40] The resulting mixture was stirred for 24 hr at room temperature and 10 ml of water was added. The organic layer was separated, the aqueous layer was extracted with ethyl acetate, and the extracts were washed with aqueous sodium bicarbonate and brine. After drying over sodium sulfate, evaporation of solvent in vacuo gave 204 mg (98.5%) of yellow, crystalline 4-carbomethoxy-5, 5-dimethyl-N-phthalimidacetyl-2-thioxothiazolidine (78) which was recrystallized from a dichloromethane-hexane mixture: mp 202-203° C; UV λ_{max}^{EtOH} 306 (ε 13750), 267 (ε 16860), 240 (ε 10710) nm; ir (Nujol) 1775, 1746, 1724, 1695

(4 C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.45 (3H, s), 1.76 (3H, s), 3.80 (3H, s), 5.05 (1H, s), 5.22 (1H, d, J=18 Hz), 5.45 (1H, d, J=18 Hz), 7.81 (4H, m); mass spectrum m/e 392 (M^+).

Anal. Calcd for $C_{17}H_{16}N_2O_5S_2$: C, 52.02; H, 4.11; N, 7.14. Found: C, 52.01; H, 4.18; N, 7.04.

Photolysis of 4-Carbomethoxy-5, 5-dimethyl-N-phthalimidacetyl-2-thiazolidone (77)

A solution of 120 mg (0.319 mmol) of 77 in 100 ml of dry tert-butanol and 20 ml of dry benzene was photolyzed at 5-8 °C for 3.5 hr under nitrogen using a Hanovia medium-pressure lamp and a Pyrex glass filter. The solvent was evaporated below 25° C and the analytical tlc (dichloromethane-ethyl acetate 21:2) of this residue showed six spots at R_f values 0.79, 0.68, 0.62, 0.44, 0.36 and 0.25. The components with R_f values 0.36 and 0.68 were isolated and purified by preparative-layer chromatography to give 55 mg of 4-carbomethoxy-5, 5-dimethyl-2-thiazolidone (76) and 10 mg of starting material 77 respectively. The ir and nmr spectra of these compounds were identical with those of the previously prepared samples.

Photolysis of 4-Carbomethoxy-5, 5-dimethyl-N-phthalimidacetyl-2-thioxothiazolidine (78)

Photolysis of 120 mg (0.306 mmol) of 78 in 120 ml of dry benzene and 20 ml of dry tert-butanol was carried out at 5-8° C for

9 hr under nitrogen using a Hanovia medium-pressure mercury lamp and a Pyrex glass filter. The reaction mixture was concentrated below room temperature under reduced pressure. The analytical tlc of the residue showed spots at R_f values 0.83, 0.77, 0.71, 0.65 and 0.35. The compounds with R_f values 0.83, 0.77 and 0.35 were isolated and purified by preparative-layer chromatography, using a mixture of dichloromethane-ethyl acetate (21:2) as solvent to give 9 mg of N-methylphthalimide (79), 21 mg of 4-carbomethoxy-5, 5-dimethyl-N-phthalimidacetyl-2-thiazolidone (77) and 26 mg of 4-carbomethoxy-5, 5-dimethyl-2-thiazolidone (76) respectively.

N-Hydroxymethylacetamide (84)

According to the method of Sekiya,[68] a mixture of 95 g (1.61 mol) of acetamide, 10 g of potassium carbonate, and 120 ml of 37% formaldehyde was stirred at 50° C for several minutes. It was then allowed to stir at room temperature overnight. Carbon dioxide was bubbled into the solution to neutralize it. The excess water was evaporated *in vacuo* below 50° C. The precipitate was filtered, 150 ml of 1:1 mixture of dry ethanol and dry benzene was added to the filtrate, and the solution was dried *in vacuo* by azeotropic distillation. This drying process was repeated several times and the residue was dried in a vacuum desiccator over phosphorus pentoxide to yield 85 g of N-hydroxymethylacetamide (84); ir (film) 3380, 1670 (C=O),

1540 cm^{-1}; nmr (d_6-DMSO) δ 1.83 (3H, s), 4.51 (2H, s), ca. 6.3 (2H, broad).

