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PART I

PHOTOCHEMISTRY AND THERMOCHEMISTRY OF γ-SULTINES

PART II

β-LACTAM SYNTHESIS

by

John C. Huang

A THESIS SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR M. Sc. IN CHEMISTRY

ABSTRACTS

Part I

A) The photo- and thermochemical extrusion of sulfur dioxide from γ-sultines

The benzfused γ-sultines required for this study were prepared by either Givens' (1) or Sharma's method (2). The photo- and thermochemistry of these and several monocyclic γ-sultines were investigated. Those γ-sultines having an aryl substituent α to the oxygen atom undergo SO_2 extrusion either thermally or photochemically via radical intermediates. In the case of monocyclic derivatives, aryl cyclopropanes are formed in fair to excellent yields. If an aryl group was absent α to oxygen no photochemistry was observed while flash vacuum thermolysis gave mixtures of cyclopropanes and alkenes. 3-Phenyl-2,1-benzoxathiole-1-oxide and 3,3-diphenyl-2,1-benzoxathiole-1-oxide yielded fluorene or its derivative as the major products upon photolysis. Fluorene was obtained as the major product upon thermolysis of the former sultine.

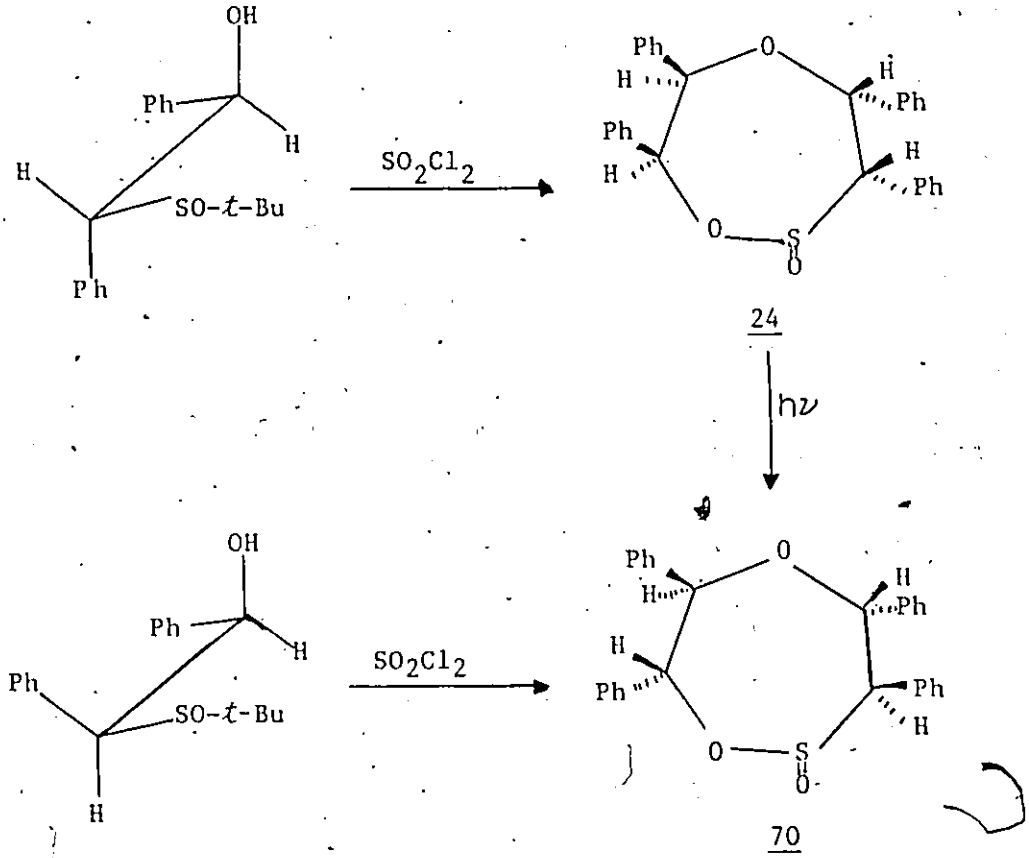
(1) R.S. Givens and W.F. Oettle, J. Org. Chem., 37, 4325, (1972)

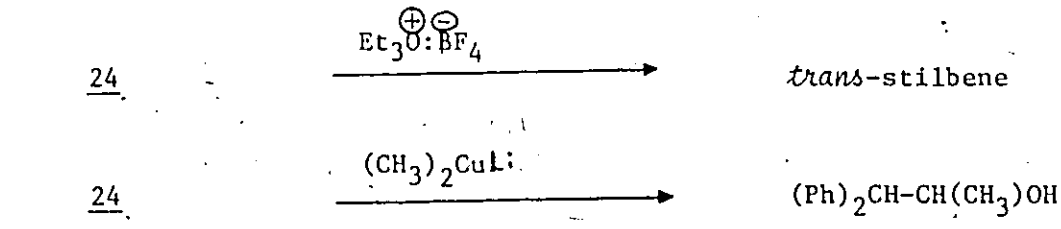
(2) N.K. Sharma, Ph.D. Thesis, University of Ottawa, 1975.

B) Seven-membered ring sultine study

The photoisomer of the 7-membered sultine 24, prepared from *erythro*-1,2-diphenyl-2-*t*-butylsulfinyl ethanol was synthesized from *threo*-1,2-diphenyl-2-*t*-butylsulfinyl ethanol and SO_2Cl_2. During the photolysis of 24 it appears that isomerization occurs at both the benzylic carbons α to oxygen and α to sulfur. The reactions of 24 with $Et_3\overset{\oplus}{O}:\overset{\ominus}{B}F_4$ and $(Me)_2CuLi$ were investigated. The major products from these reactions were *trans*-

stilbene and $(Ph)_2CH-CH(CH_3)OH$ respectively. Tentative mechanisms for these transformations are suggested.





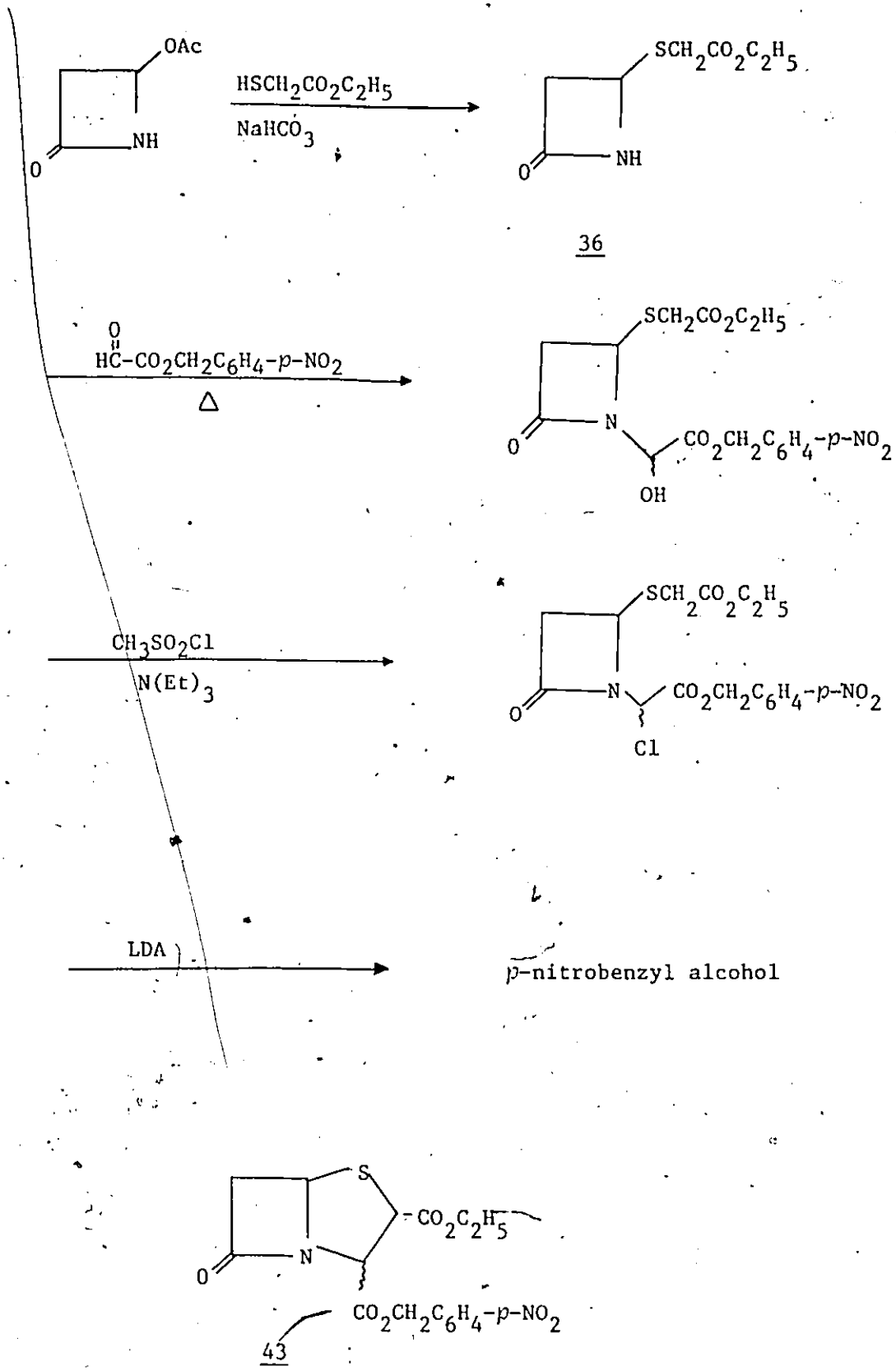
Part II

C) The β-lactam study

Two different model studies directed toward the synthesis of thienamycin were investigated.

The introduction of a hydroxymethyl group at position 3 in 4-(3-butenyl) azetidin-2-one was attempted by reacting this azetidin-2-one with 2 *n*-BuLi at 0° followed by formaldehyde. The desired product was not obtained, instead isomerization of the starting material to the bicyclic derivative 28 occured.

Construction of the thienamycin ring system was attempted starting from 4-acetoxyazetidin-2-one. Reaction with ethyl mercaptoacetate in aqueous $NaHCO_3$ solution gave the derivative 36 which upon condensation with *p*-nitrobenzyl glyoxylate and $CH_3SO_2Cl/N(Et)_3$ treatment gave 40. Attempted cyclization of 40 to 43 with lithium diisopropylamide gave *p*-nitrobenzyl alcohol as the only isolated product. None of the desired cyclized product 43 was obtained.


OAc
NH
O
HSCH2CO2C2H5
NaHCO3
SCH2CO2C2H5
NH
O
36
O
HC-CO2CH2C6H4-p-NO2
Δ
SCH2CO2C2H5
N
O
CO2CH2C6H4-p-NO2
OH
CH3SO2Cl
N(Et)3
SCH2CO2C2H5
N
O
CO2CH2C6H4-p-NO2
Cl
LDA
p-nitrobenzyl alcohol
S
CO2C2H5
N
O
CO2CH2C6H4-p-NO2
43

ACKNOWLEDGEMENT

The author wishes to express his sincere gratitude to the following:

- Especially to Dr. T. Durst for the privilege of exploring organic chemistry under his expert advice, endless patience, enthusiastic guidance and encouragement throughout this work.

- To other members of the staff of the Department of Chemistry.

- To my colleagues in Rm 211, especially J. Decesare in the course of these studies and in the writing of this thesis.

- To Bristol Laboratory, Candiac, Quebec, for supplying the important compounds 4-acetoxyazetidin-2-one and *p*-nitrobenzyl glyoxylate.

CONTENTS

LIST OF TABLES

LIST OF SCHEMES

ABBREVIATIONS

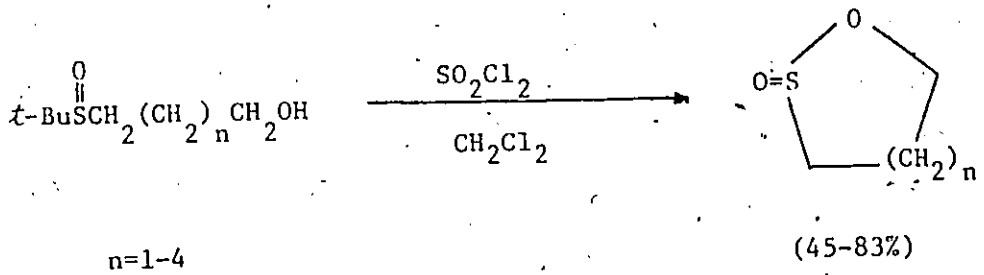
The following abbreviations have been used in this thesis.

uv	ultraviolet
IR	infrared
n.m.r.	nuclear magnetic resonance
THF	tetrahydrofuran
$h\nu$	photolysis
Δ	thermolysis
M.S.	mass spectrum
T.L.C.	thin layer chromatography
LDA	litbium diisopropylamide
$\ominus$	negative charge
$\oplus$	positive charge
pyd.	pyridine
NCS	N-chlorosuccinimide
mcpba	m-chloroperbenzoic acid
Me	methyl
Et	ethyl
s	singlet
d	doublet
t	triplet
q	quartet
b.s.	broad singlet

CHAPTER I

Introduction

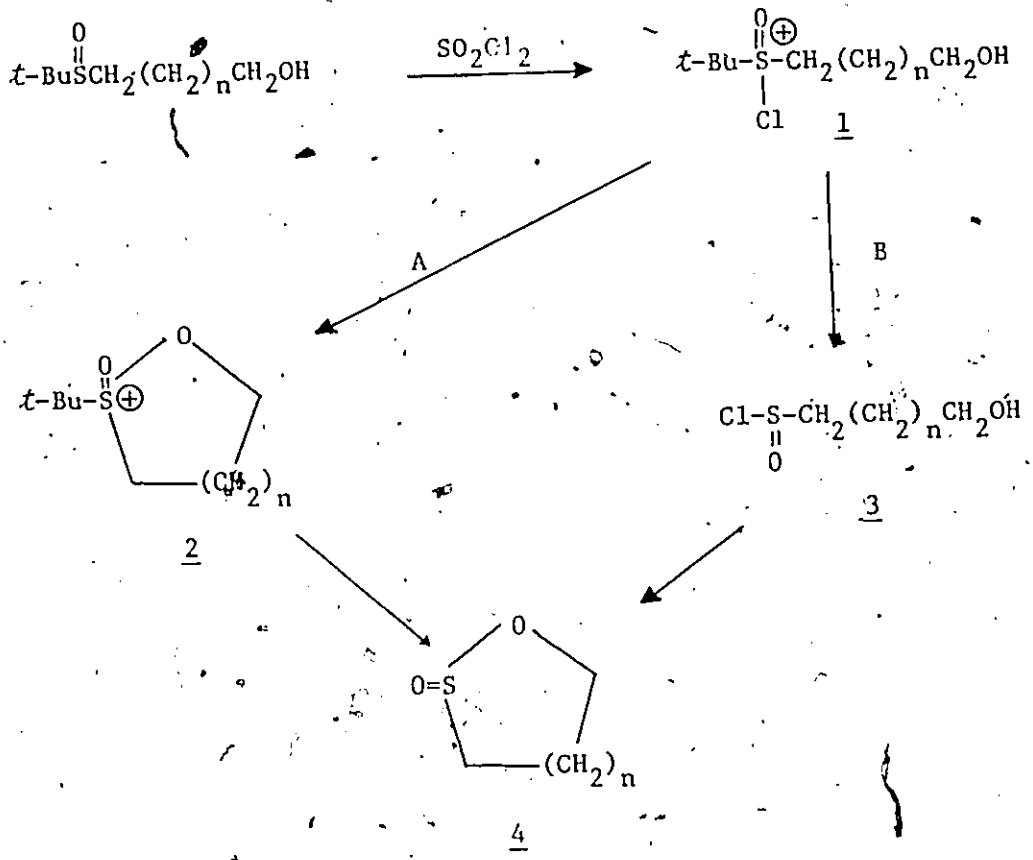
Several years ago, Sharma (1) reported a new systhesis of sultines which are cyclic esters of sulfinic acid (Scheme I). Thus, when *t*-butyl hydroxyalkyl sulfoxides were treated with sulfuryl chloride in methylene chloride for 30 minutes at room temperature, sultines were isolated in fair to excellent yields. Many specifically substituted sultines were also prepared from the corresponding hydroxy sulfoxides in addition to the parent ring systems shown below.



n=1-4 (45-83%)

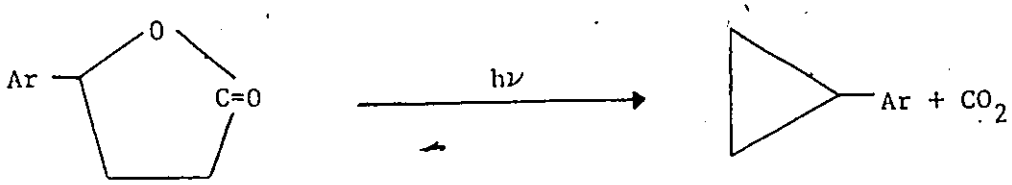
Scheme 1

Two possible mechanisms for sultine formation were suggested by Sharma. (1) Both involve the formation of a chloroxosulfonium ion 1, a species which had been shown to be an intermediate in the chlorination of sulfoxides. In mechanism A, the chloroxosulfonium ion 1 is converted to a cyclic alkoxy-oxosulfonium ion 2, via displacement of chloride ion from sulfur by the remote hydroxyl group. Succeeding cleavage of the *t*-butyl carbon-sulfur bond forms the sultine. In mechanism B, the C-S bond cleavage occurs at the stage of the generation of hydroxysulfinyl chloride 3 from the sulfonium ion 1. This hydroxysulfinyl chloride gives via subsequent intermolecular esterification a sultine 4. (Scheme 2)



Scheme 2

In Sharma's report, (2) some structural problems were left unsolved and a number of reactions of sultines were only briefly investigated, thus requiring further study. For example, the photochemical behaviour of γ-sultines was found to be similar to that of the structurally related γ-lactones. Givens and Oettle (3) have shown that a variety of aryl substituted γ-lactones of the type 6 yield aryl cyclopropanes in yields which were generally below 50%.



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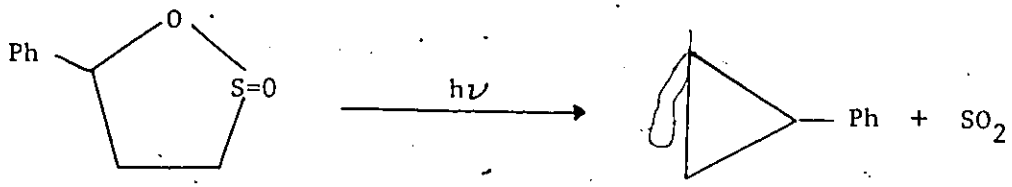
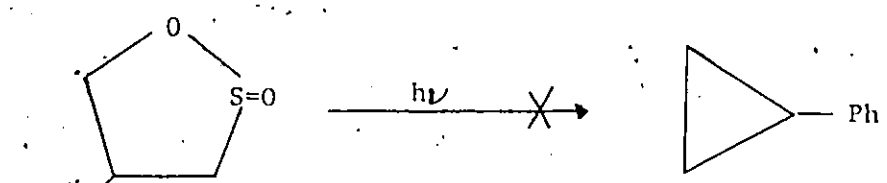
The extrusion of sulfur dioxide from γ-sultines was carried out for a selected number of monocyclic sultines and it was discovered that a 5-aryl group was needed for an easy loss of SO_2.



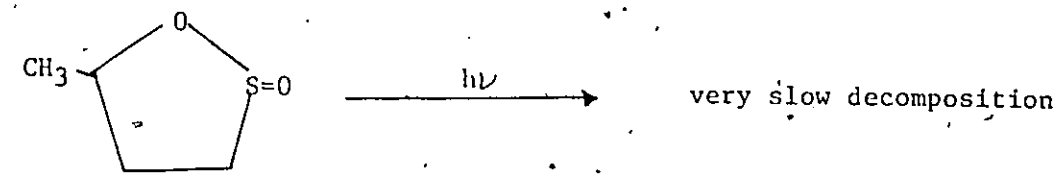
7 10 95%

but

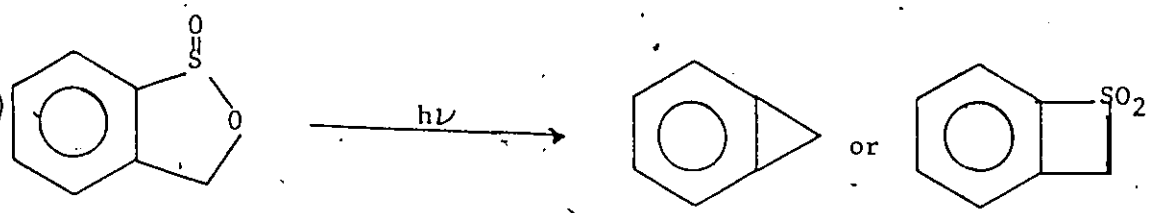


8 9

and



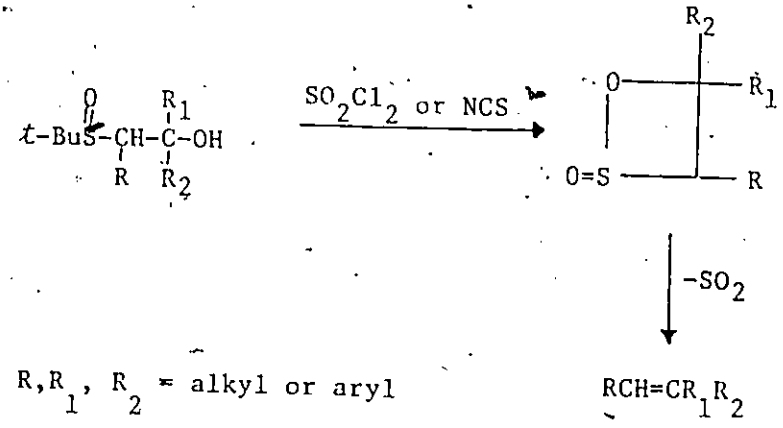
The photolysis of the benzfused sultine 11 was also briefly studied by Sharma (2) with the hope of observing either the formation of benzocyclobutene 12 or thietesulfone 13. No conclusive results were reported.



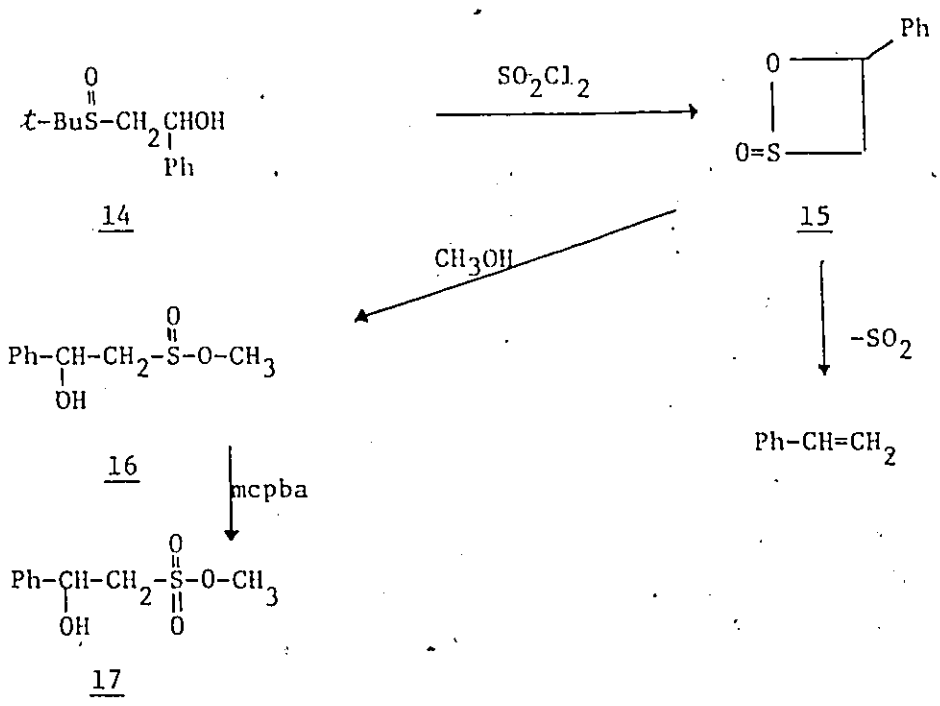
11 12 13

The photolysis of sultine 11 was considered worthy of further study. In order to facilitate isolation of possible products it was decided to synthesize a series of substituted derivatives in particular 3,3-dimethyl-2,1-benzoxathiole 1-oxide 25, 3,3-diphenyl-2,1-benzoxathiole 1-oxide 26, and the 3-phenyl-2,1-benzoxathiole 1-oxides 27 and 28 and study their photochemical behavior. Furthermore in a collaborative programme with Dr. D.J. Smith and J. Finlay of the University of Leicester, England, the flash vacuum thermolysis of these compounds was carried out thus allowing a comparison of products under the two sets of conditions. In order to complete this study, it was decided to prepare for thermolysis studies several alkyl substituted monocyclic sultines with the hope that cyclopropanes might be formed in good yield under these conditions.

The second part of this chapter concerns the study of the reaction of t-butyl-β-hydroxy alkyl sulfoxides with sulfuryl chloride or N-chlorosuccinimide (NCS) at low temperature. Dr. F. Jung *et al* (4) first observed the thermal instability of β-sultines. In their work, a number of cyclization reactions with several differend β-hydroxysulfoxides and N-chlorosuccinimide (NCS) or sulfuryl chloride were carried out at room temperature. All of them led to the formation of olefines.

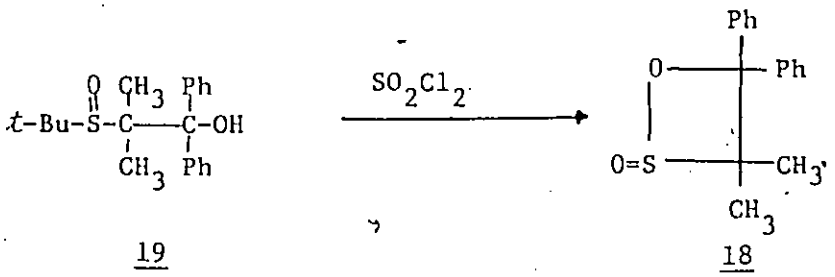


In several instances, these sultines were found to have a sufficient lifetime to allow the determination of some spectroscopic properties and interception by nucleophilic reagents. Thus the reaction of 1-phenyl-2-*t*-butylsulfinyl ethanol 14 with sulfuryl chloride in methylene chloride at room temperature for fifteen minutes followed by evaporation of the solvent in the cold gave a crude product having n.m.r. peaks which could reasonably be ascribed to the β-sultine 15. When the solution was allowed to stay at room temperature for several hours, the original spectrum was replaced by that of styrene. Addition of methanol to the reaction mixture prior to evaporation gave the β-hydroxysulfinate ester 16. Sulfinate ester 16 was further oxidized to sulfonate ester 17.

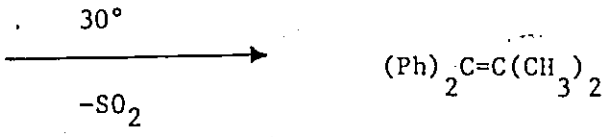


Durst and Gimbarzevsky (5) reported the synthesis and characterization of the β-sultine 18. Thus reaction of hydroxyalkyl *t*-butyl sulfoxide 19 with

N-chlorosuccinimide (NCS) in methylene chloride at room temperature or with sulfuryl chloride at -70° for 30 minutes afforded the β-sultine 18 in 45% yield.



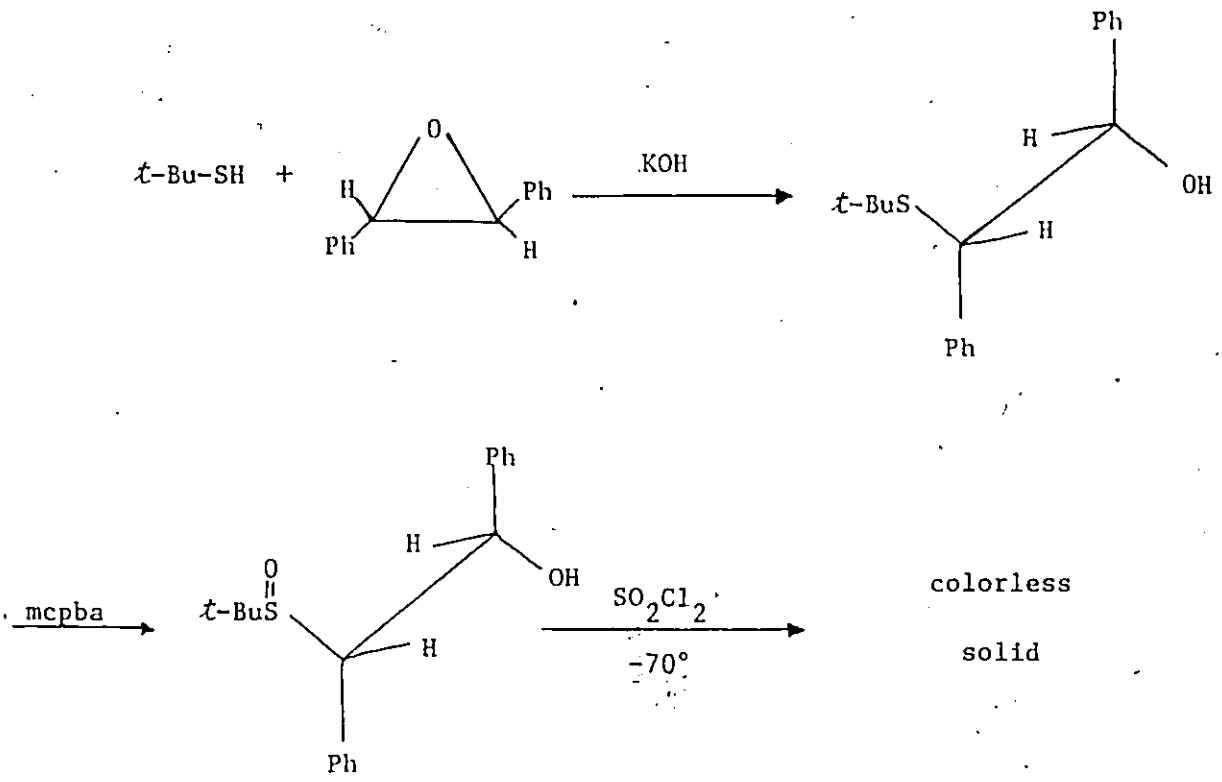
19 18



100%

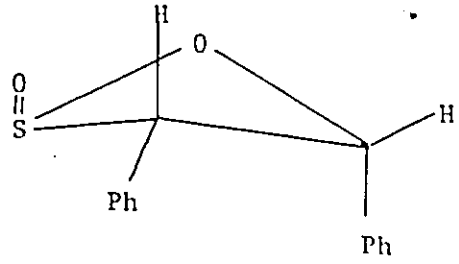
The sultine 18 was stable at room temperature for several days but later decomposed easily and quantitatively into 1,1-diphenyl-2,2-dimethylethylene and sulfur dioxide. The authors argued that the stability of sultine 18 relative to other sultines is due to an increase in adverse steric interactions in going from the ground state of 18 to the transition state for decomposition.

Based on the above conclusion, Sharma (2) rationalized that *cis*-3,4-diphenyl-β-sultine 20 should also have considerable thermal stability and thus set out to synthesize this compound according to the scheme shown below.

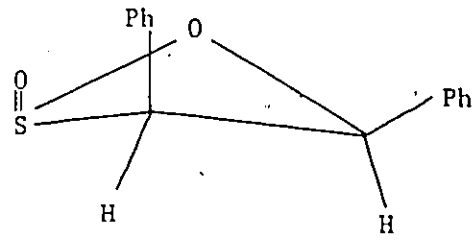


21

Treatment of *erythro*-1,2-diphenyl-2-*t*-butylsulfinylethanol 21 with 1.1 equivalents of sulfuryl chloride in dichloromethane at -70° for 15 minutes afforded a colourless solid (m.p.=160°-162°) in 60% yield. Initially this material was suspected to be a 1:1 mixture of diastereoisomers of β-sultine 22 and 23. Unfortunately, careful analysis of the spectroscopic data and analytical data did not support this hypothesis and the 7-membered ring sultine



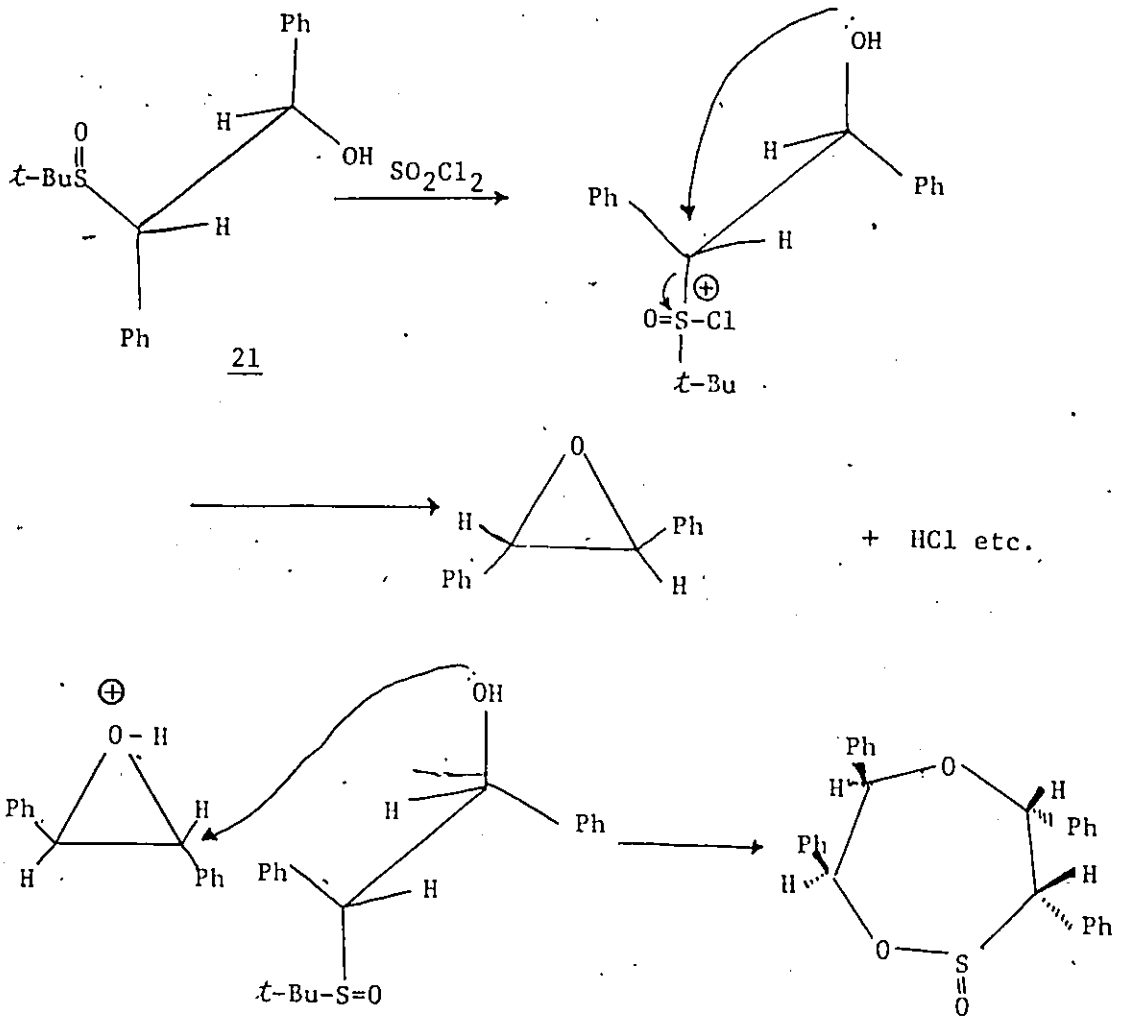
23



22

24 was proposed for the structure of this material.

This structure and a highly speculative mechanism for the formation of 24 (Scheme 3) were considered sufficiently unusual and warranted further investigation.



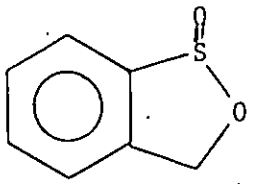
24

Scheme 3

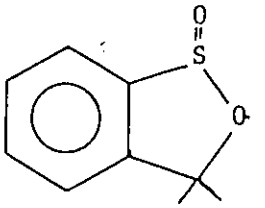
Discussion and Results

(A) Sultine Synthesis

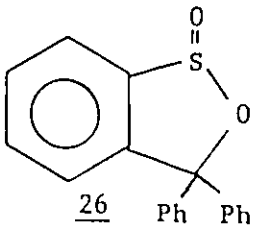
For this study the following five sultines were prepared.



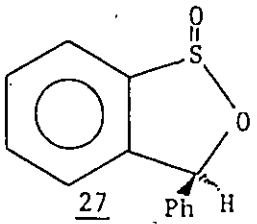
11 — 3H-2,1-Benzoxathiole 1-oxide



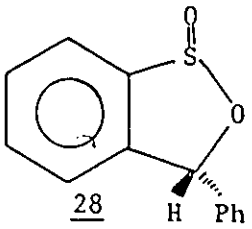
25 — 3,3-Dimethyl-2,1-benzoxathiole 1-oxide



26 — 3,3-Diphenyl-2,1-benzoxathiole 1-oxide

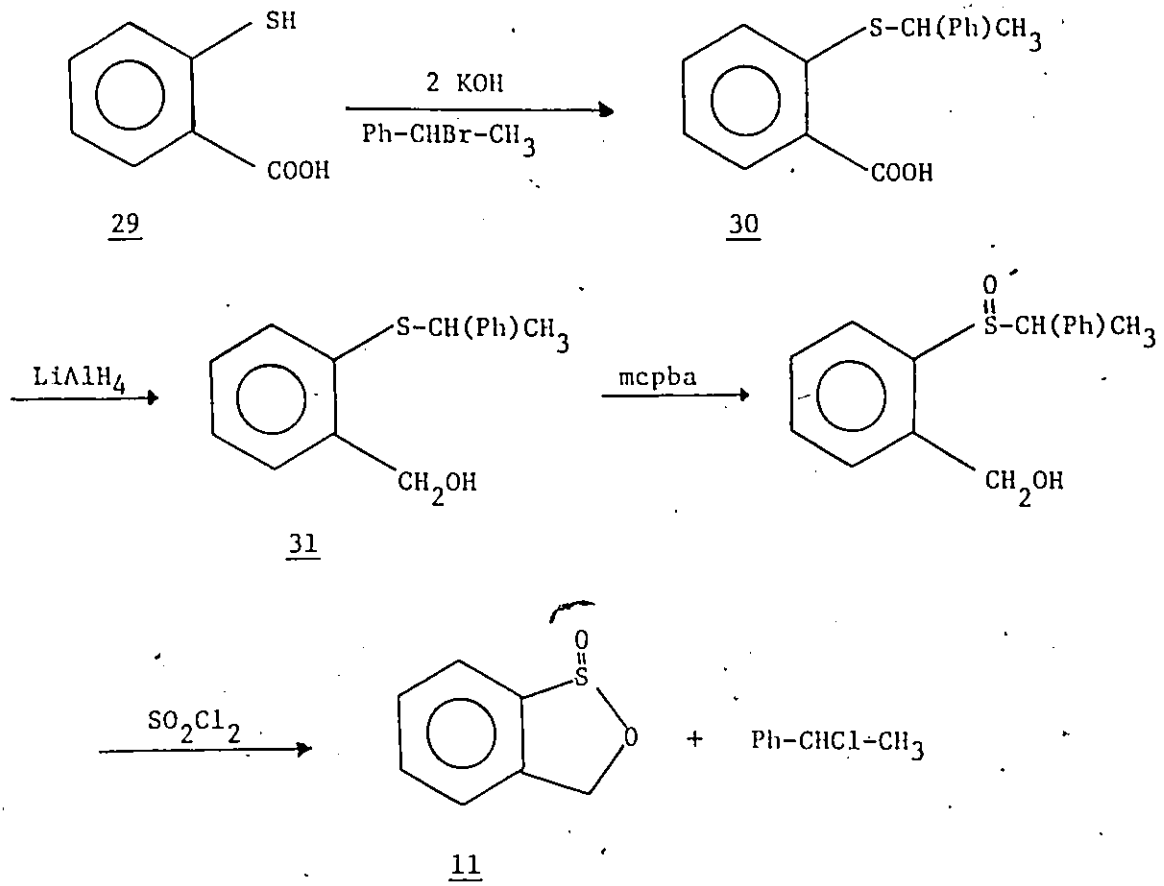


27 — cis-3-Phenyl-2,1-benzoxathiole 1-oxide



28 — trans-3-Phenyl-2,1-benzoxathiole 1-oxide

The preparation of 11 was first carried out following the route developed by Sharma (2) and is shown below.

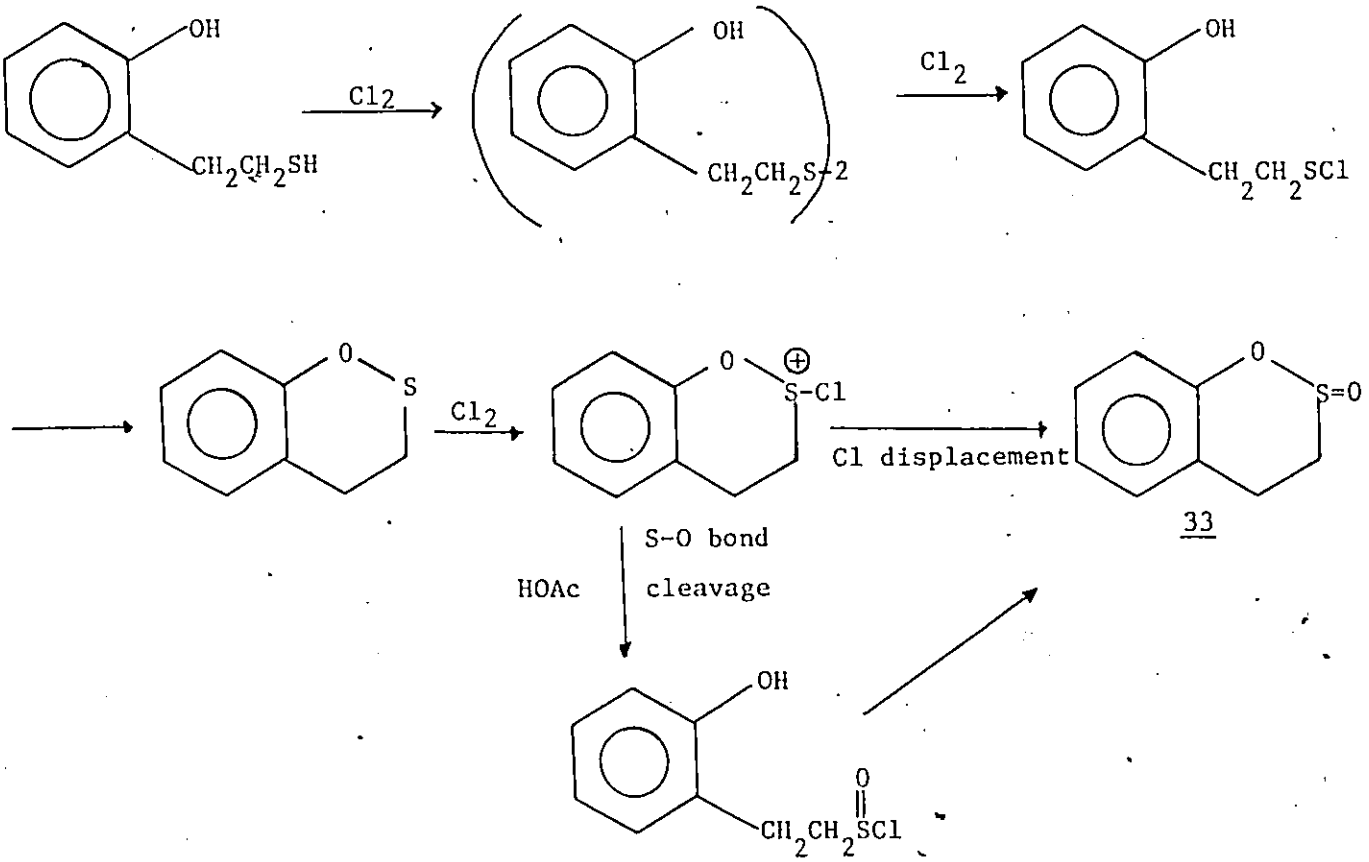


29 30 31 11

o-Mercaptobenzoic acid 29 was alkylated with α-phenethyl bromide in alcoholic KOH to give 30 in 85% yield. Reduction of 30 with lithium aluminum hydride followed by oxidation with *m*-chloroperbenzoic acid (mcpba) afforded the hydroxy sulfoxide 32 in 78% overall yield. Treatment of 32 with sulfuryl chloride according to Sharma (2) gave the parent benzfused sultine 11 (60% after chromatography) and 2-phenethyl chloride. In this

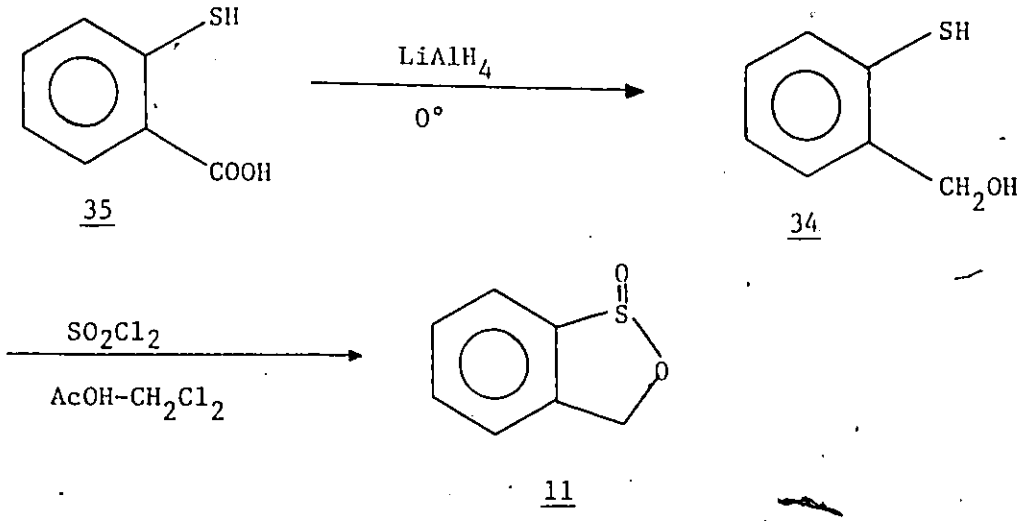
synthesis some problems were encountered with the acid 30 because of poor solubility. This however could be rectified by esterification prior to lithium aluminum hydride reduction. Due to the length of the synthesis it was decided to prepare 11 by a variation of a sultine synthesis first described by Givens and Hamilton.(9) The major advantage of this latter route was its brevity, two steps compared to the four required by the Sharma procedure.

In 1967, Givens and Hamilton (9) successfuly synthesized several sultines by controlled oxidation of mercaptoalcohols. Thus an acetic acid solution of β-(*o*-hydroxyphenyl)-ethyl-mercaptan underwent oxidative cyclization in the presence of chlorine to form 3,4-dihydro-1,2-benzoxathiin 2-oxide 33. Possible mechanisms for this reaction are shown in Scheme 4.



Scheme 4

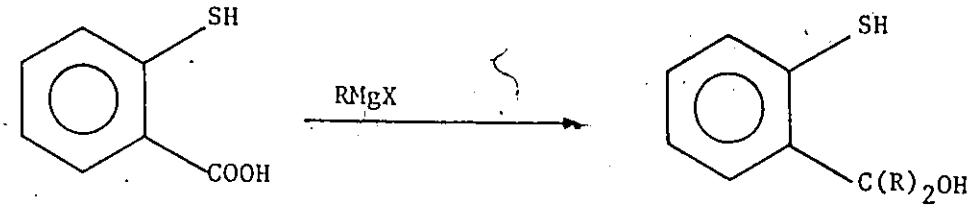
o-Mercaptobenzyl alcohol 34 was obtained in 80% yield upon lithium aluminum hydride reduction of *o*-mercaptobenzoic acid 35. This compound was very sensitive to oxygen and formed an insoluble polymer if left in the open at room temperature for several hours. The infrared and n.m.r. spectra of 34 were in agreement with its structure (see Experimental Part). When 34 was reacted with 2.1 equivalents of sulfuryl chloride in a mixture of acetic acid-methylene chloride (1:3) at 0° for 1 hour, it gave after chromatography a 40% yield of the sultine 11. The spectroscopic properties of 11 prepared in this manner were identical to that obtained via Sharma's route.(2)



35 34 11

The tertiary alcohols 36 and 37 required for the synthesis of the sultines 25 and 26 were obtained by reaction of the ethyl ester of *o*-mercaptobenzoic acid 35 with excess phenylmagnesium bromide and methylmagnesium iodide respectively. The yields of these alcohols were 95 and 86% respectively. Their structures follow from the method of synthesis and are

supported by infrared and n.m.r. data. Compound 36 showed infrared peaks at 3480 and 2540 cm^{-1} due to the OH and SH bands respectively; n.m.r. peaks occurred at 3.4 (s,1H),3.8 (s, 1H),6.4-6.6 (m, 1H) and 6.8-7.3 (m,13H). In compound 37, the OH and SH bands were found at 3640 and 2400 cm^{-1} and the n.m.r. peaks at 1.74 (s, 6H),2.74 (s, 1H),4.12 (s, 1H),7.46 - 6.86 (m, 4H). Both the mercapto alcohols 36 and 37 were cyclized immediately to the sultines because they, like 34, were susceptible to polymer formation.



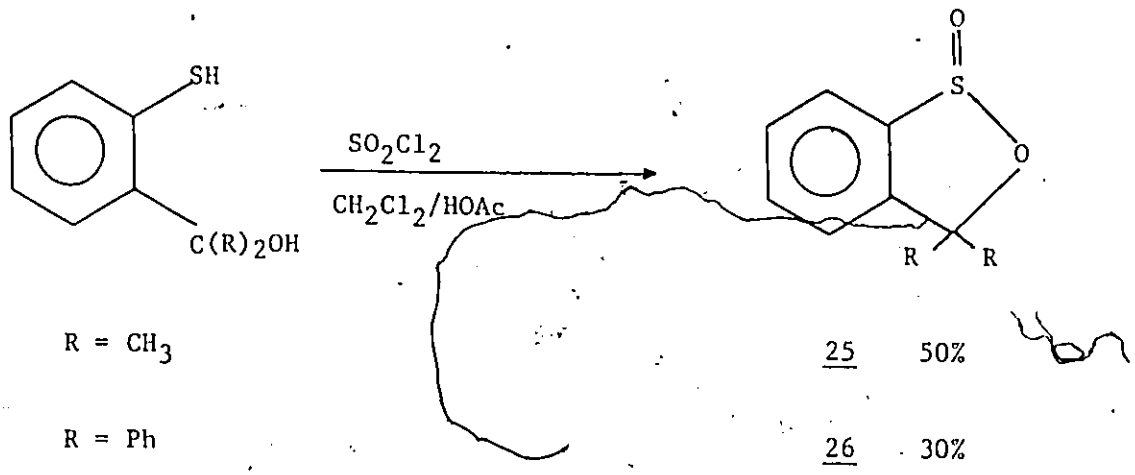
RMgX = PhMgBr

RMgX = CH_3MgI

36 R = Ph 95%

37 R = CH_3 86%

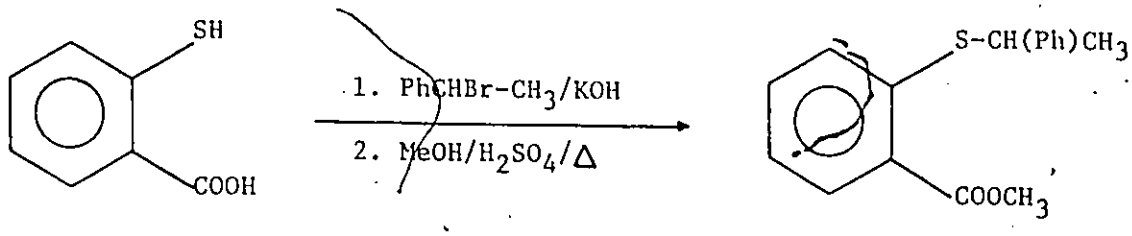
Cyclization of 36 and 37 in the same manner as with 34 gave the sultines 26 and 25 in 30 and 50% isolated yield. Both 26 and 25 displayed a strong S=O band in the 1100-1130 cm^{-1} region typical of 5-membered ring sultines.(1) Compound 26 showed only aromatic absorption in the n.m.r. while 25 gave an aromatic multiplet from δ 7.05-7.75 and two methyl singlets at δ 1.83 and 1.67. Analytical data were in agreement with the required structures.