S-Acetamidomethyl-L-cysteine Hydrochloride (85)

According to the method of Veber,[62] a mixture of 14.6 g (16.4 mmol) of N-hydroxymethylacetamide (84) and 25 g (14.3 mmol) of L-cysteine hydrochloride monohydrate, dissolved in 38 ml of water, was stirred under nitrogen and cooled in an ice-water bath. Concentrated hydrochloric acid (5.5 ml) was added dropwise to this mixture (pH ~ 0.5). The resulting solution was allowed to stir at room temperature under nitrogen for 2.5 days. The excess water was evaporated in vacuo below 40° C and remaining traces of water were removed by azeotropic distillation with a dry benzene-ethanol mixture. After the residue was dried in the desiccator in vacuo over phosphorus pentoxide, the oil crystallized. The crystalline material was dissolved in a minimum quantity of methanol and dry ether was added to the cloud point. The mixture was refrigerated for several days. The colorless crystalline solid was removed by filtration, washed with dry ether and dried in vacuo to give 16.0 g of S-acetamidomethyl-L-cysteine hydrochloride (85); mp 157-160° C decomp. (lit.[62] mp 159-163° C decomp.); ir (Nujol) 3300, 1720, 1600 cm^{-1}; nmr (d_6-DMSO) δ 1.86 (3H, s), 3.36 (2H, m), 4.08-4.46 (3H, m), 8.72 (2H, broad), 8.79 (1H, t, J=6 Hz), 10.5 (2H, broad). The nmr

spectrum shows that this compound contains an impurity, possibly thiazolidine-2-carboxylic acid. This material was used for next reaction without further purification.

N-tert-Butoxycarbonyl-S-acetamidomethyl-L-cysteine (86)[62]

To a solution of 39 g (175 mmol) of L-cysteine hydrochloride 85 in 350 ml of dry dimethylformamide was added dropwise 40.3 g (0.35 mol) of tetramethylguanidine over 15 min, while maintaining the reaction under nitrogen atmosphere and a temperature of 22-23° C. tert-Butoxycarbonylazide (27.6 g, 193 mmol) was added dropwise at 22° C over a period of 15 min and an additional 20.15 g (175 mmol) of tetramethylguanidine was added dropwise. The mixture was stirred at room temperature for 40 hr. The white precipitate was filtered and washed with ethyl acetate. The filtrate was concentrated in vacuo at 30-35° C and 150 ml of water was added. The aqueous mixture was extracted twice with 100 ml portions of ethyl acetate. After cooling the aqueous phase in an ice bath, the solution was adjusted to pH 3 with 50% aqueous citric acid and saturated with sodium chloride. The organic layer was extracted three times with 100 ml portions of ethyl acetate and the combined extract was washed three times with brine and dried over sodium sulfate. Evaporation in vacuo gave a highly viscous oil. This material was purified by column chromatography on 300 g of Florisil. Elution with an ethyl acetate-ether mixture (1:1)

gave 23.5 g (46%) of N-tert-butoxycarbonyl-S-acetamidomethyl-L-cysteine (86) which could be obtained only as an amorphous solid: (lit.[62] mp 110-112° C decomp.); ir ($CHCl_3$) 3300 (NH), 1710-1650 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.44 (9H, s), 2.05 (3H, s), 3.10 (2H, broad), 4.43 (3H, broad), 5.92 (1H, broad d, J=8 Hz), 7.82 (1H, broad), 9.41 (1H, broad).

Preparation of 88

To a solution of 1.0 g (3.42 mmol) of 86 in 10 ml of tetrahydrofuran was added a solution of 540 mg (3.77 mmol) of 56 in 1 ml of tetrahydrofuran under nitrogen at room temperature. The solution was cooled with an ice-salt bath and a solution of 776 mg (3.76 mmol) of dicyclohexylcarbodiimide in 2 ml of tetrahydrofuran was added dropwise over a period of 15 min. The resulting mixture was stirred at -5° C for 1 hr and the flask was kept in the refrigerator for 2 days. The mixture was filtered, 50 ml of ether was added to the filtrate, and the mixture was filtered again. The filtrate was evaporated in vacuo below 40° C to give a highly viscous oil. This oil was purified by column chromatography on Florisil (60 g) with ether-hexane (1:5) and ether as eluents, giving 940 mg (66%) of 88; ir (film) 3360 (NH), 1750-1650 (C=O broad), 1520 (NH) cm^{-1}; nmr ($CDCl_3$) δ 1.31 (3H, t, J=7 Hz), 1.44 (15H, s), 2.01 (3H, s), ca. 3.1 (1H, s), 3.19 (2H, m), 4.14-4.62 (5H, m), 5.72 (1H, m), 7.42 (1H, broad); mass spectrum m/e 417.194 (M^+); calcd for $C_{18}H_{31}N_3O_6S$: 417.193.