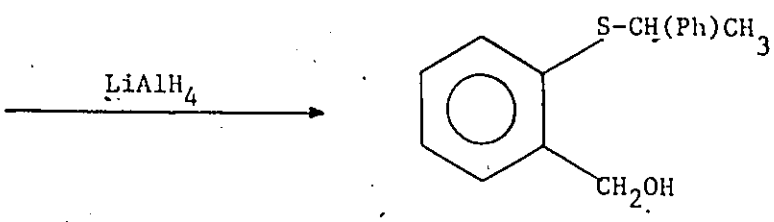
R = CH_3 25 50%

R = Ph 26 30%

The Givens' method could not be applied to the synthesis of the diastereomeric monosubstituted sultines 27 and 28 due to the unavailability of the required mercaptoalcohols by simple synthesis from 35. They were obtained by a more arduous route based on the Sharma sultine synthesis. The ester 38, prepared in 62% yield by alkylation of o-mercaptobenzoic acid with α-phenethyl bromide followed by immediate esterification, was reduced with excess lithium aluminum hydride in dry THF at 0° to give an oily orange colored alcohol 39 in 83% yield.

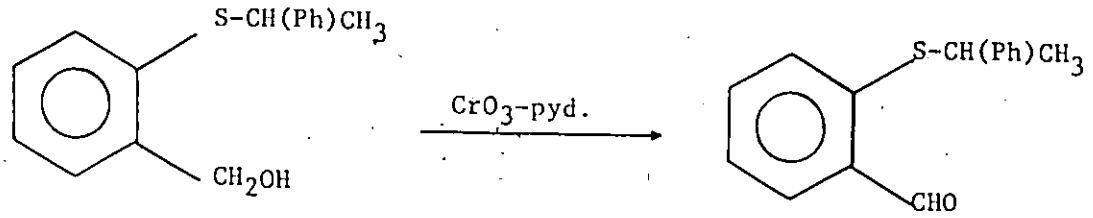


38 62%



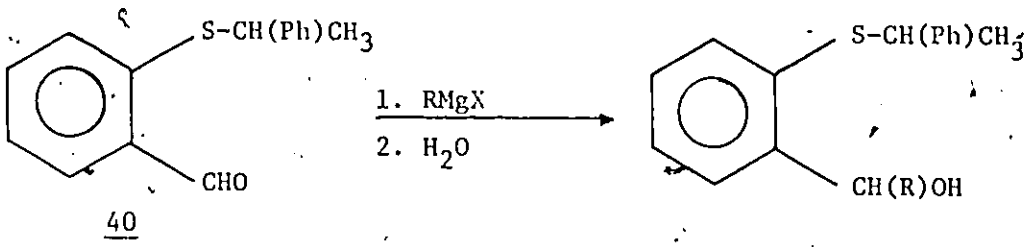
39 83%

The n.m.r. spectrum of 39 showed the peaks at 1.5-1.7 (d, J=7Hz, 3H), 2.2-2.5 (b.s, 1H), 4.1-4.5 (q, J=7Hz), 4.6 (s,2H), 7.1-7.4 (m, 9H) ppm. The OH band occurred at 3340 cm^{-1} in the infrared. The crude material was considered pure enough for the next step. Oxidation of 39 with CrO_3-pyridine gave the aldehyde 40 in 72% yield. The oxidation process was that of Ratcliffe, (6), except 15% HCl was applied in the work-up part instead of 5% HCl which helped remove excess pyridine. The aldehyde was obtained as an oily yellowish substance. The n.m.r. spectrum of 40 had peaks at 1.6 (d, J=7Hz, 3H), 4.2-4.4 (q, J=7Hz, 1H), 7.2-7.4 (s, 5H) 7.4-7.6 (m, 3H), 7.7-8.1 (m, 1H), 10.4 (s, 1H) ppm. A strong absorption at 1685 cm^{-1} in the infrared was assigned to the aldehyde C=O.



39 40

Treatment of the aldehyde 40 with excess Grignard reagent (phenylmagnesium bromide or methylmagnesium iodide), prepared from the corresponding halide and magnesium, followed by quenching with H_2O gave the alcohols 41 and 42 in 72 and 85% yields respectively.

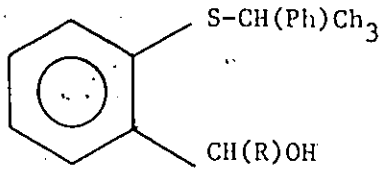


40

RMgX = PhMgBr — 41 72%

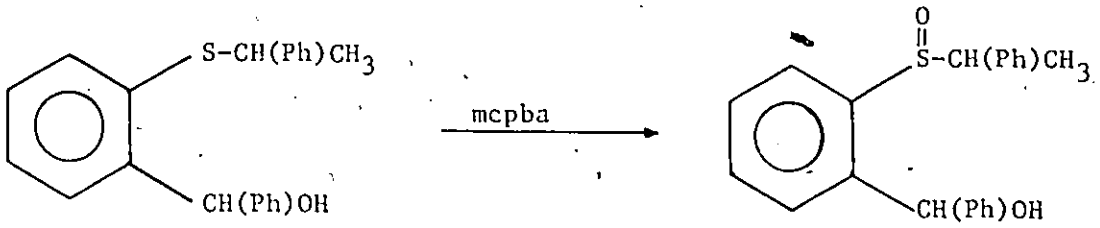
RMgX = CH_3MgI — 42 85%

Compounds 41 and 42 each contain two chiral centers and therefore can exist as diastereomers. The polarities of the isomers were very similar and they could not be separated by silica gel column chromatography. Both of the compounds 41 and 42 were light orange colored oils. The spectroscopic properties of 41 and 42 are shown below.



	n.m.r. (δ)	IR (cm^{-1})
41 R=Ph	1.6 (d, J=7Hz, 3H)	3440 (OH)
	2.3 (s, 1H)	
	4.0 (q, J=7Hz, 1H)	
	6.1 and 6.2 (2s, 1H)	
	7.0-7.5 (m, 14H)	
42 R=CH_3	1.3 (2d, J=7Hz, 3H)	3440 (OH)
	1.7 (2d, J=7Hz, 3H)	
	2.2 (b.s, 1H)	
	4.2 (m, 1H)	
	5.2 (m, 1H)	
	7.0-7.4 (m, 9H)	

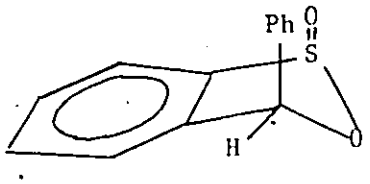
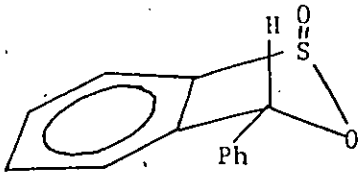
The oxidation of 41 was carried out using *m*-chloroperbenzoic acid in ethyl acetate at -30° for 2 hours. The hydroxy sulfoxide 43 was obtained in 57% yield as colorless crystals m.p. 124°-125°C after purification on silica gel column chromatography. The n.m.r. spectrum of 43 showed peaks in five different regions: 1.7 (d, J=7.5Hz, 1H), 4.1 (q, J=7.5 Hz, 1H), 5.6 (1H, OH), 7.0-7.6 (m, 14H), 7.7-8.0 (m. 1H) ppm. The infrared spectrum of 41 showed the characteristic S=O and OH absorptions at 1010 and 3300 cm^{-1}, respectively. The elemental analysis supported the structure.



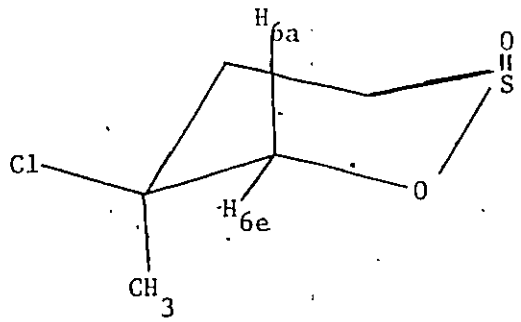
41 43 57%

The hydroxy sulfoxide 43 was treated with SO_2Cl_2 at 0° for 1 hour to give the benzfused sultine isomers 27 and 28. The diasteromeric sultines were easily separated on silica gel column chromatography. The less polar isomer 27 m.p. 122°-123°C was obtained in 41% yield, while the more polar isomer 28 m.p. 102° was obtained in 32% yield. Their spectroscopic properties are described in Table 1, below.

TABLE 1

Compound	N.M.R.	IR(cm^{-1})	M.P. °C
	6.57 (s, 1H) 7.10-7.80 (m, 9H)	1125	122-123
	7.06 (s, 1H) 7.10-7.80 (m, 9H)	1125	102

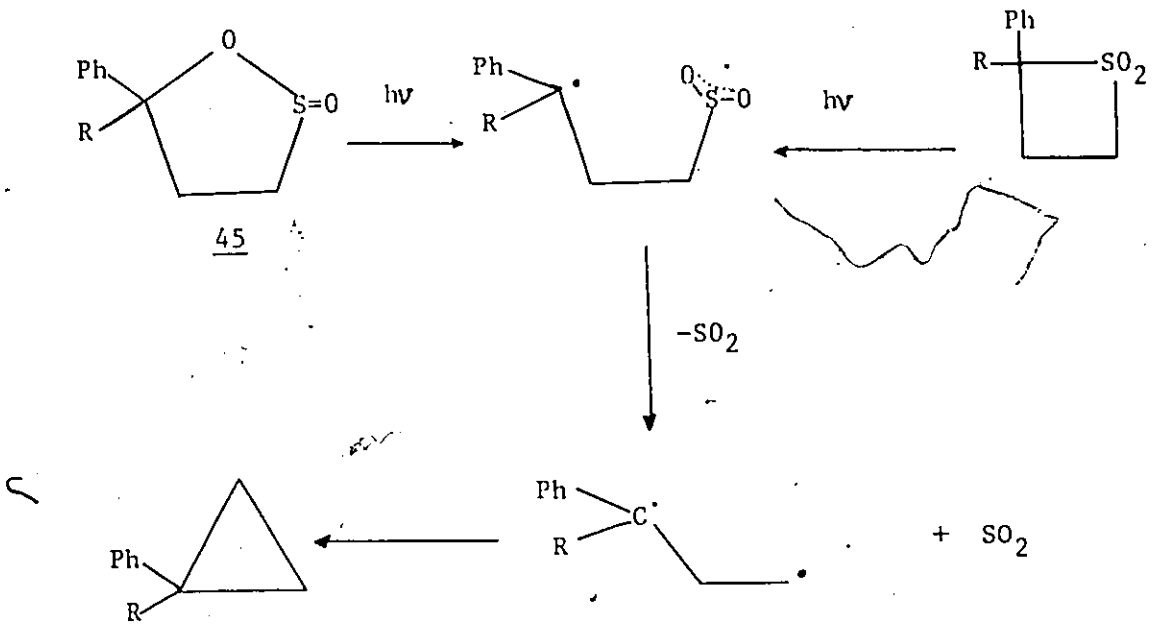
The stereochemical assignment of the less polar isomer m.p.=122°-123° as the *cis*-isomer 27 and the more polar product 28 as the *trans*-isomer was made on the following basis. In 1,2 oxathiane-2-oxide and derivatives, it has been shown that H_{6a} is deshielded by approximately 0.5 to 1.0 ppm (7,1) due to the so call syn-axial effect. For example, in the case of 4-chloro-4-methyl-1,2 -oxathane-2-oxide 44 the chemical shift of the H_{6e} occured at 4.05 ppm while that of H_{6a}, which is in a 1,3-diaxial relationship to S=O group, is shifted to 4.62 ppm. (7) For the less polar.



isomer the benzylic hydrogen occurred at 6.57 ppm whereas in the more polar isomer this hydrogen resonated at 7.06 ppm. On the basis of the shift difference discussed above for some δ-sultines we assign the structure 27 in which H and S=O are *trans* to the less polar isomer and 28 in which H and S=O are *cis* (therefore H deshielded) to the more polar isomer. The chromatographic behavior of the isomers, in which the isomer having the S=O and C-H group *cis* would be expected to be more polar because of the greater steric accessibility of the S=O group than when the phenyl and S=O groups are *cis*, also support the assignment. For example, Siegl and Johnson (8) have shown that *cis*-2-methylthiolan-1-oxide is chromatographically less polar than the *trans* isomer.

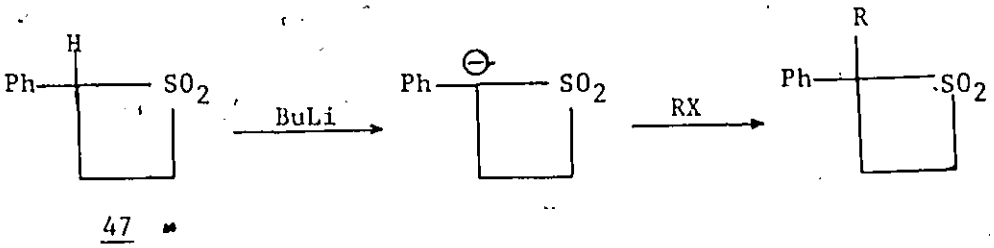
(B) Photochemistry, thermochemistry and mass spectra of benzfused γ-sultines

In Sharma's work, (2), it was found that 5-phenyl-γ-sultines 45 lost SO_2 to give the corresponding cyclopropane derivatives 46 upon irradiation at 253 nm in benzene-acetone solution. The possible mechanism for SO_2 extrusion is described below. Concurrent with our photolysis studies on sultines, Finlay and Smith (10) have found that 2-phenylthietan-1,1-dioxides 47 are also readily converted to phenyl cyclopropanes when irradiated in methanol. This finding supports the intermediacy of the diradical 49 in the photolysis of the sultine 48 suggested by Sharma. (Scheme 5)



Scheme 5

The yields of cyclopropanes by the sulfone route were also very high and in fact it appears that this route to phenylcyclopropanes may have considerably more scope since substituted sulfones can easily be prepared via the carbanion of 47. (10)

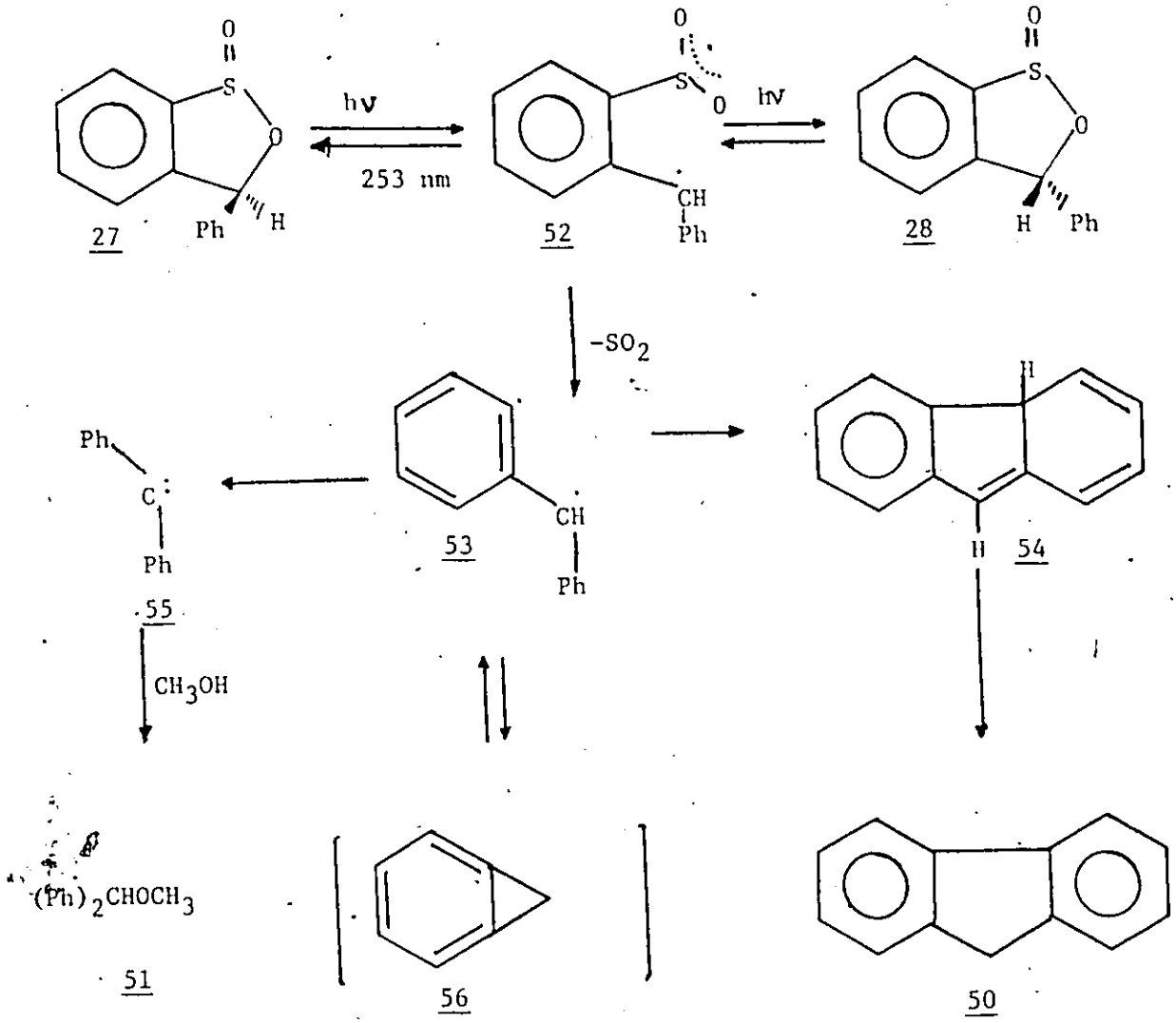


The photolysis of the benzfused sultine 11 was proposed as a potential route to benzocyclopropene, (2) however Sharma found that 11 was photochemically quite stable and after prolonged irradiation only general decomposition seemed to occur. As mentioned earlier, the substituted sultines 25, 26, 27, and 28 were considered more suitable because the presence of the phenyl or methyl substituents should make possible products more easily isolable.

Photolysis of the diastereomerically pure sultine 27 in methanol under N_2 at 253 nm for 5 hours afforded an approximate 1:1 mixture of 27 and its diastereomer 28. Prolonged irradiation, 14 hours, of the mixture led to a product mixture from which fluorene 50 and diphenylmethyl methyl ether 51 were isolated in 27 and 32% yield, respectively. Fluorene was identified by comparing its n.m.r. spectrum whth that of an authentic sample.(12) Diphenylmethyl methyl ether showed n.m.r. peaks at 3.3 (s, 3H), 5.2 (s, 1H), and 6.9-7.5 (m, 10H) ppm; these peaks were identical with those of an authentic sample prepared by dropwise addition of benzhydryl chloride to a refluxing mixture of potassium carbonate in methanol. (13)

The epimerization of the diastereomic sultines 27 and 28 upon irradiation is consistent with the formation of a diradical intermediate 52 which can collapse back to either starting material with loss of stereochemistry at both sulfur and carbon. The rationalization of the formation of fluorene 50 and the ether 51 via this diradical 52 is shown below. Thus diradical 52 could further lose SO_2 to give the intermediate 53. Fluorene can be obtained from the diradical 53 by a cyclization to 54

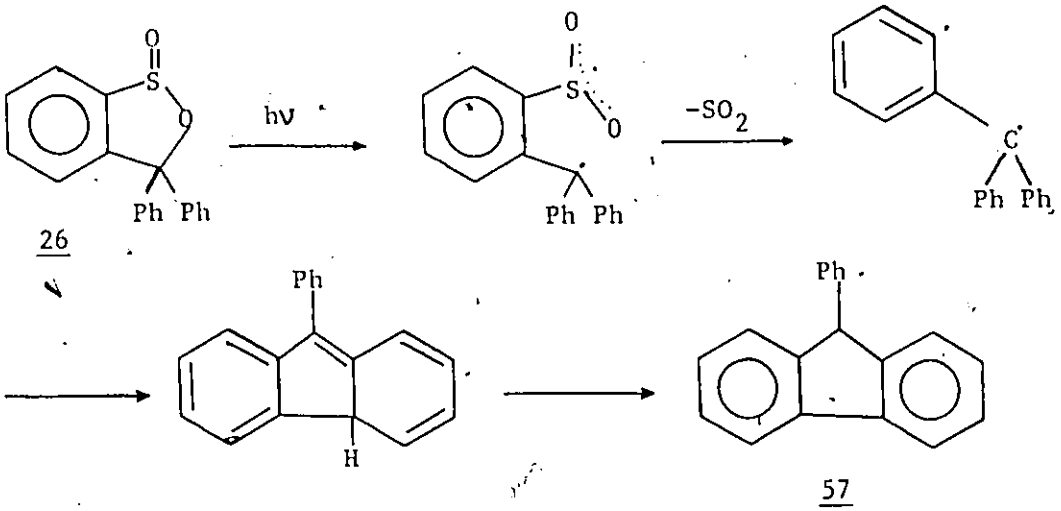
followed by a 1,3 hydrogen shift while 51 is most readily explained as resulting from conversion of 53 to the carbene 55 and subsequent insertion of this carbene into the O-H bond of methanol. Examples of the trapping of this carbene by methanol to form 51 are well documented. (14)



The benzocyclopropene 56, if it formed, would not have been expected to be

stable under the reaction conditions and be reconverted to 53. The conversion of compounds of the type 56, via a diradical such as 50 to other products has been shown to occur above 20°. (16)

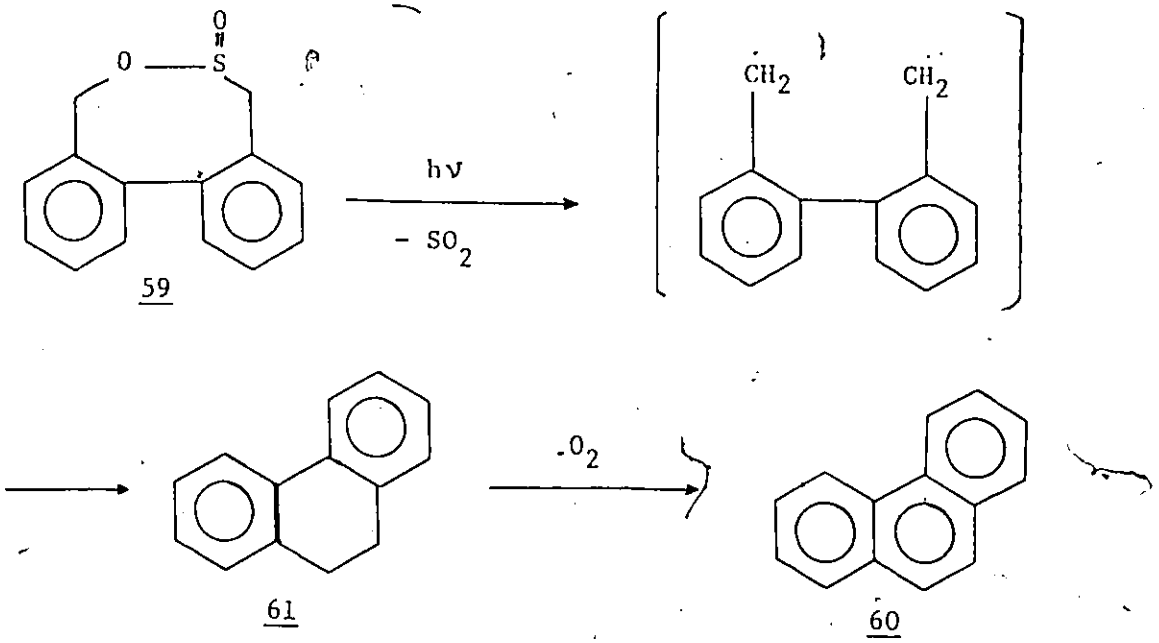
Under conditions similar to those above, the sultine 26 gave 9-phenyl fluorene 57 as the only isolable product in 42% yield. Compound 57 was identified by comparison with an authentic sample prepared by Cockerill's method. (15) His procedure consisted of reacting fluorenone with phenylmagnesium bromide to give 9-hydroxy-9-phenyl fluorene 58 in 80% yield. Reduction of the tertiary alcohol with zinc in acetic acid yielded 57 (56%). The physical and spectroscopic properties of 57 from the two routes were identical. The mechanism of the formation of 57 from 26 follows the same pattern as that of fluorene from 27 or 28 and is shown below.



Upon photolysis of the compounds 27 and 28 two types of products were isolated, *i.e.*, ether 51 and fluorene derivatives, neither of which required the intermediacy of benzocyclopropenes but suggest that possibly under appropriate experimental conditions e.g. lower temperatures, benzocyclopropenes might be obtained. (16)

In contrast to the phenyl substituted benzfused sultines 26 and 27, the dimethyl derivative 25 gave no isolable products after 20 hours of irradiation. At this stage of irradiation, starting material had disappeared but a large number of products had formed as judged by analytical thin layer chromatography and the n.m.r. spectrum of the crude reaction product.

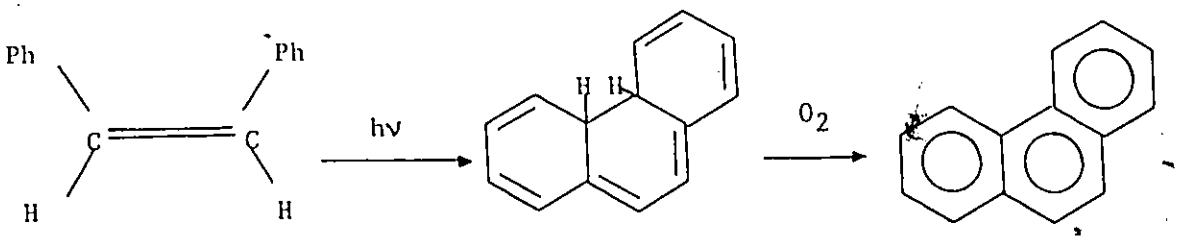
The eight membered ring sultine 59, kindly donated by professor D.H. Harpp (McGill), when photolyzed in methanol for 18 hrs at 25°, gave a 1:1 mixture of phenanthrene 60 and 9,10-dihydrophenanthrene 61. In another experiment, 62, and 61 were obtained in about a 1:10 ratio. Their genesis could be described as shown below.



59 61 60

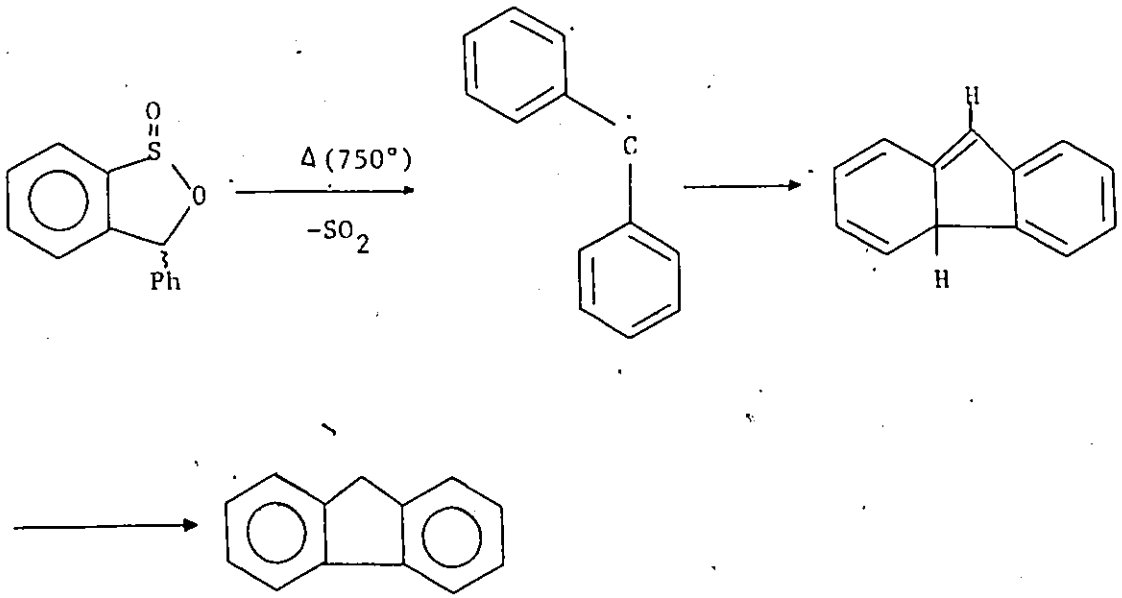
The formation of 9,10-dihydrophenanthrene is easily rationlized and phenanthrene itself is presumably formed by a dehydrogenation of the dihydro derivative possibly due to the presence of oxygen in the reaction mixture.

Such examples can be found in the photochemical transformation of stilbene to phenanthrene.(17) Stilbenes can be converted to phenanthrenes by irradiation with uv light in the presence of an oxidizing agent such as dissolved molecular oxygen:



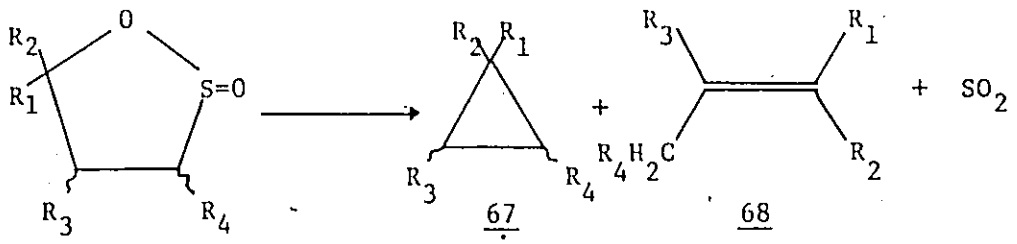
The variation in the product ratio may be due to variation in the amount of oxygen present in the irradiation vessel.

The thermolysis of a number of sultines supplied by us was carried out over the past year by Finlay and Smith. (18) Thermolysis of either of the monophenyl substituted sultines 27 or 28 at 750°C gave fluorene as the only product; its formation can be accounted by a scheme which is identical to that proposed for the analogous photochemistry. (page 23)



50

Thermolysis of the monocyclic sultines 62, 63, 64, 65, and 66 gave several products and occasionally recovered starting materials depending on the reaction temperature and the sultine structure.



67 68

unless stated all R groups = H

62 R_1 = Ph

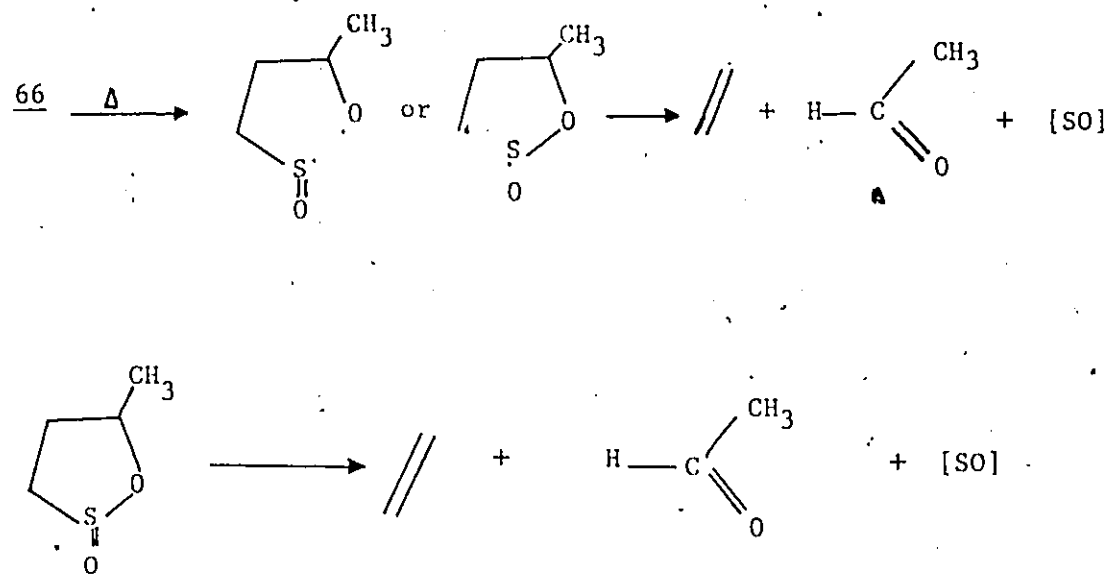
63 R_1 = Ph, R_4 = CH_3

64 R_3 = CH_3

65 R_3 = Ph

66 R_1 = CH_3

The 5-phenyl sultine 62 at 750° gave quantitatively phenylcyclopropane which isomerized to allyl benzene and α-methyl styrene. Below 750° some starting material was always recovered. In contrast 4-phenyl-γ-sultine 65 yielded no phenyl cyclopropane and only methyl styrene and starting material or 1-phenyl propene when thermolyzed at 750°. The 5-methyl-γ-sultine 66 at 750° gave 37% methylcyclopropane and 67% butenes, while 3-methyl-γ-sultine 64 yielded 45% cyclopropane, 35% of butenes and 17% of acetaldehyde, the latter possibly occured via the fragmentation shown below.



The thermolysis results are summarized in Table 2.

Table 2

The Thermolysis of γ-sultines

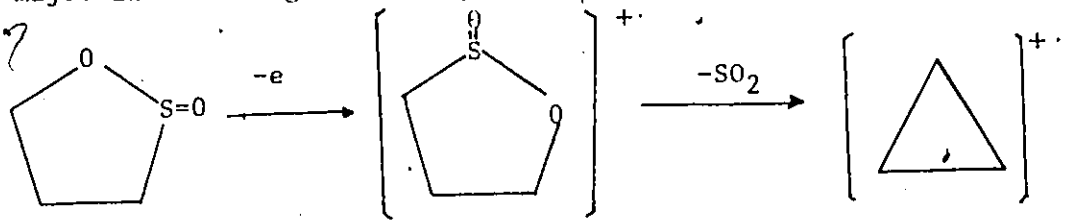
Compound	Temperature °C	Product %			
		Starting Material	67	68	Others
62	550	84	15		
	600	62	37		
	650	24	75		
	750		100		
	850		36	37	alkyl benzenes 27
63	750		100		
64	650	87		13	
	700	70		30	
	750		37	62	
65	750	a*		a*	
66	750		45	35	acetaldehyde 17

a* Product ratios could not be determined due to overlap of the peaks of α-methylstyrene and starting material.

Thus it seems that sultines are not good intermediates for the synthesis of cyclopropanes under either thermolysis or photolysis unless an aryl group is present α to the oxygen i.e., at position 5. Under thermolysis some cyclopropanes are formed from other sultines but the yields are only fair and the product is contaminated with a variety of other decomposition products.

It has often been observed that either or both the photochemistry and thermochemistry (flash vacuum thermolysis) of a compound parallels the mass spectral behavior.

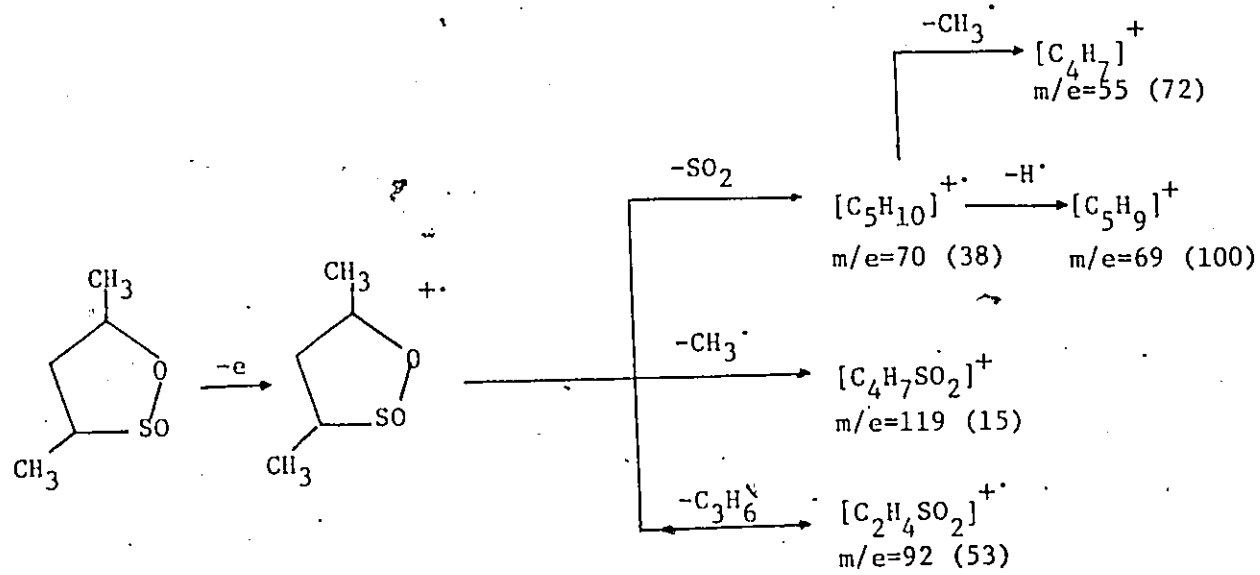
Sharma (2) had already pointed out that in the mass spectra of a variety of substituted γ-sultines the loss of sulfur dioxide constituted the major initial fragmentation pathway.



base peak

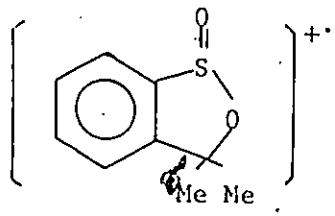
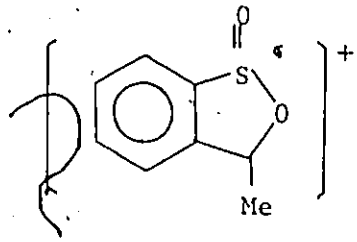
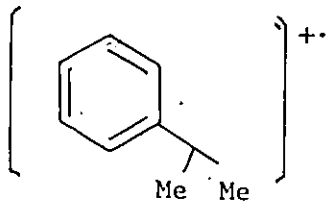
m/e=42

In the substituted derivatives, the loss of a substituent fragment, e.g. CH_3 can become quite prominent, however, the SO_2 loss remains an important pathway.

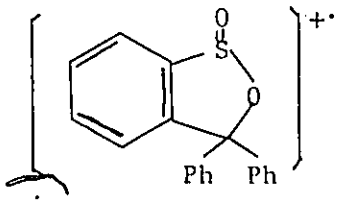


As with the monocyclic γ-sultines, the benzfused sultines also show a very important loss of SO_2. In fact, this process accounts for the base peak in the mass spectra of the sultines 25 and 26. Other fragmentation which are prominent in the mass spectrum of sultine 25 are loss of either SO or CH_3 from the molecular ion. The possible formulae of the key fragments in the mass spectrum of sultine 25 are shown in Table 3.

Table 3

Fragments	m/e (relative abundance)	
	182 (78)	parent peak $M^{+\cdot}$
	167 (32)	$M^{+\cdot}$ - 15
	118 (100)	$M^{+\cdot}$ - 64
$[C_8H_4SO]^{+\cdot}$	148 (88)	$M^{+\cdot}$ - CH_4-H_2O
$[C_9H_{10}O]^{+\cdot}$	134 (52)	$M^{+\cdot}$ - SO
$[C_8H_7]^{+}$	103 (68)	$M^{+\cdot}$ - SO_2-CH_3
$[C_7H_7]^{+\cdot}$	91 (52)	$M^{+\cdot}$ - 91
$[C_6H_5]^{+}$	77 (78)	$M^{+\cdot}$ - 105

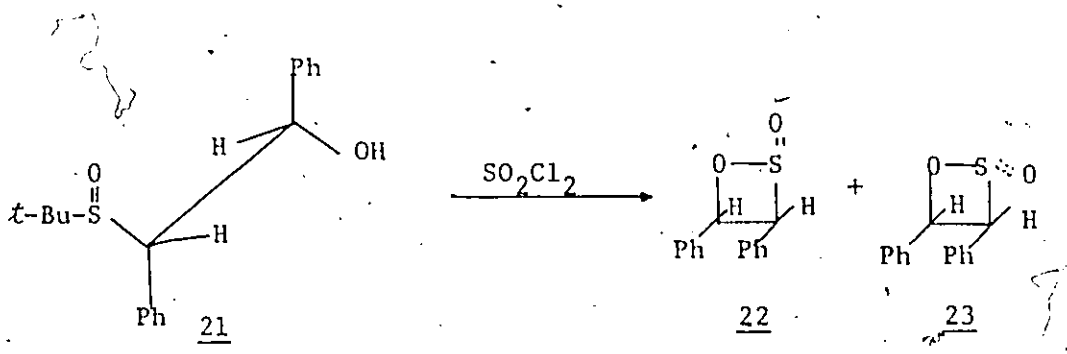
The major peaks in the mass spectrum of the diphenyl benzfused sultine 26 are shown below. A number of peaks including m/e=242 (loss of SO_2), m/e=165 ($M^{+\cdot} - SO_2-C_6H_5$) and m/e=258 ($M^{+\cdot} - SO$) are quite easy to rationalize. Others such as the fragment at m/e=197 (44) are difficult to visualize. This peak is apparently due to a loss of C_6H_5S and must be the result of a rearrangement followed by cleavage of two bonds.

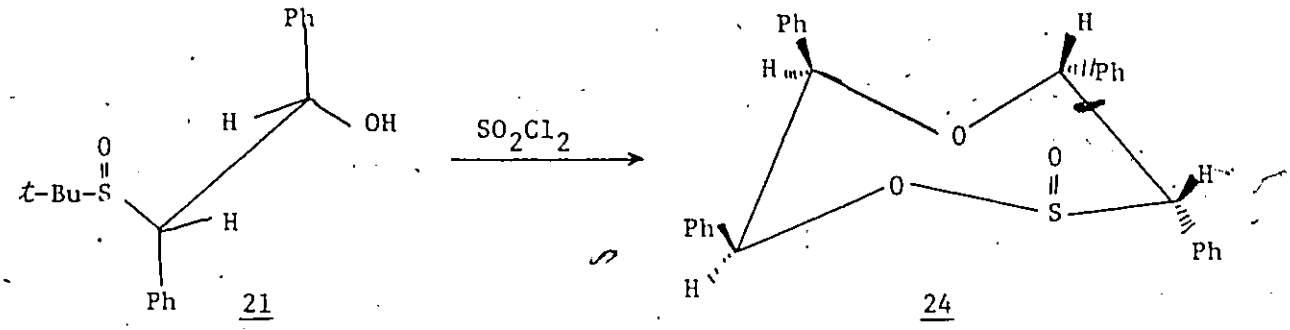
Fragments	m/e (relative abundance)	
	306 (1)	$M^{+\cdot}$
$[C_{19}H_{14}]^{+\cdot}$	242 (100)	$M^{+\cdot} - SO_2$
?	197 (44)	$M^{+\cdot} - 109$
$[C_{13}H_9]^{+}$	165 (76)	$M^{+\cdot} - SO_2-C_6H_5\cdot$
$[C_{19}H_{11}]^{++}$	119.5 (40)	$M^{+\cdot} - SO-H_3O\cdot$
$[C_7H_5O]^{+}$	105 (41)	$M^{+\cdot} - 201$
$[C_6H_5]^{+}$	77 (62)	$M^{+\cdot} - 229$

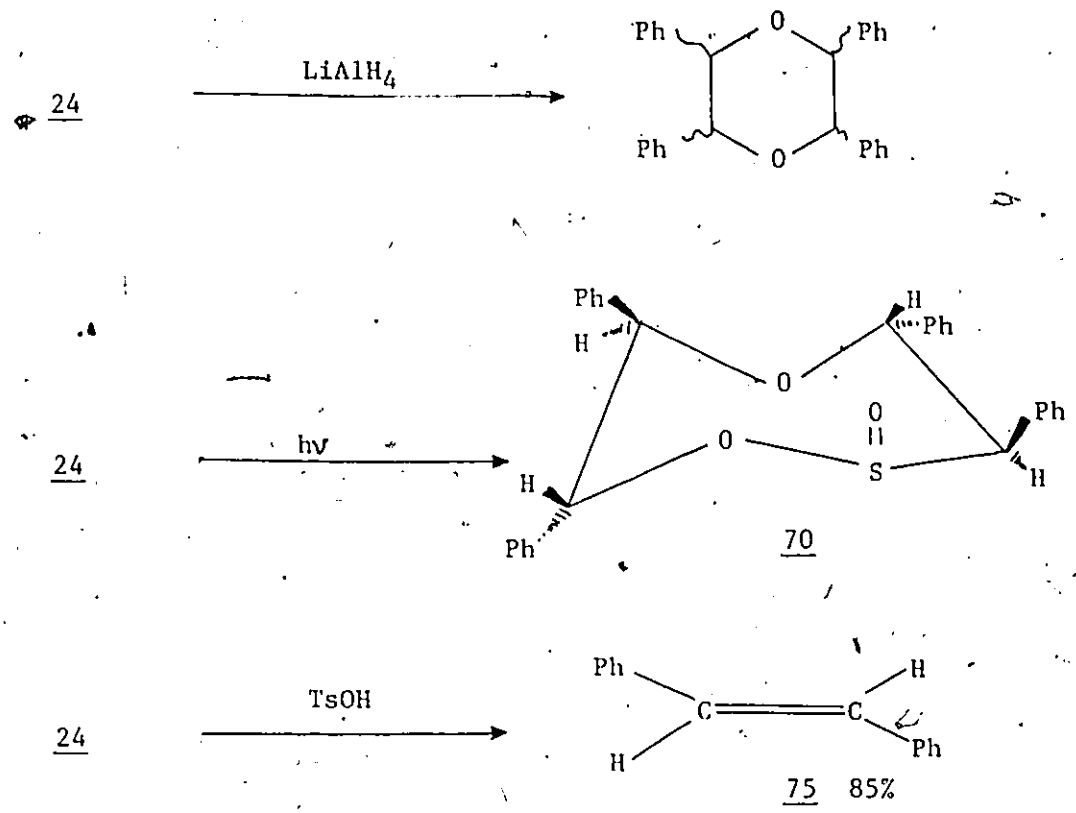
In summary it appears that the major fragmentation observed in the mass spectra of γ-sultines i.e. the extrusion of sulfur dioxide is mirrored by the behavior of these compounds on photolysis and flash vacuum thermolysis.

(C) The seven membered ring sultines

As mentioned in the introduction, Sharma had found that reaction of the *erythro*-hydroxy sulfoxide 21 with sulfuryl chloride did not lead to the expected *cis*-diphenyl-1,2-oxathietan-2-oxide (22 or 23) but rather to a material which he had identified as the seven membered ring sultine 24. Sharma's structural assignment was based mainly on analytical and spectroscopic data. (1) A number of chemical reactions were also carried out which are shown below.







These reactions could partly be rationalized based on Sharma's structure. However none were convincing enough to prove the structure. Therefore it was decided to try to obtain more evidence for structure 24.

First we synthesized the *threo*-hydroxy sulfoxide 68 in order to cyclize it to an isomer of 24. Since a second of the other 15 possible diastereoisomers of 24 had already been prepared by the photolysis of 24, the preparation of a new isomer and its possible photoisomer would greatly add to the total spectroscopic data available for these types of structures.

t-Butyl benzyl sulfoxide 67, m.p. 71°-72°C, was synthesized in 70% overall yield by refluxing a mixture of *t*-butyl mercaptan and benzyl chloride with alcoholic KOH, followed by treatment with *m*-chloroperbenzoic acid at -30° and chromatography of the resulting material. This sulfoxide was characterized by comparison of its m.p. and spectroscopic properties

with the known values. (19)

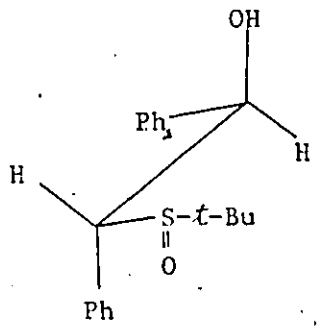
$$t\text{-BuSH} + \text{Ph-CH}_2\text{Cl} \xrightarrow[\Delta]{\text{KOH}} t\text{-Bu-S-CH}_2\text{-Ph}$$

$$t\text{-Bu-S-CH}_2\text{-Ph} \xrightarrow[-30°]{\text{mcpba}} t\text{-Bu-S(=O)-CH}_2\text{-Ph}$$

67 70%

The treatment of sulfoxide 67 with methyllithium at -70° followed by addition of benzaldehyde gave two diastereoisomers of 1,2-diphenyl-2-*t*-butyl-sulfinyl ethanol. The spectroscopic data of the more polar isomer, obtained in 60% yield, were found to be identical to that of the *erythro* isomer 21 made by Sharma. The less polar isomer 68 m.p. 167°-168°, isolated in 32% yield, showed the characteristic S=O group and OH group at 1020 and 3340 cm^{-1}, respectively and n.m.r. peaks at 1.2 (s, 9H), 4.0 (d, J=10Hz, 1H), 5.3 (d, J=10Hz, 1H), 6.0 (OH), 7.0 (s, 10H). On the basis of the observed J_{vic} value, the dihedral angle for H-C-C-H in 68 is close to 180°. (20)

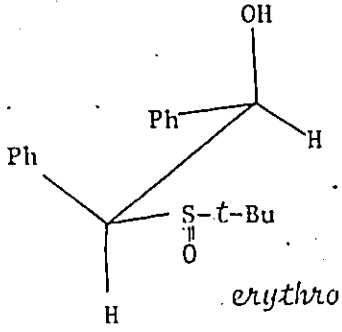
67 $\xrightarrow[2.\ \text{Ph-CHO}]{1.\ \text{MeLi/-70°}}$



threo 68

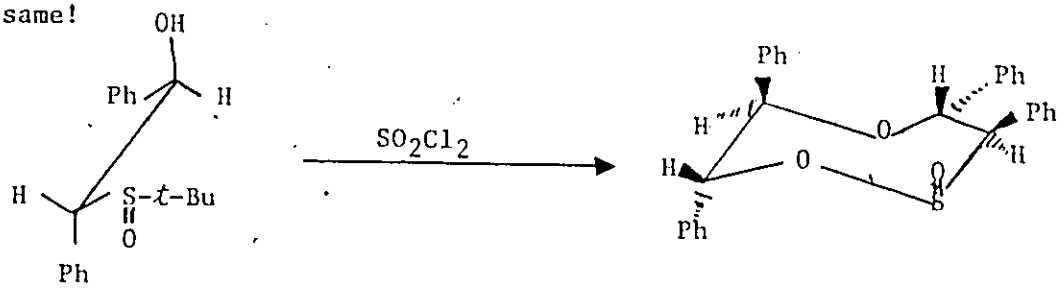
32%

+

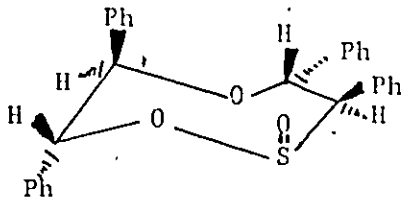


erythro 21 60%

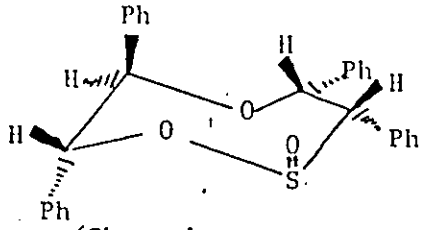
The cyclization of *threo*-1,2-diphenyl-2-*t*-butylsulfinyl ethanol 68 with SO_2Cl_2 following Sharma's procedure gave the seven membered ring sultine 70, m.p. 161°-163° and diphenyl acetaldehyde 71, both in 30% yield. The n.m.r. and IR data of sultine 70 are given below and compared with those of Sharma's photoisomer. Surprisingly the compounds are the same!