Preparation of 87

To a solution of 2.5 g (8.54 mmol) of 86 in 34 ml of dry tetrahydrofuran at 0° C under nitrogen was added a solution of 0.984 g (8.54 mmol) of N-hydroxysuccinimide in 1.5 ml of dry tetrahydrofuran followed by a solution of 2.03 g (9.82 mmol) of dicyclohexylcarbodiimide in 7 ml of dry tetrahydrofuran. The mixture was stirred at -5° C for 2 hr and the flask was placed in the refrigerator overnight. The mixture was filtered and 20 ml of ether was added to the filtrate. The ether solution was filtered and the filtrate was evaporated under reduced pressure leaving a highly viscous oil which was purified by column chromatography on Florisil (60 g) with ether as eluent. This yielded 0.50 g (15%) of 87; (lit.[56] mp 106-108° C) ir (film) 3400, 1810, 1780, 1740, 1720, 1670 cm^{-1}; nmr ($CDCl_3$) δ 1.45 (9H, s), 2.02 (3H, s), 2.98 (2H, m), 3.77 (4H, s), 4.38 (2H, d, J=6 Hz), ca. 4.5 (1H, m), 5.58 (1H, broad d, J=8 Hz), 6.95 (1H, broad).

Photolysis of Compound 88

Photolysis of 287 mg (0.681 mmol) of 88 in 160 ml of distilled benzene was carried out at 20° C for 25 hr, using a Hanovia medium-pressure mercury lamp and a Pyrex filter. The solvent was removed in vacuo to give 295 mg of a brown oil, the tlc of which showed two major spots at R_f 0.33 and 0.27. This mixture was

separated and purified by preparative layer chromatography with ether as solvent, to give 68 mg of 91a (R_f 0.33): ir (film) 3350 (NH), 1745 (C=O), 1655 (broad C=O), 1515 (NH broad) cm^{-1}; nmr ($CDCl_3$) δ 1.27 (3H, t, J=7 Hz), 1.50 (9H, s), 1.85 (3H, broad s), 2.05 (3H, s), 2.87 (2H, m), 4.23 (2H, q), 4.3-4.8 (4H), 5.07 (2H, d, J=3 Hz), 5.68 (1H, d, J=8 Hz), 7.66 (2H); mass spectrum m/e 417 (M^+). In addition, 42 mg of 91b (R_f 0.27): ir (film) 3400 (NH), 3130, 1745-1650 (C=O and C=C, broad) cm^{-1}; nmr ($CDCl_3$) δ 1.25 (3H, t, J=7 Hz), 1.45 (9H, s), 1.78 (3H, broad s), 2.02 (3H, s), 2.90 (2H, d, J=6.5 Hz), 4.22 (2H, q), 4.3-4.6 (4H), 5.06 (2H, d, J=3.5 Hz), 6.76 (1H, d, J=8 Hz), 7.57 (2H); mass spectrum m/e 417 (M^+) was obtained. These two compounds are evidently diastereomers.