68 70



70

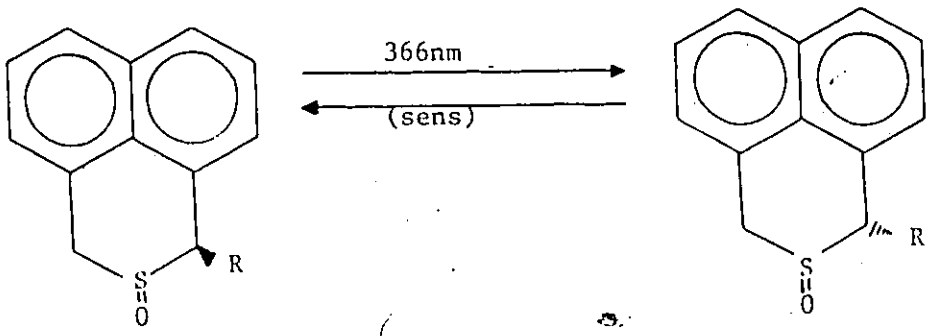


(Sharma's photoisomer)

72

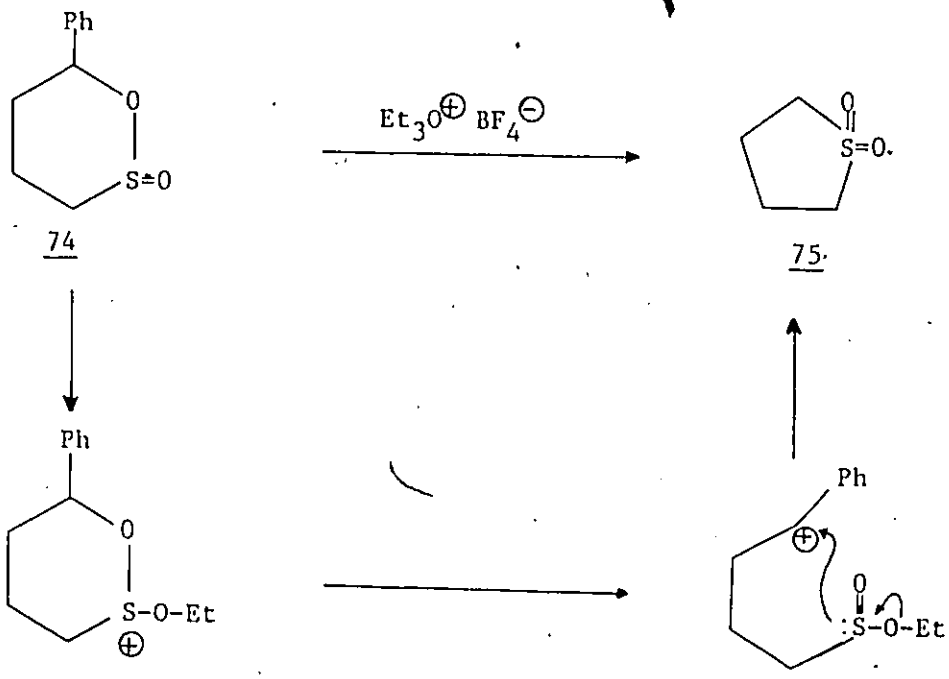
IR:	1120	1120
n.m.r.	4.03 (d.,J=11Hz, 1H)	4.02 (d, J=11Hz, 1H)
	4.44 (d, J=4Hz, 1H)	4.43 (d, J=4Hz, 1H)
	5.88 (d, J=11Hz, 1H)	5.86 (d, J=11Hz, 1H)
	6.69 (d, J=4Hz, 1H)	6.67 (d, J=4Hz, 1H)
	6.77-7.5 (m, 20H)	6.7-7.4 (m, 20H)

Based on Sharma' mechanism (2) for the formation of the seven membered ring sultines shown on page 8, the structure of the product from the *threo*-isomer could possibly have been 70, which has in each set of the dibenzyl units the phenyl groups *trans* to each other. Thus it appears that Sharma's assignment of his photoisomer is incorrect. Sharma (2) had made that assignment mainly on a chemical argument which was based on the known photochemistry of sultines bearing a phenyl group α to oxygen. (2) Such photochemistry had been shown to occur with isomerization at the benzylic carbon. Sharma used this idea to propose the structure 72 for the photoisomer. He, however, pointed out the compound 70 would better fit the observed coupling constants but nevertheless preferred 72 for the above stated chemical reasons. Structure 70 could be rationalized as the photoisomer if one assumes that isomerization is possible at both the benzylic carbons α to oxygen and α to sulfur. Isomerization at a benzylic position α to sulfur has been observed in the sulfoxide 73 (22) and thus it seems reasonable that it might also occur in sultines.



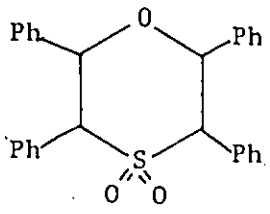
73

Two other reactions were carried out on 24 to prove the seven membered ring structure. It had been shown in this laboratory (23) that sultines such as 74 bearing a phenyl group α to oxygen isomerized cleanly to a five membered ring sulfone upon exposure to Meerwein's Reagent ($Et_3O^{\oplus}\ BF_4^{\ominus}$). The proposed mechanism is shown below.



74 75

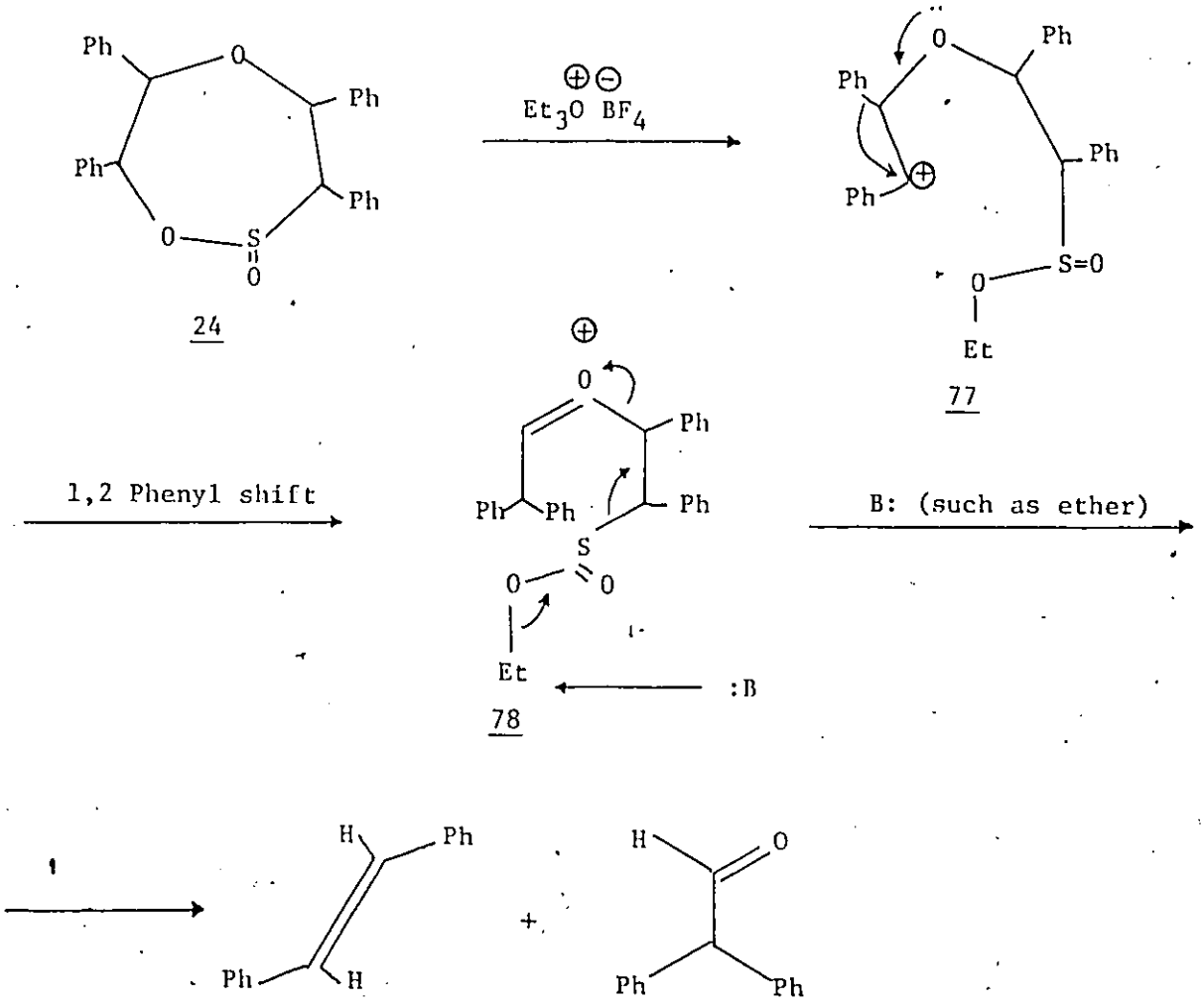
Such a ring contraction if it could be made to occur on the seven membered ring sultine 24 should give 76.



76

When sultine 24 was treated with $Et_3O^{\oplus}\ BF_4^{\ominus}$, no sulfone was obtained.

Instead, about 45% of *trans*-stilbene was recovered as the only isolable product. The possible mechanism of formation of *trans*-stilbene is described below.

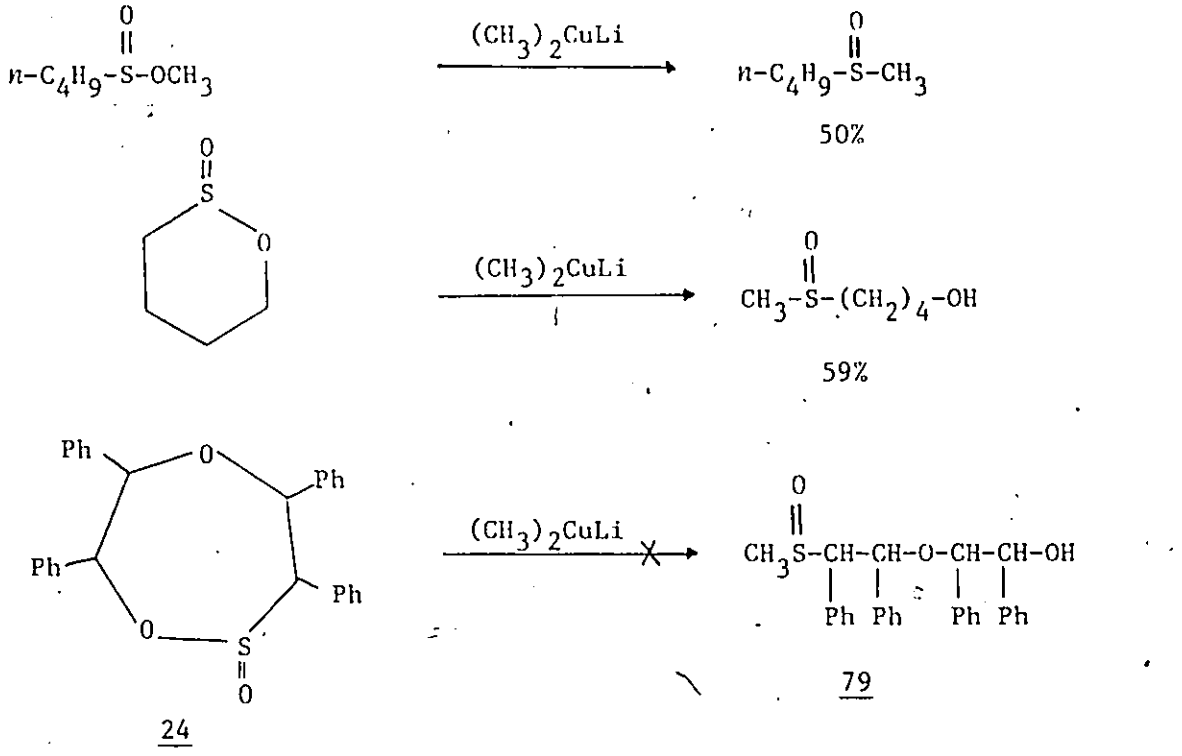


24 77 78

Formation of the intermediate 77 followed by a 1,2 phenyl shift would give 78. Further fragmentation of this species to diphenylacetaldehyde, *trans*-stilbene, and SO_2 (see arrows) could be imagined. Unfortunately, we could not establish the formation of diphenylacetaldehyde. This

reaction is somewhat similar to the p-toluene sulfonic acid treatment of the seven membered ring compound described by Sharma (24) which gave *trans*-stilbene in 85% yield.

In 1976, Harpp (25) reported the conversion of sulfinate esters to sulfoxides with lithium dimethylcuprate in fair yields. A few examples are given below. Therefore we decided to try the reaction of the sultine 24 with this reagent in the hope of isolating the corresponding sulfoxide 79.

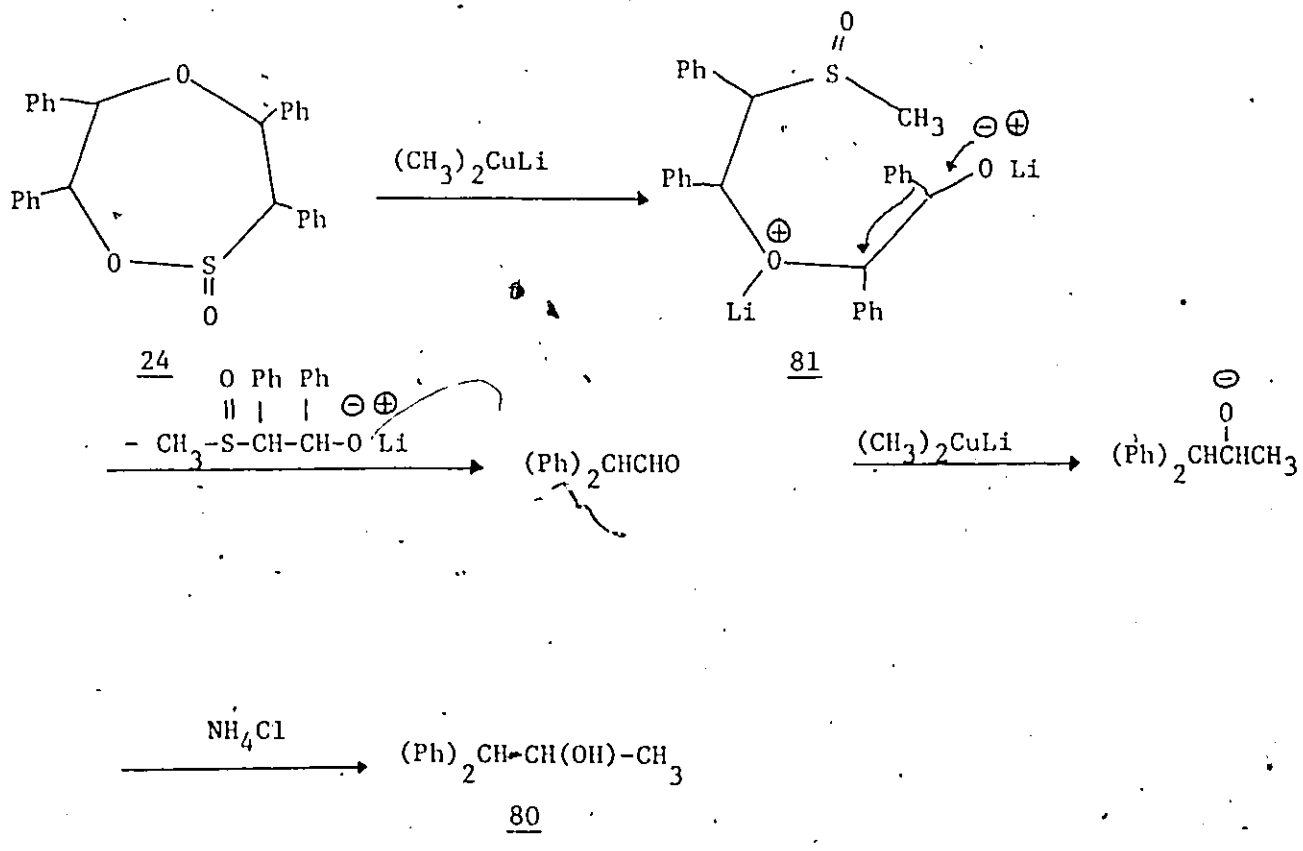


24 79

Treatment of sultine 24 with lithium dimethylcuprate in dry ether followed by quenching with saturated ammonium chloride gave 1,1-diphenyl-propan-2-ol 80 in 70% yield. This was another surprising result in view

of the proposed sultine structure. A possible mechanism to explain this result is shown below. If the intermediate 81 were formed upon initial reaction with $(CH_3)_2CuLi$, then complexation of a Lewis acid at the 5-oxygen followed by a 1,2 phenyl shift could give diphenyl acetaldehyde. The simple addition reaction of this product with $(CH_3)_2CuLi$ would furnish the isolated alcohol. Again, it was not possible to isolate the proposed hydroxy sulfoxide byproduct, possibly because of its high polarity.

As in the case of Sharma's research, the structure of the seven membered ring sultine remains to be confirmed. These compounds if correctly identified give an unusual and surprising variety of products whose formation from the seven membered ring sultine structure is often rather hard to explain.

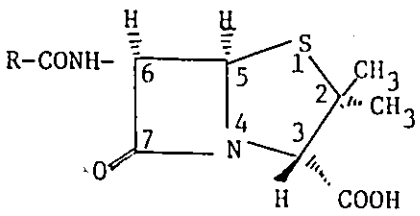


CHAPTER II

Introduction

The constant need for new antibiotics with either different and/or broader antibacterial activities has caused scientists to carry out research in this area for many years. The penicillins 1 and cephalosporins 2 represent an important and widely used class of antibiotics. The key structural feature which is common to both types of compounds is the strained β-lactam ring. Biologically it is thought that the penicillins and cephalosporins act as acylating agents and interfere with the growth of the cell walls of bacteria. (1) In solution, all the β-lactam antibiotics can polymerize to peptides and form gels with cross-linked polysaccharide chains. These are quite similar to the structure of the cell wall of bacterium. It is possible that di- and tripeptide molecules of the antibiotic itself undergo incorporation into the cell wall, leading to structural weakness and disintegration when the cell divides. (2)

Among the problems associated with the medical use of penicillins 1 (and cephalosporins 2) is an allergic reaction by a significant part of the population and a growing resistance of some bacteria toward penicillins. The bacteria have become capable of generating an enzyme called β-lactamase which destroys the β-lactam ring in the antibiotic and thereby inactivates the antibiotic. (3)



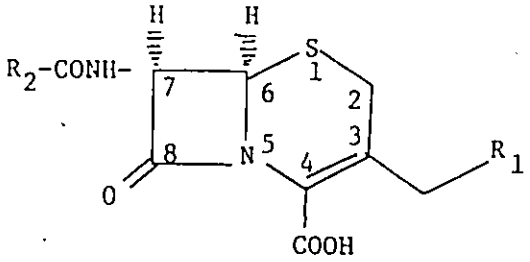
1

R= $-CH_2O-Ph$ Penicillin V

R= $-CH_2-Ph$ Penicillin G

R= $-CH_2CH=CHCH_2CH_3$ Penicillin F

R= $-n-C_7H_{15}$ Penicillin K



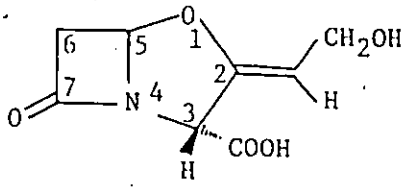
2

R_1= $-OCOCH_3$ Cephalosporin C

R_2= $-(CH_2)_3-\underset{\underset{COOH}{|}}{CH}-NH_2$

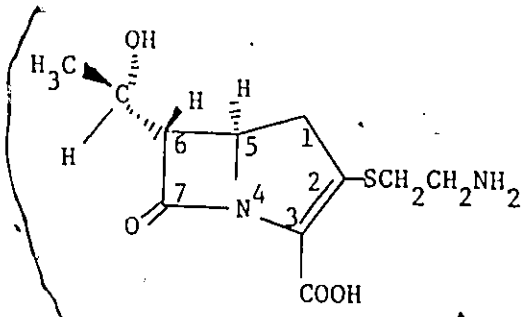
R_1= -H Cephalexin

R_2= $-CH(NH_2)Ph$



3

Clavulanic acid



4

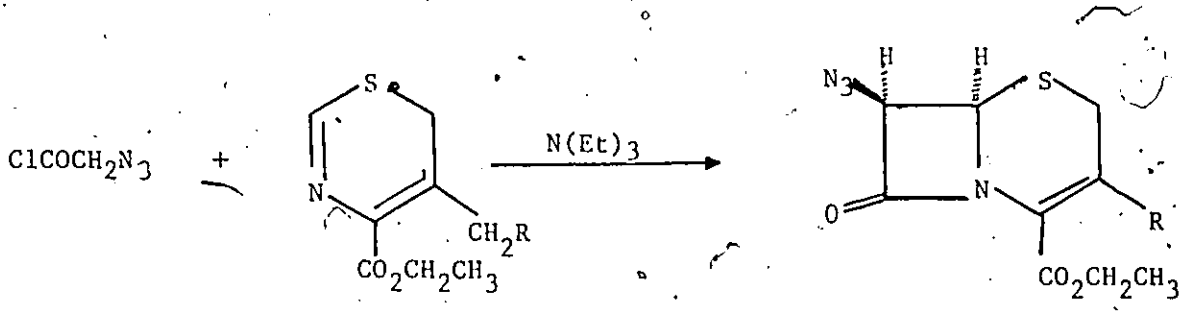
Thienamycin

In the past several years, two new types of pharmacologically active β-lactams have been isolated from fermentation brews. The two structural types are illustrated by clavulanic acid 3 and thienamycin 4.

Thienamycin, isolated from *streptomyces cattleye* is reported to be highly active against penicillin resistant bacteria.(4) Clavulanic acid, isolated from *streptomyces clavuligerus* (5), on the other hand is not an antibiotic itself; it functions as a β-lactamase inhibitor and is therefore capable of binding irreversibly to the enzyme β-lactamase which is produced by some bacteria to inactivate some penicillins and cephalosporins.

The total systhesis of penicillins and cephalosporins is difficult and inefficient. For example, Sheehan's(6) total systhesis of 6-amino-penicillanic acid 5 required many steps and occurred in very low yield. Similarly the Woodward (7) synthesis of Cephalosporin C also required many steps and occurred in low overall yield.

Recently scientists at Merck and Co. have reported a considerably more efficient route to cephalosporins based on the reaction between azidoacetyl chloride 6 and thiazine 7 in the presence of triethylamine. This generates in good yield the 7-azidocepham 8 from which cephalosporin derivatives can be readily prepared (8,9).

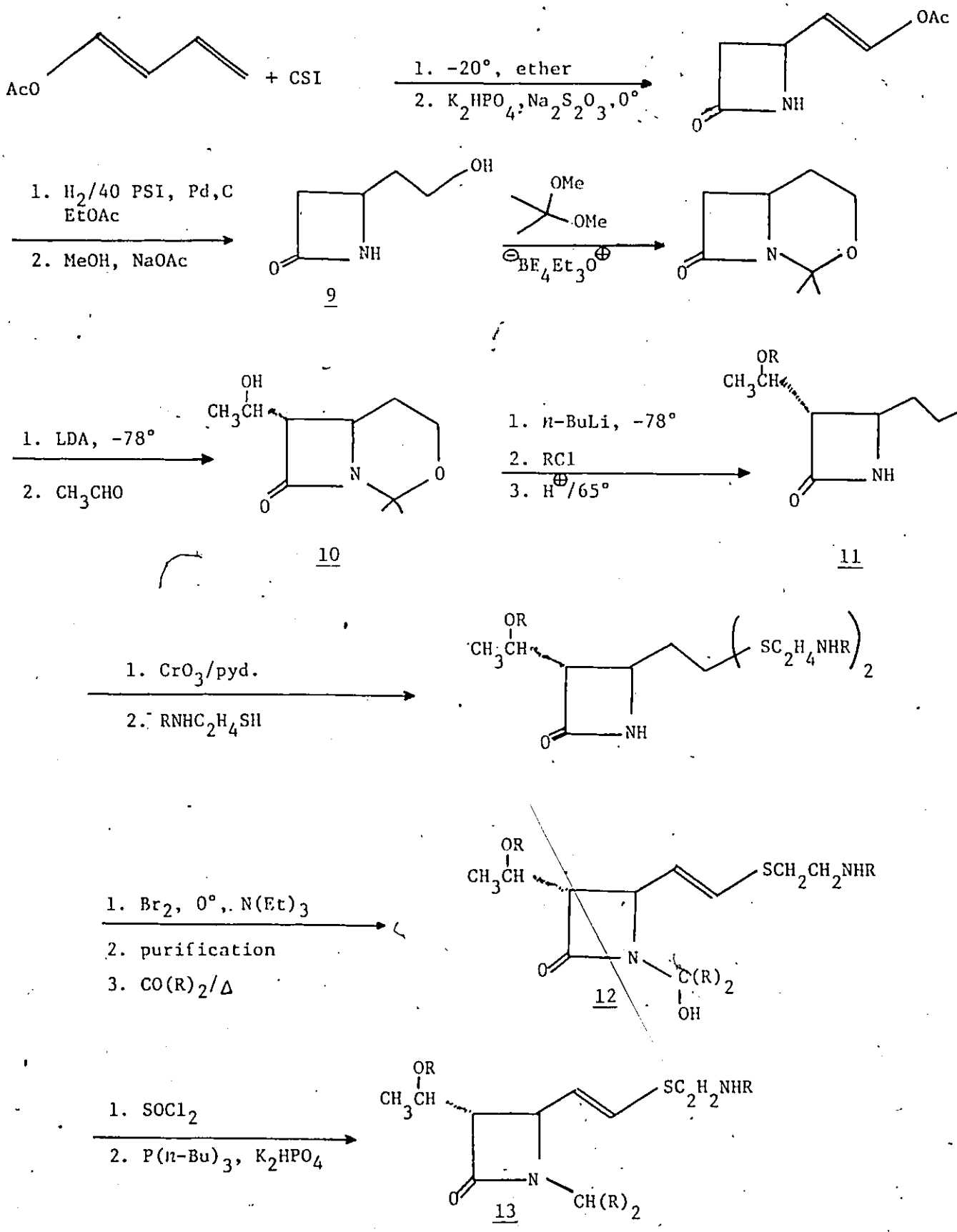


6 7 8

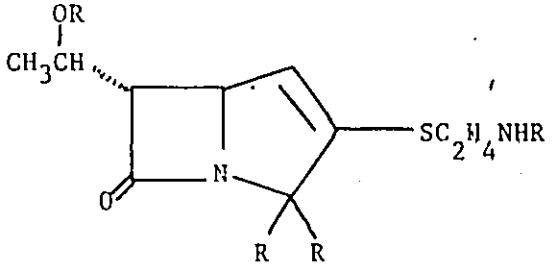
Despite these synthetic advances both penicillins and cephalosporins are more economically prepared by fermentation processes. Many semi-synthetic penicillins and cephalosporins are made by modification of those available from fermentation.

Comparison of the structures of penicillins and cephalosporins with those of thienamycin shows that the latter is simpler and might be easily accessible by total synthesis. In particular the stereochemistry about the β-lactam ring is in the more stable *trans* configuration compared to *cis* in 1 and 2. The absence of the sulfur atom in the second ring in 4 also potentially simplifies the synthetic problem.

The first synthetic thienamycin was prepared in 1977 by Johnston and his co-workers. (4) They reported that 4-(2-hydroxyl) ethyl-β-lactam 9 was available from 1-acetoxy butadiene and chlorosulfonyl isocyanate (CSI), followed by reductive hydrolysis of the chlorosulfonyl group and then hydrogenation and deacetylation. Conversion of the β-lactam 9 with 2,2-dimethoxypropane to an acetonide, followed by treatment with lithium diisopropylamide (LDA) then acetaldehyde gave the *trans* hydroxyethyl derivative 10 as a mixture of epimers at the hydroxyl bearing carbon.

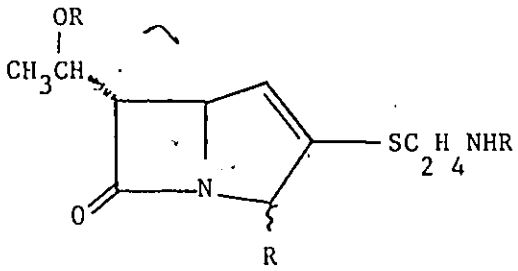

AcO
+ CSI
1. -20°, ether
2. K_2HPO_4, $Na_2S_2O_3$, 0°
OAc
NH
O
1. H_2/40 PSI, Pd,C
EtOAc
2. MeOH, NaOAc
OH
9
OMe
OMe
$\ominus BE_4Et_3O\oplus$
N
O
1. LDA, -78°
2. CH_3CHO
OH
CH_3CH
10
1. n-BuLi, -78°
2. RCl
3. $H^\oplus$/65°
OR
11
1. CrO_3/pyd.
2. $RNHC_2H_4SH$
SC_2H_4NHR
1. Br_2, 0°, $N(Et)_3$
2. purification
3. $CO(R)_2/\Delta$
SCH_2CH_2NHR
$C(R)_2$
12
1. $SOCl_2$
2. $P(n\text{-}Bu)_3$, K_2HPO_4
$CH(R)_2$
13

1. Br_2, 0°
2. $N(Et)_3$, DMF
3. AgF



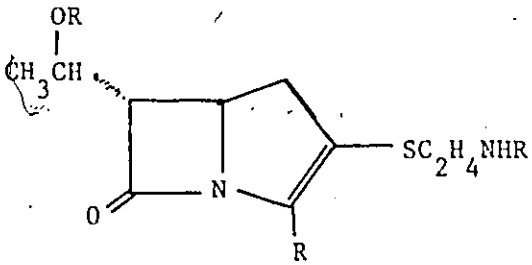
14

1. Collidine, LiI, Δ
2. Diisopropylamine; DMSO



15 (major)

and



16 (minor)

R = $-CO-CH_2(C_6H_4)-p-NO_2$

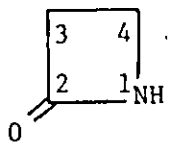
16 → 4

1. Pd/C
2. H_2O/K_2HPO_4

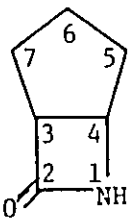
Esterification of the hydroxyl group of compound 10 with $p\text{-}NO_2C_6H_4CH_2OCCl$ (O) and subsequent treatment with HOAc gave compound 11. Oxidation of compound 11 with CrO_3 in pyridine, followed first by thioacetylation with $p\text{-}NO_2C_6H_4\text{-}CH_2O\text{-}CNHCH_2CH_2SH$ (O), bromination and dehydrobromination gave β-lactam 12. Condensation of 12 with bis-(p-nitrobenzyl)-ketomalonate, then replacement of OH with H by chlorination and reduction afforded 13. Ring closure and elimination of HBr from the cyclic product were achieved by bromination then cyclization, followed by dehydrobromination. Decarboxylation of 14 and isomerization of the double bond gave a mixture of 15 and 16. The compound 16 afforded thienamycin by hydrogenolysis with Pd/C in a water-dioxane-ethanol-K_2HPO_4 mixture.

The overall yield of Johnston's method was less than 0.1%. It was felt that more efficient methods of generating the ring system of thienamycin should be possible. This short part of this thesis reports the results of several approaches.

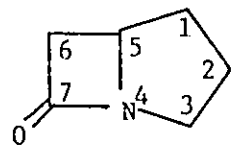
In order to avoid confusion the following numbering systems for mono- and bicyclic β-lactams will be used in this thesis. It conforms to the Chemical Abstracts numbering system.



I



II

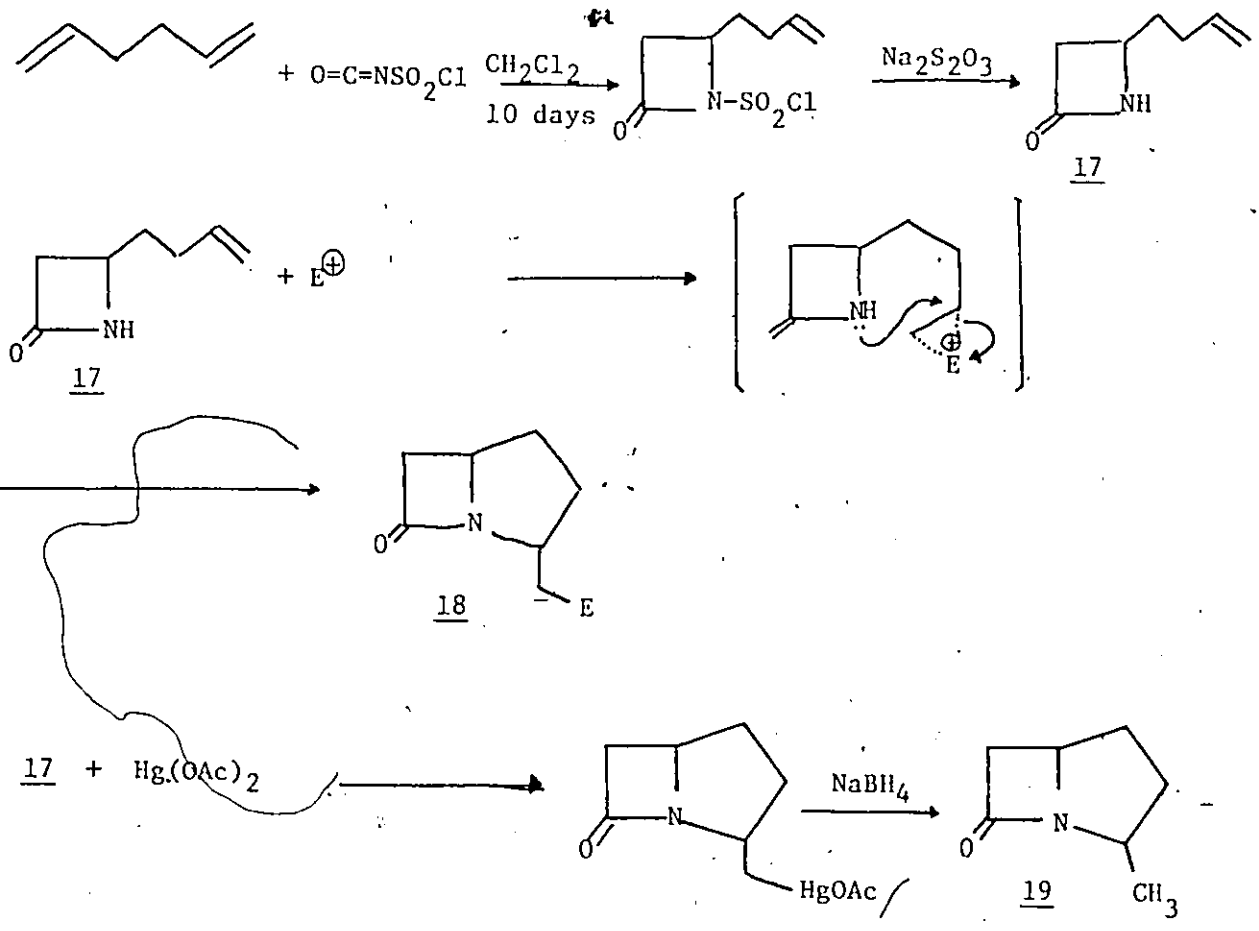


III

Discussion and Results

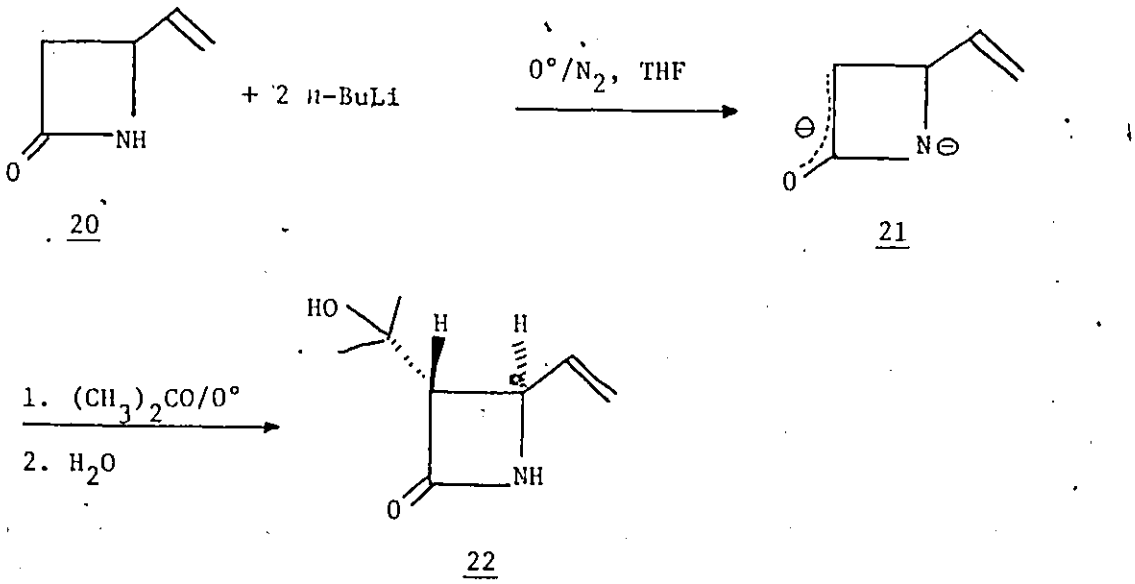
Two aspects of the thienamycin structure were investigated. The first one concerned itself with the introduction of a substituent on C-6 similar to that found in thienamycin while the second involved two approaches for the generation of the thienamycin ring system.

The compound 17, prepared earlier in our laboratory by R. Legault (10) was considered a promising intermediate to potential thienamycin derivatives. It is readily avaiable from the cycloaddition reaction between 1,5-hexadiene and chlorosulfonyl isocyanate, followed by $Na_2S_2O_3$ reduction. (11) It had been envisaged that compound 17 could possibly be converted into the bicyclic system 18 by some type of electrophilic addition to the vinyl group followed by participation of the slightly basic amide nitrogen.



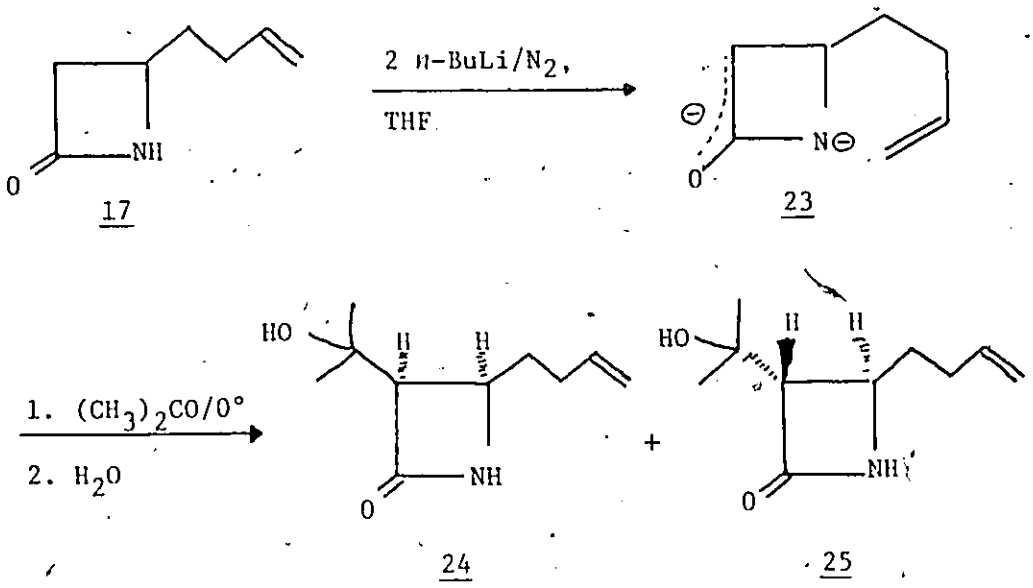
Indeed, in a preliminary experiment, it had been shown that reaction of 17 with $Hg(OAc)_2$ followed by $NaBH_4$ yielded the bicyclic derivative 19 in about 60% yield.

The introduction of a hydroxyalkyl group α to the carbonyl group in simple β-lactams had also been reported from this laboratory.(12) It had been shown that reaction of the vinyl β-lactam 20 with 2 equivalents of *n*-butyllithium at 0° followed by dry acetone afforded, via the dianion 21, the hydroxy alkylated β-lactam 22.



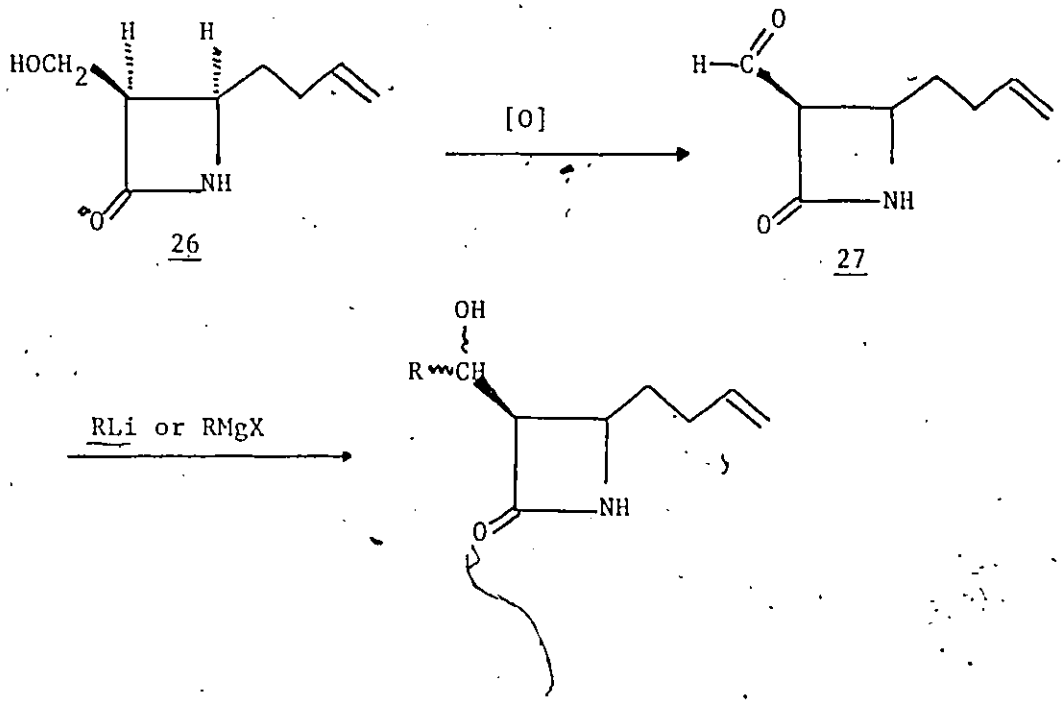
20 21 22

The reaction of the dianion 23, prepared from compound 17 and 2 equivalents of *n*-butyllithium in THF for 60 minutes with acteone had been studied by R. Legault (13) who reported 60% yield of a 1:1 mixture of the products 24 and 25.



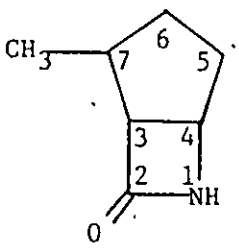
The high *cis* and *trans* ratio was considered somewhat unusual, since in the hydroxy alkylation of the dianion 21, mainly the *trans* isomer 22 had been formed. Also, at the time this work was begun the stereochemsitry about the β-lactam ring in thienamycin had not been known and it was suspected, by analogy with the penicillins, to be *cis*. Thus the finding that hydroxy alkylation of 17 gave a large percentage of the *cis* isomer 24 was considered an important observation. It was therefore decided to try the reaction of 23 with formaldehyde to produce the hydroxymethyl derivative 26 hopefully in the same favourable *cis*/*trans* ratio. Such a product could also serve as an entry to other derivatives via oxidation to the aldehyde 27 and reaction with alkyllithium or Grignard reagents.

A further advantage of the reaction of formaldehyde with 23, compared with other aldehydes is that only one additional chiral centre is introduced thus hopefully facilitating the purification of the initial condesation product. There was a reasonable expectation based on Cram's Rules that the formyl derivative 27 might react with organometallics in a stereoselective manner. Very little stereochemical preference would be expected in the condensation of 23 with an aldehyde.



When the dianion 23 was generated in the usual manner and quenched with gaseous formaldehyde, none of the desired compound 26 was formed. Instead a small amount of product isomeric with starting material was isolated. The product was obtained as white granules, m.p.90.5°-91°. Its infrared spectrum still showed a β-lactam carbonyl at 1770 cm^{-1} together with an NH band at 3450 cm^{-1}. The n.m.r. showed peaks at 1.2 (d, J=6Hz, 3H), 1.3-2.2 (m, 5H), 3.3-3.5 (m,1H), 4.0 (slightly broadened triplet, J=4Hz,1H) and

6.1 (N-H). These data together with an acceptable elemental analysis were in agreement with the structure 28.



28

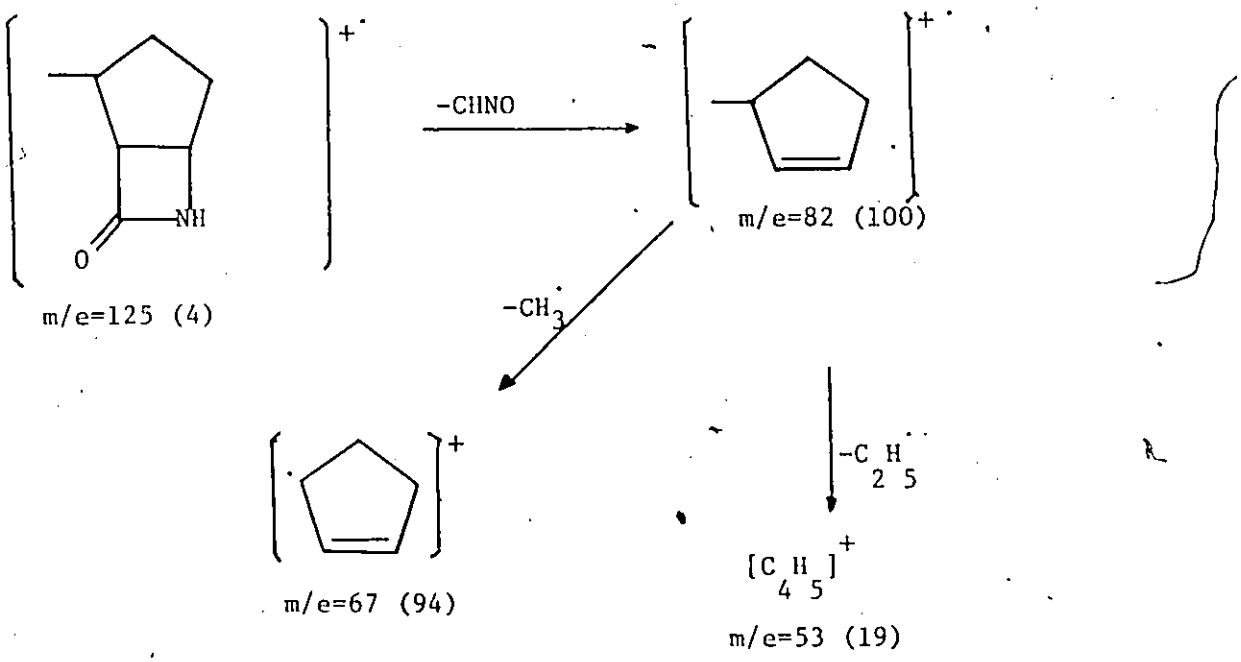
Inspection of a molecular model of 28 showed that the hydrogen at carbon 4 had a dihedral angle of approximately 90° with one of the hydrogens of the adjacent methylene group, thus rationalizing its appearance as a triplet.

The mass spectrum of 28 showed the following major peaks.

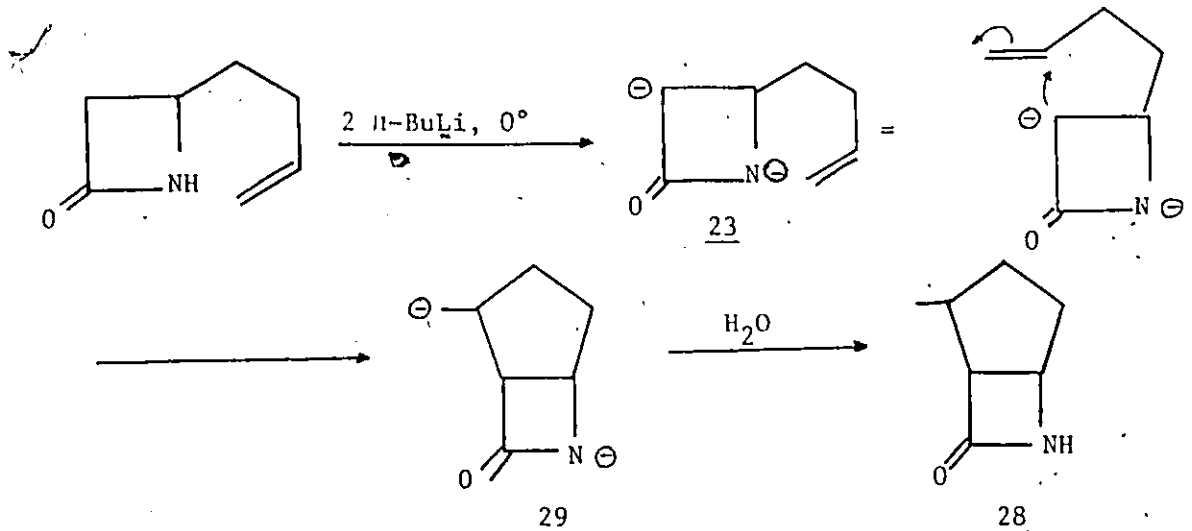
m/e	relative abundance
126	7
125	4
82	100
67	94
53	19

The strong M+1 peak may be due to a bimolecular proton transfer. Such transfers are sometimes observed for compounds containing hetero atoms if a large sample is employed. (14)

The base peak at m/e =82 is compatible with the structure 28. It represents the loss of the elements of CHNO from the molecular ion. This can be rationalized as resulting from a cycloreversion of the β-lactam ring. The peaks at m/e=67 and 53 are probably due to the loss of $CH_3^{\cdot}$ and $C_2H_5^{\cdot}$ fragments from the m/e=82 fragment.