Attempted Cyclization of 91a and 91b

A solution of 202 mg (0.467 mmol) of a mixture of 91a and 91b in 10 ml of tetrahydrofuran was adjusted to pH 4 with acetic acid. Mercuric acetate (164 mg, 0.514 mmol) was added in one lot and the resulting solution was readjusted to pH 4 with acetic acid and stirred for 1 hr at room temperature. Hydrogen sulfide was bubbled into the solution to precipitate mercuric ion and the mixture was filtered.[62] The filtrate was adjusted to pH 7 with aqueous sodium bicarbonate and the solution was evaporated in vacuo. The residue was taken up into ethyl acetate and the extract was washed with brine and dried

over sodium sulfate. Removal of solvent in vacuo gave 76 mg of a highly viscous oil: ir (film) 3400 (NH), 1740-1650 (broad C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.29 (6H, t), 1.40 (18H, s), 1.74 (6H, broad s), 3.3-3.6 (4H, m), 4.27 (4H, q), ca. 4.6 (2H), 5.08 (4H, d), 6.00 (2H, m), 7.56 (2H). The spectral properties of this compound are in accord with its formulation as a disulfide.

N, N'-Diphenylacetylcystine (94)[64]

L-Cystine (93) (10 g, 41.6 mmol) was dissolved in 33 ml of 10% aqueous sodium hydroxide and diluted with 33 ml of water. The resulting solution was cooled to 20° C with an ice-water bath and 12.9 g (83.2 mmol) of α-phenylacetyl chloride was added dropwise over a period of 1 hr. During the addition, another 33 ml of 10% aqueous sodium hydroxide was added in several portions to maintain the mixture slightly alkaline. After additional stirring for 1 hr, concentrated hydrochloric acid was added until the pH reached 1-2. After the solvent was decanted, the gummy material was washed with water and ether. The precipitate was dissolved in hot aqueous ethanol (1:1) and hot water was added to cloud point. The mixture was allowed to stand overnight and the precipitate was filtered and washed with hot carbon tetrachloride to remove phenylacetic acid. The solid was dried in vacuo over phosphorus pentoxide to give 12.81 g (74%) of 94; mp 137-139° C (lit.[64] mp 119-120° C); ir (Nujol) 3420 (NH), 3300-2500

(COOH), 1745, 1720, 1665 (C=O) cm^{-1}; nmr (d_6-DMSO) δ 3.18 (4H, m), 3.50 (4H, s), 4.52 (2H, m), 7.26 (10H, s), 8.53 (2H, d, J=8 Hz).

S-Phenacyl-N-phenylacetylcysteine (95)[63]

To a solution of 2.0 g (4.2 mmol) of N, N'-diphenylacetylcystine (94) in ca. 100 ml of dry, liquid ammonia at the boiling point was added 560 mg (24.4 mmol) of sodium metal in portions until a blue color persisted for a few minutes. Acetic acid was added to discharge the color and then 1.3 g (8.4 mmol) of phenacyl chloride was added in portions for 20 min. The mixture was stirred at the boiling point for 2 hr and the ammonia was evaporated in vacuo. To the residue was added 100 ml of water and the aqueous solution was extracted with ethyl acetate. The extract was washed twice with aqueous sodium bicarbonate. The combined alkaline extract was neutralized with dilute hydrochloric acid and extracted twice with ethyl acetate. The extracts were washed four times with brine and dried over sodium sulfate. Removal of the solvent gave 2.3 g (67.1%) of 95 as an oil which crystallized on standing for several days: mp 153-156° C (lit.[69] mp 143-155° C). This compound was used without further purification.

N, N'-Bis-tert-butoxycarbonylcystine (96)

Following the method of Photaki,[65] 25 ml of tert-butoxycarbonyl-azide was added during 15 min to a cold, stirred suspension of 10.5 g

(43.7 mmol) of L-cystine (93) in a mixture of 435 ml of dioxane and 175 ml of 0.5 N sodium hydroxide. Stirring was continued at room temperature for 18 hr. During the first 9 hr, 90 ml of 1 N sodium hydroxide was added in nine equal portions. The mixture was filtered to remove the precipitate of cystine which had not reacted. Dioxane was removed by evaporation in vacuo and the remaining solution was extracted with ethyl acetate. The aqueous layer was acidified with cold dilute sulfuric acid. After evaporation of some water in vacuo, refrigeration of the residue followed by filtration gave 2.7 g (14.0%) N, N'-bis-tert-butoxycarbonylcystine (96): mp 139-141.5° C decomp. (lit.[65] mp 145-146° C); ir (Nujol) 3500 (NH), 3400-2600 (COOH), 1745, 1690 (C=O), 1515 cm^{-1}; nmr (d_6-DMSO) δ 1.39 (18H, s), 2.94 (2H, dd, J=13.7 and 8.2 Hz), 3.28 (2H, dd, J=4.2 and 13.7 Hz), 4.15 (2H, m), 4.82 (2H, s), 6.44 (2H, d, J=7.5 Hz).