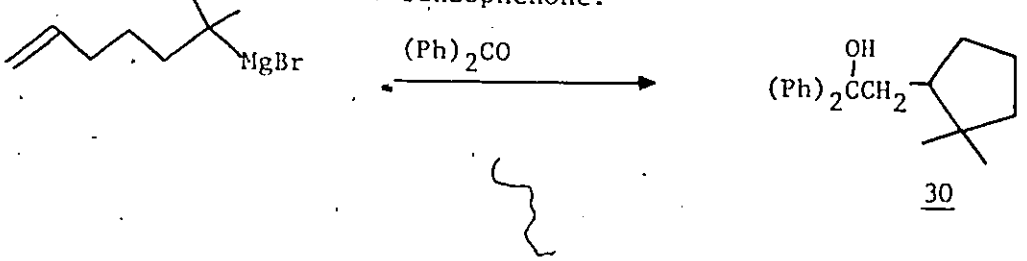


The formation of 28 can be rationalized as resulting from a generation of the dianion 23, followed by intramolecular addition to the terminal vinyl group thereby obtaining 29, quenching of which leads to 28.



Presumably the paraldehyde contained some water which was carried into the reaction mixture during the pyrolysis of the formaldehyde polymer. The reaction of β-lactam 17 with 2 equivalents of *n*-butyllithium overnight followed by H_2O quenching afforded compound 28 in 35% yield.

The intramolecular addition of a Grignard reagent to a terminal vinyl group has been known for some time and recently described again by Ashby. (15) Thus the Grignard reagent generated from 6-methyl-6-bromo-1-heptene gave 30 in 46% yield, in which the initially formed Grignard reagent had cyclized prior to reaction with the benzophenone.

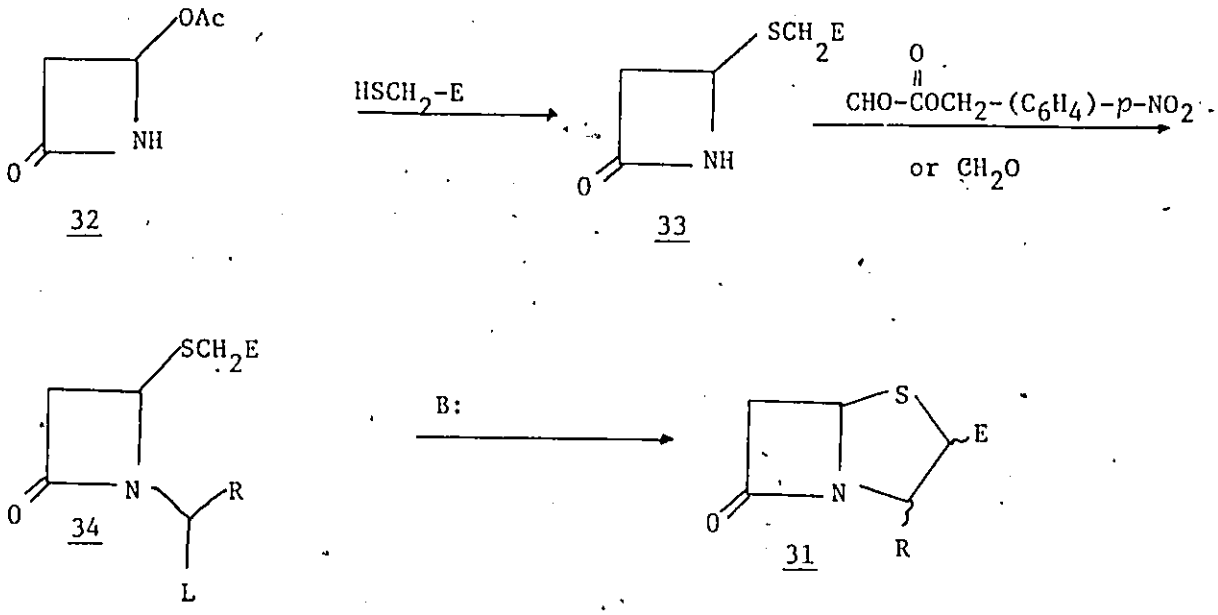


30

Shortly after this work was complete the structure of thienamycin became known as 4 in which the stereochemistry about the β-lactam ring was *trans*. Thus the need to produce the *cis* stereochemistry about the β-lactam ring was no longer required and this aspect was discontinued.

Two approaches to the thienamycin ring system were briefly investigated. The first approach envisaged the preparation of the bicyclic derivative 31 starting with the readily available 4-acetoxy azetidin-2-one 32 (16) as shown in Scheme 1.

An Approach to Thienamycin Ring System



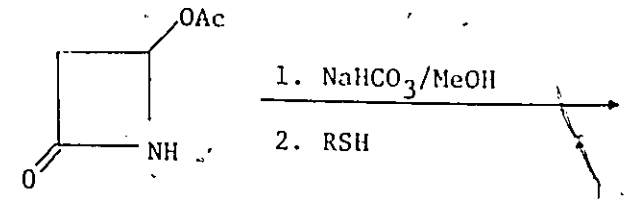
R = H or $CO_2CH_2(C_6H_4)$-p-NO_2 E = electron withdrawing group L = Leaving group

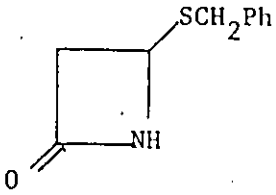
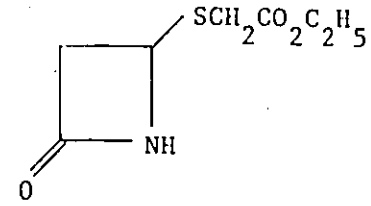
Scheme 1

The first step was the introduction of a thioalkyl group at C-4 carrying an electron withdrawing group α to the sulfur atom. This would be followed by the condensation of 33 with *p*-nitrobenzyl glyoxylate (16) thereby producing 34. This type of reaction and subsequent conversion of the initial hydroxy group into a Cl has been reported by Woodward et.al. (7). Finally it was hoped that a cyclization of 34 (L=Cl) might occur under basic conditions to give 31.

The 4-thioalkyl β-lactams were prepared by stirring a solution of the acetoxy β-lactam with either α-toluenethiol or ethyl 2-mercapto-

acetate thereby giving the desired compounds 35 and 36 in 86% and 90% yield respectively.

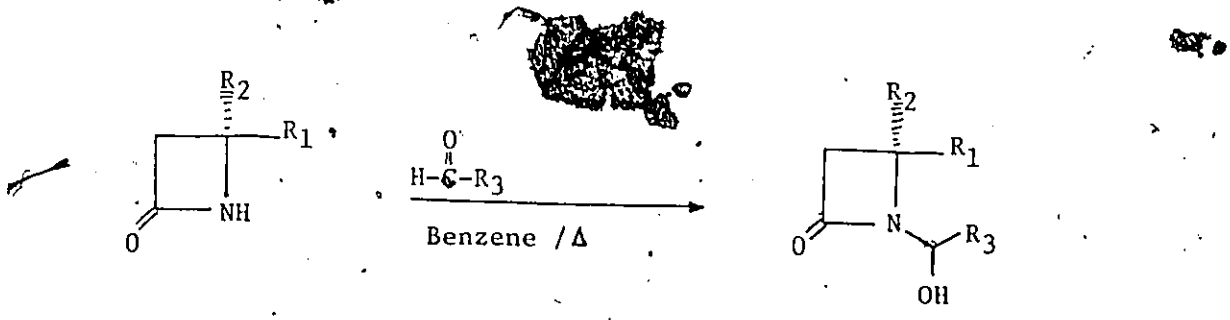


β-Lactam derivatives	Mercaptans	Yield
 35	$HSCH_2Ph$	86%
 36	$HSCH_2CO_2C_2H_5$	90%

The infrared spectra of both 35 and 36 gave bands in the region 1750 to 1770 cm^{-1} and 3340 cm^{-1} expected for the β-lactam carbonyl and the amide N-H group respectively. The position of the n.m.r. peaks for compound 35 were essentially identical with those reported by Clauss *et al*, (18), those for the ester 36 which had not been previously prepared were as expected and are reported in the Experimental Section.

Condensation of β-lactams with aldehydes was reported by Woodward and his co-workers (19) to occur simply upon heating in an inert solvent such as benzene or toluene. These condensations were carried out using the

β-lactam 36 and the 4-methyl-4-vinyl β-lactam 37 with both formaldehyde and *p*-nitrobenzyl glyoxylate as the aldehyde components. The results are shown in Table 1.

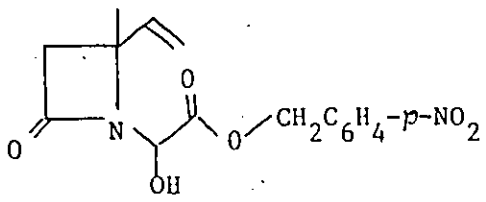
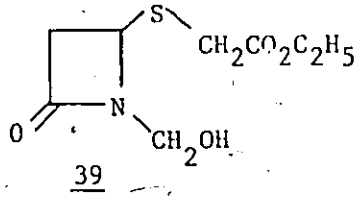
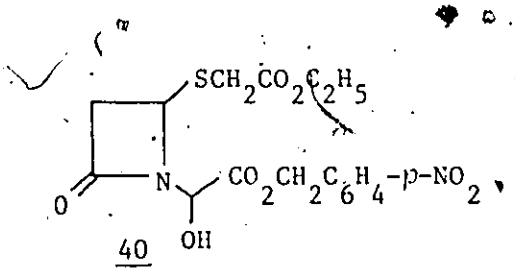


	R_1, R_2	R_3	Yield	Refluxing Time
38	R_1=-CH_3 R_2=-$CH=CH_2$	-CO_2CH_2-C_6H_4-*p*-NO_2	85%	7 hours
39	R_1=-$SCH_2CO_2C_2H_5$ R_2= H	H	80%	2½ hours
40	R=-$SCH_2CO_2C_2H_5$	-CO_2CH_2-C_6H_4-*p*-NO_2	50%	5 hours

Table 1

The yields of the condensation products varied from good to fair. The course of the reaction could not be followed by Thin Layer Chromatography since the R_f values of both the starting materials and products were very similar. N.m.r. spectroscopy was more useful due to the presence of a long range coupling effect. The hydrogen on C-3 was coupled to the hydrogen on nitrogen in the starting materials. This disappeared on substitution of the N-H. In addition, the chemical shift of the

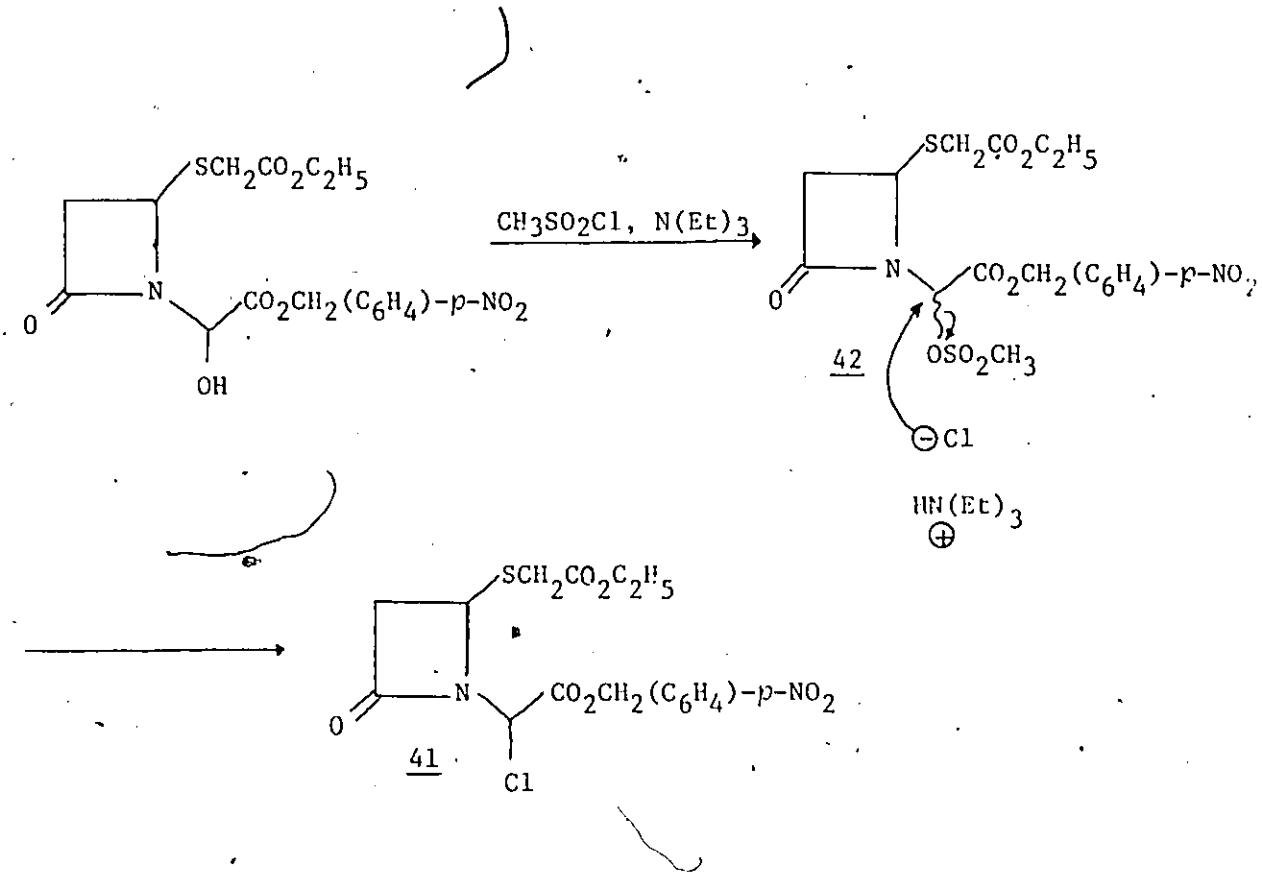
hydrogens on C-4 of the β-lactam 38, 39, 40 were slightly different from that of the corresponding N-substituted β-lactams. The structural identification of the reaction products was based on their n.m.r. and IR spectra. These are shown below.

Compound	N.m.r.	IR
 38	1.6 (s, 3H)	1100
	2.8 (s,2H)	1350
	3.7 (b.s., 1H)	1540
	4.8-6.1 (m, 6H)	1750-1770
	7.3-8.1 (q,4H)	3450
 39	1.3 (t, J=7Hz, 3H)	1740
	2.9-3.7 (m, 2H)	1780
	3.4 (s, 2H)	3480
	4.2 (q, J=7Hz, 2H)	
	4.7 (b.d., 3H)	
	5.0 (m, 1H)	
 40	1.3 (t, J=7Hz, 3H)	1780
	2.8-3.6 (m, 4H)	3500
	4.0 (q, J=7Hz, 2H)	
	4.5 (b.s., 1H)	
	4.8 (m, 1H)	
	5.1-5.3 (m, 3H)	
	7.1-8.0 (q, 4H)	

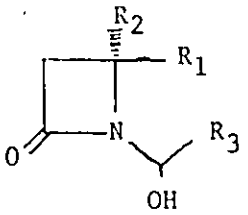
Compounds 38 and 40 were obtained as isomeric mixtures due to the additional chiral centre in the N side chain. They could not be separated either by Thin Layer Chromatography or by Column Chromatography. In the n.m.r. spectrum of 40, the existence of the two isomers was shown by the presence of two singlets at 5.2 ppm and 5.3 ppm. A hydroxyl group is not a good leaving group and conversion to a better leaving group such as a mesylate or halide was necessary. The first experiment was carried out on compound 40.

A mixture of 40 and methanesulfonyl chloride in methylene chloride was reacted with triethylamine at room temperature. This reaction afforded, after chromatography, not the mesylate 41 but the chloride 42 in 52% yield. Compound 42 showed the absence of an OH peak in the infrared, in the n.m.r. spectrum absorptions were found at δ=1.3 (t, J=7Hz, 3H); 3.0-3.7 (m, 4H, due to the hydrogens α to the β-lactam carbonyl and the CH_2 group flanked by S and $CO_2C_2H_5$ groups); a quartet at δ=4.1 (J=7Hz, 2H); a multiplet from δ=5.0-5.3 assignable to the C-4 hydrogen and the benzylic CH_2 group; two singlets at 6.0 and 6.1 (total 1H, due to the CHCl of the two possible isomers); and the four aromatic hydrogens as an approximate AB quartet at 7.4 and 8.1. Because of its instability, the chloro compound 41 was not further purified or sent for elemental analysis.

The mechanism of the formation of 41 is shown below. The initially formed mesylate 42 reacts further with chloride ion of the byproduct, triethylamine hydrochloride, to give compound 41.



Attempted formation of either the mesylate or the corresponding chloride from the β-lactam alcohol 39 and 38 gave no identifiable products. Presumably these products are too unstable to be isolated and undergo solvolysis of the leaving group, possible accompanied by β-lactam ring opening. The difference between 40 and 39 is easy to understand but the chloride from 39 might have been expected to be similar to that from 40.



$\xrightarrow[N(Et)_3]{CH_3SO_2Cl}$ unidentified compounds

39 R_1=-$SCH_2CO_2C_2H_5$

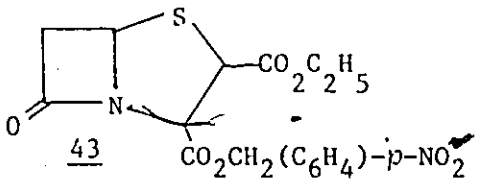
R_2=-H

R_3=-H

38 R_1=-CH_3

R_2=-C_2H_5

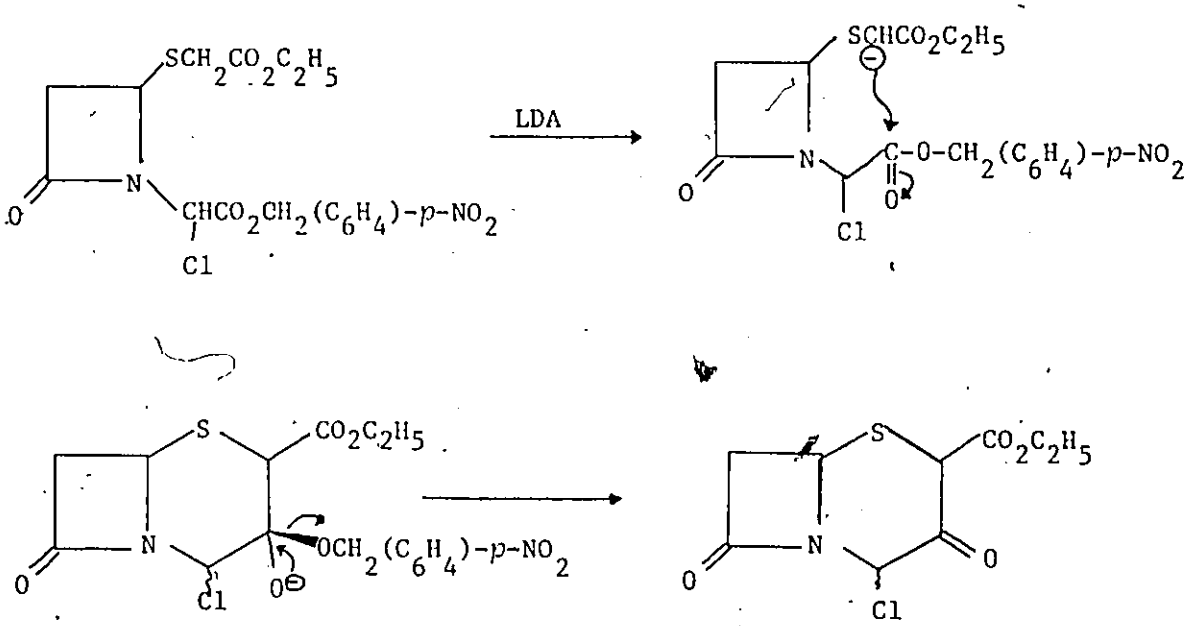
R_3=-$CO_2CH_2(C_6H_4)$-*p*-NO_2



43

Ring closure of the chloro derivative 41 to 43 was attempted using lithium diisopropylamide (LDA) in THF at 0°. Shortly after addition of 41 to the lithium diisopropylamide (LDA) solution a small amount of white crystalline substance precipitated. More of this material was collected from the THF solution and identified as *p*-nitrobenzyl alcohol by comparison

of its m.p. and n.m.r. spectrum with that of the data available in the Aldrich N.M.R. DATA. (20) No other identifiable product was obtained from the reaction. The formation of *p*-nitrobenzyl alcohol is rationalized as shown below. The result suggests that this type of cyclization "North to South" as presented can not be used to construct the five membered ring of thienamycin because of the ease of attack at the carbonyl group via a six membered ring intermediate. In retrospect this result is not surprising.



CHAPTER III

Melting points were determined with a Thomas Hoover Apparatus and are not corrected; boiling points are also uncorrected. Infrared spectra were recorded on Beckman IR-20 and Unicam SP-1100 Infrared Spectrophotometers. The n.m.r. spectra were obtained on Varian Associates HA-100 and T-60 Spectrometers using $CDCl_3$ as solvent. The chemical shifts are reported as ppm downfield from internal tetramethylsilane (TMS). The mass spectra were recorded using an AEI MS-9 Spectrometer. Elemental analysis were carried out by Galbraith Laboratories, Knoxville, Tennessee. Most of the chemicals used during the course of this work were supplied by Aldrich Chemical Co.; Fisher Scientific, Chemical Samples Co. The solvents for chromatography used meet A.C.S. Reagent Grade Specification or were distilled prior to use. Alkyllithiums were supplied by Foote Mineral Co. or Ventron Co. Silical gel 60, supplied by Brinkmann Instruments (Canada) Ltd., was used for Column Chromatography. Usual workup refers to partitioning between water and an organic solvent, drying of the organic extracts over anhydrous magnesium sulfate and evaporating the solvent using a rotary evaporator.

(A) Experimental Section of Benzfused Sultines

o-mercaptobenzyl Alcohol 34

This compound was prepared in 80% yield by reduction of *o*-mercaptobenzoic acid 35 with $LiAlH_4$ in THF. The crude reduction product was a slightly orange oil; n.m.r.: 3.3 (b.s., OH and SH), 4.6 (s, 2H), 7.0-7.4 (m, 4H); IR: 3360 and 2530 cm^{-1}.

2-(*o*-mercaptophenyl)-propan-2-ol 37

A stirred solution of 4.90 g of methyl *o*-mercaptobenzoate (prepared by H_2SO_4 catalyzed esterification of the corresponding acid) was dissolved in 200 ml of dry ether at 0° under N_2 and reacted with 50.5 ml of 1.7 M CH_3Li. The reaction was stirred for 5 minutes then washed with 200 ml of 10% HCl. The separated aqueous layer was saturated with NaCl and the reextracts were dried and evaporated to yield 4.22 g (86%) of the desired product as a yellowish oil; n.m.r.: 1.7 (s, 6H), 2.7 (b.s., 1H), 4.1 (b.s., 1H) and 6.9-7.5 (m, 4H). IR: 3640 and 2400 cm^{-1}. The substance was considered sufficiently for the next transformation.

(*o*-Mercaptophenyl)-diphenylmethanol 36

Phenylmagnesium bromide (80 mmole) was prepared in 100 ml of ether. To this solution was added 4.6 g (27.2 mmole) of methyl *o*-mercaptobenzoate. The solution was stirred for about 30 minutes at room temperature. The usual Grignard workup gave 8.2 g (95%) of crude product; n.m.r.: 3.4 (s, 1H), 3.8 (s, 1H), 6.4-6.6 (m, 1H) and 6.8-7.3 (m, 13H). IR: 3480, 2540 cm^{-1}, no C=O. The crude product was sufficiently pure for the next step.

3H-2,1-Benzoxathiole 1-oxide 11

To a solution of 5.71 g of *o*-mercaptobenzyl alcohol in 100 ml of a 9:1 mixture of CH_2Cl_2 and acetic acid at 0° was added 4.4 ml of SO_2Cl_2 in 20 ml of methylene chloride, dropwise. The mixture was stirred for 1 hour and washed with 200 ml of 10% Na_2CO_3. The organic extracts were dried and the solvent evaporated. The crude brown oil was chromatographed on 300 g of silica gel. The sultine 11 was eluted with 1:5 ethyl acetate-hexane; yield 2.6 g, 40%. The infrared and n.m.r. spectra were identical to those of the compound previously prepared by a different route. (1)

3,3-Dimethyl-2,1-benzoxathiole 1-oxide 25

To a mixture of 0.511 g of *o*-mercaptophenyl-propan-2-ol and 2 ml of acetic acid in 25 ml of CH_2Cl_2 at 0° was added dropwise 0.25 ml of SO_2Cl_2 in 5 ml of CH_2Cl_2. The reaction was subsequently stirred for one hour and then worked up as in the case of 11. The crude product was chromatographed on 30 g of silica gel. Elution with hexane yielded 0.274 g (50%) of sultine 25, colorless oil, b.p. 125°/4.5mm, n.m.r.: 1.67 (s, 3H), 1.83 (s, 3H), 7.05-7.75 (m, 4H); IR: 1130 and 1105 cm^{-1} (S=O); m.s. were: 182 (78), 167 (32), 148 (88), 134 (52), 118 (100), 103 (68), 91 (52), 77 (78).

3,3-Diphenyl-2,1-benzoxathiole 1-oxide 26

A solution of 0.56 ml (6.9 mmole) of sulfuryl chloride dissolved in 10 ml of CH_2Cl_2 was added dropwise with stirring to 2.03 g (6.9 mmole) of (*o*-mercaptophenyl)-diphenylmethanol 36 in 70 ml of CH_2Cl_2 and 10 ml of acetic acid at 0°. The reaction mixture was stirred for 1 hour after

completion of the addition then washed with 10% Na_2CO_3 until the pH of the aqueous layer was 8. The crude organic product was chromatographed on 150 g of silica gel using hexane-ethyl acetate (4:1) as eluent. The sultine 26 was obtained as colorless crystals, 0.651 g (30%), m.p. 125°-126°. N.m.r.: 7.1-7.8 (m); IR: 1110 and 1120 cm^{-1}; m.s. calcd. for $C_{19}H_{14}O_2S$: 306; found: 306, other peaks (relative intensity): 258 (4), 242 (100), 197 (44), 165 (76), 118 (40), 105 (47), 77 (62).