N-tert-Butoxycarbonyl-S-phenacylcysteine (97)

To a solution of 1.1 g (2.5 mmol) of 96 in 100 ml of dry liquid ammonia at the boiling point was added 400 mg of sodium metal in portions until a blue color persisted for several minutes. Ammonium chloride was added to discharge the color and 850 mg (6.05 mmol) of α-chloroacetophenone was added in portions. The mixture was stirred for 2 hr and the ammonia was evaporated in vacuo. To the residue was added 100 ml of water and the aqueous solution was extracted with

ethyl acetate. The aqueous phase was acidified with concentrated hydrochloric acid and extracted twice with ethyl acetate. These extracts were combined and washed with brine. After drying the organic solution over sodium sulfate, evaporation of the solvent gave 719 mg (42.4%) of 97 which was recrystallized from ethyl acetate-hexane: mp 150-153° C decomp. (lit.[69] mp 154-155° C decomp.); ir (Nujol) 3480 (NH), 3500-2500 (COOH), 1750, 1735, 1685 (C=O) 1510 cm^{-1}; nmr (d_6-DMSO) δ 1.38 (9H, s), 2.90 (2H), 4.06 (2H, s), 4.21 (1H, m), 6.92 (1H, d, J=7.5 Hz), 7.58 (3H, m), 7.98 (2H, m).

Synthesis of 98

To a solution of 1.59 g (4.68 mmol) of 97 in 20 ml of dry tetrahydrofuran was added dropwise a solution of 804 mg (5.62 mmol) of 56 in 3 ml of dry tetrahydrofuran. The resulting solution was cooled with an ice-water bath and a solution of 1.06 g (5.15 mmol) of dicyclohexylcarbodiimide in 3 ml of dry tetrahydrofuran was added dropwise during 15 min. The mixture was stirred for 1 hr at 0° C and at room temperature for 3 days. During this period, a white precipitate appeared. The reaction mixture was filtered, the filtrate was evaporated in vacuo, and the residue was extracted with ethyl acetate. The extract was washed with aqueous sodium bicarbonate and brine. After drying over sodium sulfate, removal of the solvent gave a viscous oil which was purified by column chromatography, using

alumina as adsorbant and benzene-ether (2:3) as eluent, to yield 513 mg (23.7%) of 98; ir (film) 3410 (NH), 1740 (shoulder), 1710, 1680 (C=O), 1600, 1500 cm^{-1}; nmr ($CDCl_3$) δ 1.29 (3H, t, J=7 Hz), 1.50 (15H, broad s), 2.9-3.4 (3H), 4.02 (2H, s), 4.26 (2H, q), ca. 4.6 (1H, m), 5.70 (1H), 7.56 (3H, m), 7.98 (2H, m); mass spectrum m/e 464.196 (M^+); calcd. for $C_{23}H_{32}N_2O_6S$: 464.198.

Photolysis of 98

Photolysis of a solution of 216 mg (0.465 mmol) of 98 in 160 ml of benzene was carried out at 6° C for 2 hr under nitrogen, using a Hanovia medium-pressure mercury lamp and a Pyrex filter. During the reaction, small aliquots were removed for product analysis. The solvent was removed in vacuo to give 180 mg of a brown oil which was purified by preparative-layer chromatography, with benzene-ether (1:1) as eluent, to give 70 mg of a new product. This compound showed ir bands (film) at 3400 (NH), 1750-1650 (broad C=O) cm^{-1} and nmr resonances ($CDCl_3$) at δ 1.26 (3H, t, J=7 Hz), 1.28 (3H, t, J=7 Hz), 1.43 (18H, broad s), 1.78 (6H, broad s), 2.9-3.3 (4H, m), 4.22 (4H, each q), 4.3-4.6 (2H, m), 5.03 (4H, d, J=5 Hz), ca. 5.5 (2H, broad), and ca. 7.3 (2H, broad).

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