2-(1-phenylthioethyl)-benzyl alcohol 39

A solution of 0.40 g of $LiAlH_4$ in 100 ml of CH_2Cl_2 was added to a solution of 5.46 g (20 mmole) of methyl 2-(1-phenylthioethyl)-benzoate 38 (prepared in 62% yield by alkylation of *o*-mercaptobenzoic acid with α-phenyl bromide followed by immediate esterification (1)). The mixture was stirred for 2.5 hours. 5% NaOH was introduced slowly into the reaction mixture until the excess $LiAlH_4$ disappeared. The organic extracts were dried and evaporated to give 4.07 g (83%) of the desired compound; n.m.r.: 1.5-1.7 (d, J=7Hz, 3H), 2.2-2.5 (b.s., OH), 4.1-4.5 (q, J=7Hz, 1H), 4.6 (s, 2H), 7.1-7.4 (m, 9H) ppm; IR: 3340 cm^{-1}.

2-(1-phenylthioethyl)-benzaldehyde 40

2-(1-phenylthioethyl)-benzyl alcohol 39 (14.0 g) was dissolved in dry pyridine (87 ml) and reacted with 35 g of CrO_3 using the procedure of Ratcliffe and Rodehurst (2). The yield of the aldehyde 40 was 10.0 g (72%), pale yellow oil, n.m.r.: 1.6 (d, J=7Hz, 3H), 4.3 (q, J=7.5Hz, 1H), 7.2-7.4 (m, 3H), 7.7-8.1 (m, 1H), 10.4 (s, 1H); IR: 1685 cm^{-1}.

Sulfide-alcohol 42

The above aldehyde 40, (1.45 g, 6.0 mmole), dissoved in 20 ml of dry ether was added to a solution of CH_3MgI prepared from 2.28 g of methyl iodide and 0.5 g of Mg in 20 ml of dry ether. The reaction mixture was stirred for an additional hour after completion of the addition, then poured into 50 ml of H_2O. Separation, drying and evaporation of the organic extracts gave 1.30 g (85%) of alcohol 42; n.m.r.: 1.3 (2d, J=7Hz, 3H), 1.7 (2d, J=7Hz, 3H), 2.2 (OH), 4.2 (m, 1H), 5.2 (m, 1H), 7.0-7.4 (s, 9H). IR: 3400 cm^{-1}.

Sulfide-alcohol 41

Aldehyde 40 (3.5 g), dissolved in 10 ml of dry ether was added to a solution of PhMgBr prepared from 4.30 g of bromobenzene and 1.8 g of Mg in 50 ml of dry ether. The reaction mixture was stirred for an additional hour after completion of the additon, then poured into 50 ml of H_2O. Separation, drying and evaporation of the organic extracts gave 3.30 g (72%) of alcohol 41, IR: 3440 cm^{-1}. n.m.r.: 1.6 (d, J=7Hz, 3H), 2.3 (s, 1H), 4.0 (q, J=7Hz, 1H), 6.1 and 6.2 (2s, 1H), 7.0-7.5 (m, 14H).

Sulfoxide-alcohol 43

To alcohol 41, dissolved in 100 ml of ethyl acetate at -30° was added dropwise with vigorous stirring 2.09 g of mcpba in 30 ml of ethyl acetate. The reaction mixture was kept at -30° for 2 hours, washed with 100 ml of 10% $Na_2S_2O_3$ and 2x100 ml of 10% NaOH solution. The crude oily product was chromatographed on 250 g of silica gel. Elution with 1:2 CH_2Cl_2-hexane gave 2.00 g (57%) of sulfoxide-alcohol 43 m.p. 124°-125°. n.m.r.: 1.7 (d, J=7.5Hz, 3H), 4.1 (q, J=7.5Hz, 1H), 5.7 (s, 1H), 7.0-7.6 (m, 14H), 7.7-8.0 (m, 1H). IR: 1010 and 3300 cm^{-1}. anal. calculated:

C 75.00, H 5.95, S 9.52; found C 74.91, H 6.07, S 9.68.

3-Phenyl-2,1-benzoxathiole 1-oxide (27, 28)

To a solution of 2.00 g of alcohol 43 in 70 ml of CH_2Cl_2 at 0° was added dropwise 0.80 g of SO_2Cl_2 in 15 ml of CH_2Cl_2. The reaction mixture was kept at 0° for 1 hour and then the solvent was remove on the rotary evaporator. Chromatography on 150 g of silica gel provided on elution with 4:1 hexane-ethylacetate both isomers.

Isomer I: 41% yield; m.p. 122°-123° (CH_2Cl_2-hexane); IR: 1125 cm^{-1}; n.m.r.: 6.57 (s, 1H), 7.10-7.80 (m, 9H). Anal. Calcd. for $C_{13}H_{10}O_2S$: C 67.82, H 4.35, S 13.91; found: C 67.59, H 4.44, S 13.70.

Isomer II: 32% yield; m.p. 102° from CH_2Cl_2-hexane; IR: 1125 cm^{-1}; n.m.r.: 7.06 (s, 1H), 7.10-7.80 (m, 9H). Anal. calcd. for $C_{13}H_{10}O_2S$: C 67.82, H 4.35, S 13.91; found C 67.99, H 4.48, S 13.83.

(B) Photolysis Reactions

Thses were carried out using a Rayonet type photochemical apparatus. The photolysis was carried out under N_2 until T.L.C. indicated the disappearance of starting material.

Photolysis of Sultine 26

Sultine 26 (363 mg) was dissolved in 120 ml of anhydrous methanol and photolysed at 253 nm in a Rayonet apparatus for 14 hours. Nitrogen was passed through the reaction mixture during the photolysis. At the end of the photolysis period the reaction mixture was foggy yellow. The solvent was removed on a rotary evaporator and the product chromatographed on 80 g of silica gel. Elution with a 10:1 hexane-ethyl acetate gave two fractions. The less polar material (126 mg, 42%) was identified as

9-phenylfluorene by comparison with an authentic sample prepared by the reduction of 9-hydroxy-9-phenylfluorene with zinc in acetic acid. (3) A more polar fraction of a yellowish oil (80 mg) was not identified. Its n.m.r. spectrum showed only aromatic absorption from 7.06-7.83 ppm (m).

Photolysis of 3-phenyl-2,1-benzoxathiole 1-oxide in methanol

Sultine (107 mg, mixture of isomers 27 and 28) was irradiated for 14 hours in 120 ml of anhydrous methanol, under N_2 as above. The reaction mixture changed from colourless to foggy yellow. The solvent was evaporated and the resulting dark brown paste was chromatographed. The less polar product 20 mg (27%) had n.m.r. peaks at 3.9 (s, 2H) and 7.1-7.9 (m, 8H) and was identified as fluorene by comparison of its spectrum with that of a standard sample. (4)

Further elution furnished 29 mg (32%) of a colourless oil, n.m.r. 3.3 (s, 3H), 5.2 (s, 1H), 6.9-7.5 (m, 10H) ppm; IR: 1090 cm^{-1}; which was identified as diphenyl methyl ether by comparison with authentic sample (5) prepared in 80% yield by dropwise addition of benzhydryl chloride to refluxing mixture of potassium carbonate in methanol.

In a second experiment the photolysis of a single isomer was interrupted after approximately 5 hours. N.m.r. investigation of the crude reaction product indicated the presence of approximately equal amounts of both isomers together with some fluorene and diphenyl methyl ether.

Photolysis of Sultine 59

A solution of 302 mg of sultine 59 in 120 ml of CH_3OH was photolyzed

as above under a stream of N_2 for 18 hours. During the photolysis the solution changed from colourless to yellow and the walls of the reaction vessel became coated with polymer. The solvent was evaporated and the brown paste obtained was chromatographed. Elution with hexane gave 161 mg of a 1:1 mixture of 9,10-dihydrophenanthrene and phenanthrene (n.m.r. analysis). In another experiment, the solution was initially purged with N_2 then photolyzed for 17 hr. The product was a mixture of 9,10-dihydrophenanthrene and phenanthrene in about 10:1 ratio.

(C) Seven Membered Ring Sultine Studies

t-Butyl-benzyl-sulfide

A solution of 40.5 g (0.45 mole) of *t*-butyl mercaptan and 28 g (0.5 mole) of KOH in 200 ml of 1:1 of methanol : H_2O was added 57 g (0.45 mole) of benzyl chloride. The stirred solution was refluxed overnight. The mixture was washed 3x200 ml of methylene chloride. The organic extracts were dried and evaporated to give 75 g (93%) of oil. b.p.= 65°/100mm, n.m.r.: 1.3 (s, 9H), 3.7 (s, 2H), 7.1-7.4 (s, 5H).

t-Butyl-benzyl-sulfoxide 67

To a stirred solution of 20 g (0.11 mole) of *t*-butyl-benzyl-sulfide in 150 ml of ethyl acetate at -30° was added dropwise a solution of 22.78 g *m*-chloroperbenzoic acid in 100 ml of ethyl acetate. The solution was stirred for 50 min. after the completion of the addition. The mixture was washed with 2x300 ml of 10% $Na_2S_2O_3$, then with 2x200 ml of 5% NaOH.

The organic layer was dried and evaporated to give 18.5 g of crude product. The crude material was purified by vacuum sublimation to give 16.3 g (75%) of white crystalline material (m.p. 71°-72°). n.m.r.: 1.5 (s, 9H), 3.7 (AB quartet H_A=3.6, H_B= 3.9, J_{AB}= 12Hz), 7.2 (s, 5H) ppm; IR: 1010 cm^{-1}.

Threo-1,2-diphenyl-2-*t*-butylsulfinyl ethanol 68

To a stirred solution of 2.34 g (11.9 mmole) of *t*-butyl benzyl sulfoxide in 70 ml of anhydrous THF (freshly distilled over $LiAlH_4$) was added 9.2 ml. of 1.3 M methyllithium under N_2 at -70° (dry ice-acetone). Benzaldehyde, 1.27 g (11.9 mmole), was introduced via syringe into the anion solution. The solution was stirred for another 10 minutes after completion of the addition. The mixture was washed with 50 ml of H_2O, then 2x50 ml of CH_2Cl_2. The extracts were dried and evaporated to furnish 3.38 g of crude product. The mixture was chromatographed on 250 g of silica gel using hexane-ethyl acetate (4:1) as eluent to give 1.10 g of *threo*-1,2-diphenyl-2-*t*-butylsulfinyl ethanol (m.p. 167°-168°, R_f=0.49;4:1 of hexane-ethyl acetate) and 2.15 g (63%) of *erythro*-1,2-diphenyl-2-*t*-butylsulfinyl ethanol 21, R_f=0.10; 4:1 of hexane-ethyl acetate. The *erythro* form was identified by comparison of its spectroscopic data (n.m.r. and IR) with an authentic sample. (1) The *threo*-1,2-diphenyl-2-*t*-butyl-sulfinyl ethanol had n.m.r. peaks at 1.2 (s, 9H), 4.0 (d, J=7.5Hz, 1H), 5.3 (d, J=7.5Hz, 1H), 6.0 (OH), 7.7-7.4 (s, 10H); IR peaks at 3340 and 1020 (S=O) cm^{-1}.

Analysis: calcd. for $C_{18}H_{22}O_2S$: C 71.52, H 7.28, S 10.59: found: C 71.27 H 7.36, S 10.47.

Synthesis of 3,4,6,7-tetraphenyl-1,5-dioxa-2-thiepane-2-oxide 70

To a stirred solution of 0.747 g (2.48 mmole) of *threo*-hydroxy sulfoxide 68 in 60 ml of methylene chloride was added 0.335 g (0.20 ml) of sulfuryl chloride at -70°. After 20 minutes the volatile materials were removed from the solution. The crude mixture was subjected to column chromatography on silica gel using CH_2Cl_2 as eluent. A trace amount of diphenylacetaldehyde and 0.327 g (30%) of 70 (m.p. 161°-163°) were obtained. The sultine 70 had n.m.r. peaks at 4.03 (d, J=11Hz, 1H), 6.69 (d, J=4.0Hz, 1H), 6.77-7.50 (m, 20H) ppm; IR peaks at 1120 (S=O) cm^{-1}.

Synthesis of 3,4,6,7-tetraphenyl-1,5-dioxa-2-thiepane-2-oxide 24

This compound was prepared in 50% yield from 0.302 g of *erythro*-hydroxy sulfoxide 21 and 0.135 g (0.08 ml) of SO_2Cl_2 following Sharma's procedure. (1) The spectroscopic data and m.p. were identical with those reported by Sharma.

Reaction of 24 with triethyloxinum tetrafluoroborate

To a stirred solution of 0.443 g (1.01 mmole) of sultine 24 in 20 ml of CH_2Cl_2 was added dropwise 1.2 ml of 1 M triethyloxinum tetrafluoroborate. The solution was stirred overnight. The volatile materials were removed on the rotary evaporator. The crude product was chromatographed on 70 g of silica gel using hexane as the eluent to give 0.165 g of *trans*-stilbene (46%) identified by n.m.r. comparison. (6)

Reaction of 3,4,6,7-tetraphenyl-1,5-dioxa-2-thiepane-2-oxide 24 with lithium dimethlycuprate

A solution of 0.074 g of sultine 24 in 30 ml of anhydrous ether was added dropwise to the solution of lithium dimethylcuprate (7) which was prepared by addition of 0.034 g of purified copper (I) iodide in 10 ml of anhydrous ether to 0.32 ml of 1.6 M methyllithium under N_2 at 0°. The mixture was stirred for 15 minutes and hydrolyzed with 10 ml of saturated aqueous ammonium chloride. The colour changed from pink to blue. After stirring for another 20 minutes at room temperature, the aqueous layer was extracted with 3x40 ml of methylene chloride. The organic extracts were dried and evaporated to give a dark paste. Chromatography of the crude products on 10 g of silica gel with CH_2Cl_2 afforded 0.025 g of an oily compound (R_f=0.25; 2:1 of CH_2Cl_2-ethyl acetate). This compound was identified as 1,1-diphenylpropan-2-ol by comparison with an authentic sample (8) prepared by addition of 1,1-diphenylpropene to a refluxing mixture of diethylaluminum chloride in benzene followed by hydrolysis.

(D) β-lactam studies

Preparation of 4-(3-butenyl) azetidin-2-one 17

A solution of 5.68 g (40 mmole) chlorosulfonylisocyanate (CSI) in 20 ml of CH_2Cl_2 containing 4.30 g (52.5 mmole) of 1,5-hexadiene was kept at room temperature for 2 weeks. The colour changed to dark brown. The dark brown solution was added dropwise to 50 ml of 25% Na_2SO_3. The pH of the mixture was kept in the 7-8.5 range by addition of 50% KOH. The mixture was extracted with 3x200 ml of CH_2Cl_2. The extracts were dried and evaporated to give a brown oil which was distilled to give 2.52 g (50%) of the desired compound (b.p. 83°-84°/20mm). n.m.r.: 1.5-2.3 (m,4H), 2.3-3.3 (m, 2H), 3.4-3.8 (m, 1H), 4.8-5.2, (m, 2H), 5.4-6.1 (m, 1H), 6.8

(b.s., NH) ppm. IR: 1760-1770 (C=O), 3450 (NH) cm^{-1}.

Reaction of β-lactam 17 with *n*-butyllithium and formaldehyde

To a stirred solution of 0.746 g (6.0 mmole) of β-lactam 17 in 30 ml of THF was added 15 ml of 1.6 M *n*-butyllithium at 0° under a N_2 atmosphere. The colour of the solution changed to light yellow. The solution was stirred for 1.5 hours and then cooled to -30°. Formaldehyde, generated by heating 0.610 g of polyformaldehyde, was then introduced in the solution. The mixture was stirred for 10 minutes then quenched with 40 ml of H_2O. The aqueous layer was extracted with 2x40 ml of CH_2Cl_2. The crude product, 0.826 g, was obtained after drying and removal of the solvent. The crude product was chromatographed on 100 g of silica gel with 3:1 CH_2Cl_2-ethyl acetate giving 0.420 g (56%) of the starting material and 0.201 g (26%) of a white crystalline product, m.p. 90°-91°, R_f=0.36 (3:1 hexane-ethyl acetate), which was subsequently identified as β-lactam 28. The n.m.r. showed the peaks at 1.2 (d, J=7Hz, 3H), 1.3-2.2 (m, 5H), 3.3-3.5 (m, 1H), 4.0 slightly broadened triplet, 6.1 (NH) ppm. The IR peaks occured at 1760 (C=O) and 3450 (NH) cm^{-1}.

Analysis calcd. for $C_7H_{11}NO$: C 67.36, H 8.90, N 11.13; found: C 67.20, H 8.80, N 11.20. Mass spectrum of m/e (relative abundance): 126 (7.4), 125 (3.7), 82 (100), 67 (94), 53 (19).

Isomeration of β-lactam 17 to β-lactam 28

To a stirred solution of 0.422 g of β-lactam 17 in 40 ml of THF was

added 5.2 ml of 1.3 M n-butyllithium at 0°. The colour of the solution changed to dark brown. The solution was stirred overnight, quenched with H_2O and worked up as above. The crude product was chromatographed on 80 g of silica gel with 400 ml of 3:1 CH_2Cl_2-ethyl acetate affording 0.230 g (55%) of colourless crystals and 0.152 g (36%) of starting material. The colourless crystals, m.p. 90°-91°, were spectroscopically identical to those obtained above.

Preparation of 4-thiobenzylazetidin-2-one 35 from 4-acetoxy azetidin-2-one 32

To a solution of 0.302 g (2.34 mmole) of 32 (10) in 15 ml of 8% of $NaHCO_3$/MeOH was added a solution of 0.299 g (2.41 mmole) of benzyl mercaptan in 5 ml of 8% of $NaHCO_3$/MeOH. The solution was stirred for 1 hour. The mixture was washed with 50 ml of H_2O and extracted with 3x50 ml of CH_2Cl_2. Usual workup gave 0.560 g of crude yellow compound which was chromatographed on 80 g of silica gel using 1:1 CH_2Cl_2-ethyl acetate as eluent. β-Lactam 35 was obtained as pale yellow oily compound (R_f=0.38, 1:1 CH_2Cl_2-ethyl acetate), 0.460 g (86%). n.m.r.:2.5-3.4 (m, 2H), 3.7 (s, 2H), 4.5 (m, 1H), 6.6 (b.s., NH), 7.1 (s, 5H) ppm. IR: 1760-1770 (C=O) and 3300 (NH) cm^{-1}.

Preparation of azetidin-2-one-4-thioactetic acid ethyl ester 36 from 4-acetoxy azetidin-2-one 32

To a solution of 2.25 g (17.5 mmole) of β-lactam 32 in 40 ml of 8%

of $NaHCO_3$/MeOH was added 2.12 g (17.6 mmole) of ethyl mercaptoacetate in 5 ml of 8% of $NaHCO_3$/MeOH. The solution was subsequently stirred for 1.5 hours and then worked up as in the case of 35. The crude compound was chromatographed on 400 g of silica gel giving 2.76 g (90%) β-lactam 36, as a pale yellow oil (R_f=0.32 1:1 hexane-ethyl acetate). N.m.r.:1.3 (t, J=7Hz, 3H), 2.7-3.5 (m, 4H), 4.1 (q, J=7Hz, 2H), 4.8 (m, 1H), 6.8 (b.s., NH) ppm. IR: 1740-1780 (C=O) and 3450 (NH) cm^{-1}.

Reaction of 37 with *p*-nitrobenzyl glyoxylate. Formation of 38

A solution of 0.296 g (2.67 mmole) of β-lactam 37 and 0.606 g (2.67 mmole) of *p*-nitrobenzyl glyoxylate in 50 ml of benzene was refluxed in a Dean-Stark apparatus for 7 hours. (10) Evaporation of the solvent gave 0.850 g of a light yellow paste after removal of the solvent. The crude product was chromatographed on silica gel using 5:2 CH_2Cl_2 and ethyl acetate giving β-lactam 38 (0.766 g, 85%) as a colourless oily compound (R_f=0.45, 5:2 CH_2Cl_2-ethyl acetate). N.m.r.: 1.6 (s, 3H), 2.8 (s, 2H), 3.7 (b.s.,1H), 4.8-6.1 (m, 6H), 7.3-8.1 (q, 4H) ppm. IR: 1100, 1350, 1540, 1750-1770, 3450 cm^{-1}.

Reaction of 37 with formaldehyde Formation of 39

The mixture of 0.431 g (2.28 mmole) of 37 and 10 ml of 37% formaldehyde in 50 ml benzene was refluxed in a Dean-Stark apparatus for 2.5 hours. Evaporation of the organic solution gave 0.607 g of pale yellowish oily product. Chromatography on 80 g of silica gel with 4:1 CH_2Cl_2-ethyl acetate yielded 0.401 g (80%) of β-lactam 39 (R_f=0.40, 4:1 CH_2Cl_2-ethyl acetate).

N.m.r.: 1.3 (t, J=7Hz, 3H), 2.8-3.7 (m, 2H), 3.4 (s, 2H), 4.2 (q, J=7Hz, 2H), 4.7 (b.d., $-CH_2O-$ and OH), 5.0 (m, 1H) IR: 1765 and 3500 cm^{-1}.

Reaction of 36 with p-nitrobenzyl glyoxylate Formation of 40

The solution of 0.637 g of β-lactam 36 and 0.763 g of p-nitrobenzyl glyoxlyate in 40 ml of benzene was refluxed for 5 hours. The solution was evaporated to give 0.80 g of crude paste. The paste was chromatographed on silica gel. The β-lactam 40 was eluted with 5:2 CH_2Cl_2-ethyl acetate. Yield: 0.671 g (48%). N.m.r.: 1.3 (t, J=7Hz, 3H), 2.8-3.6 (m, 4H), 4.0 (q, J=7Hz, 2H), 4.5 (b.s., 1H), 4.8 (m, 1H), 5.1-5.3 (m, 3H), 7.1-8.0 (q, 4H) ppm. IR: 1750-1780, 3500 cm^{-1}.

Chlorination of β-lactam 40

To a solution of 0.521 g (1.3 mmole) of β-lactam 40 and 0.150 g of methanesulfonyl chloride in 15 ml of CH_2Cl_2 was added 0.131 g of triethylamine. The solution was stirred for 4 hours. Evaporation of the solvent gave a brown paste. The crude product was chromatographed on silica gel. The yield of β-lactam 42 (R_f= 0.55, 5:2 CH_2Cl_2-ethyl acetate) was 0.311 g (57%). N.m.r.: 1.3 (t, J=7Hz, 3H), 3.0-3.7 (m, 4H), 4.1 (q, J=7Hz, 2H), 5.0-5.3 (m, 3H), 6.0-6.1 (2s, 1H), 7.4-8.1 (q, 4H). IR: 1750-1780 cm^{-1}.

The reaction of β-lactam 42 with lithium diisopropylamide

To a stirred solution of 0.050 g (0.5 mmole) of diisopropylamine in 5 ml of anhydrous THF (freshly distilled over $LiAlH_4$) was added 0.30 ml of 1.6 M MeLi at 0° under a N_2 atmosphere. The color changed to pale yellow. To the stirred solution was introduced 0.200 g (0.5 mmole) of β-lactam 42. The reaction colour changed from yellow to red. The solution was stirred

for an additional 10 minutes then quenched with H_2O. The mixture was extracted with 3x40 ml of CH_2Cl_2. The extracts were dried and evaporated to afford 0.050 g of a pale yellow compound. The compound was recrystallized from hexane to give 0.035 g of white crystals (m.p. 92°-93.5°) and identified as *p*-nitrobenzyl alcohol by comparison of its n.m.r. spectrum with that of an authentic sample. (9)

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Claims to Original Research

A. Benzfused Sultines

1. The sysntesis of 3H-2,1-benzoxathiole 1-oxide and several of its derivatives had been achieved. The parent and disubstituted derivatives were best obtained by SO_2Cl_2-HOAc treatment of the precursor mercaptoalcohols. (Givens' method) While 3-monosubstituted derivatives were prepared by SO_2Cl_2 induced cleavage of a hydroxy sulfoxide. (Sharma's method)
2. Photolysis of 3-phenyl and 3,3-diphenyl 2,1-benzoxathiole 1-oxide has been shown to afford fluorene and 9-phenylfluorene, respectively, as the major products. The mechanism of the transformation was discussed.

B. Seven Membered Ring Sultines

1. The photoisomer 70 of 3,4,6,7-tetraphenyl-1,5-dioxa-2-thiepane-2-oxide 24 was synthesized from *threo*-1,2-diphenyl-2-*t*-butylsulfinyl ethanol. It is suggested that during the photolysis isomerization occurs at both the benzylic carbons δ to oxygen and α to sulfur.
2. The reacton of 24 with $Et_3\overset{\oplus}{O}\ \overset{\ominus}{BF_4}$ gave *trans*-stilbene. Reaction of 24 with $(CH_3)_2CuI$ gave 1,1-diphenylpropan-2-ol. Both of the reaction mechanisms were briefly discussed.

C. β-Lactam Synthesis

1. The reaction of 4-(3-butenyl) azetidin-2-one with 2 equivalents of *n*-butyllithium gave a bicyclic isomer of the starting material.

The mechanism of this reaction was discussed.

2. The reaction of 4-acetoxyazetidin-2-one with mercaptans and $NaHCO_3$ gave the corresponding 4-thioalkyl derivatives in excellent yield.
3. The condensation of N-unsubstituted β-lactams with formaldehyde or *p*-nitrobenzyl glyoxylate gave alcohols resulting from addition of the N-H group of the lactam to the carbon-oxygen double bond. Mesylation of the β-lactam alcohols derived from the additon of the glyoxylate ester with methansulfonyl chloride/triethylamine resulted in replacement of the OH group by Cl, presumeably via displacement of the initially formed mesylate by chloride ion.
4. The reaction of β-lactam 41 with LDA gave *p*-nitrobenzyl alcohol but no isolable cyclization product.