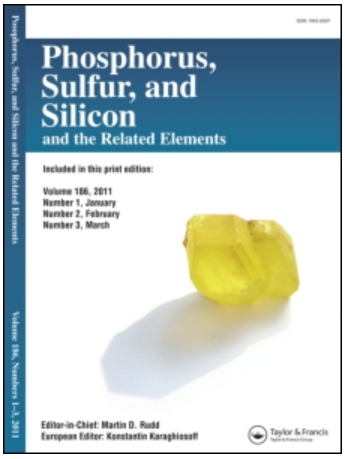

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THE CHEMISTRY OF OPTICALLY ACTIVE SULFUR COMPOUNDS PART III

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1976, Vol. 2, pp. 51–94

THE CHEMISTRY OF OPTICALLY ACTIVE SULFUR COMPOUNDS PART III

by

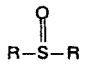
Abraham Nudelman

The Weizmann Institute of Science, Department of Chemistry, Rehovot, Israel

CONTENTS

I. INTRODUCTION

The chemistry of optically active sulfur compounds has proven to be one of great interest and challenge as demonstrated by the prolific publications in this area. An ever larger number of different types of compounds with sulfur as center of chirality are being synthesized and it is expected that in future publications additional members of this group will be described. Thus far the following chiral sulfur compounds have been prepared: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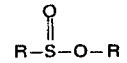
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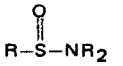
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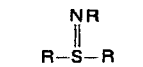
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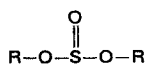
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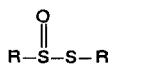
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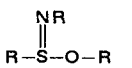
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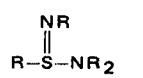
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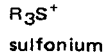
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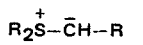
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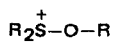
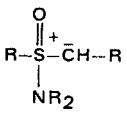

sulfoxonium salts


aminosulfonium salts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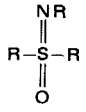
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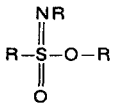
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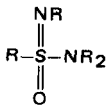
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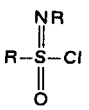
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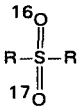
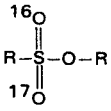
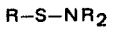
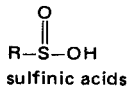

[^{16}O, ^{17}O] sulfones


[^{16}O, ^{17}O] sulfonates


di- and polysulfides


sulfenamides

In addition, chirality as detected by spectroscopic methods has been observed in the following compounds: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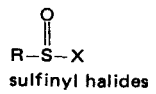
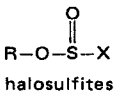

sulfinyl halides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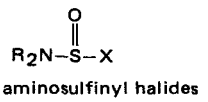

aminosulfinyl halides

The first two reports of this series[1a,b] discussed articles dealing with optically active sulfur compounds published before June 1971. This third paper reviews additional publications up to the end of 1973. A similar format to that used in Part II will be presented. References quoted in the previous articles will be indicated by I- or II- followed by the corresponding number assigned in the corresponding article. A few selected references dealing with chiral di- and polysulfides are included,[141] but no attempts have been made to abstract them. Following is a list of recent review articles or books related to, or where frequent references are made to optically active sulfur compounds.

GENERAL REFERENCES

1. *a.* A. Nudelman, *Int. J. Sulfur Chem.*, *B*, **6**, 1 (1971). The Chemistry of Optically Active Sulfur Compounds. Part I.
   b. A. Nudelman, *Int. J. Sulfur Chem.*, *B*, 7, 241 (1972). The Chemistry of Optically Active Sulfur Compounds, Part II.
   c. D. J. Cram, J. Day, D. J. Garwood, D. R. Rayner, D. M. von Schriltz, T. R. Williams, A. Nudelman, F. G. Yamagishi, R. E. Booms, and M. R. Jones, *Int. J. Sulfur Chem.*, *C*, 7, 103 (1972). The Stereochemistry of Substitution Reactions at Sulfur.
   d. Peter H. Laur in "Sulfur in Organic and Inorganic Chemistry", Vol. 3, A. Senning, Ed., Marcel Dekker, Inc., New York, 1972, Chapter 24.
   e. J. W. Henderson, *Chem. Soc. Rev.*, **2**, 397 (1973). Chirality in Carbonium Ions, Carbanions and Radicals.
   f. A. Ejchart and J. Jurczak, *Wiad. Chem.*, **24**, 857 (1970). The Nonequivalence of NMR Spectra of Enantiomers in Optically Active Solvents.
   g. O. N. Sorensen, *Int. J. Sulfur Chem.*, *B*, **6**, 321 (1971). Tetravalent Sulfur (With Coordination Number Three) as Center of Chirality in Organic Molecules.
   h. S. H. Wilen in "Tables of Resolving Agents and Optical Resolutions", E. L. Eliel, Ed., University of Notre Dame Press, Notre Dame, London, 1972.
   i. J. L. Kice, *Int. J. Sulfur Chem.*, *C*, **6**, 3 (1971). Aspects of Nucleophilic Substitution at Different Oxidation States of Sulfur.
   j. F. Montanari, *Int. J. Sulfur Chem.*, *C*, **6**, 137 (1971). Neighboring-Group Participation in Sulfinyl-Oxygen.
   k. T. Oishi and M. Mori, *Int. J. Sulfur Chem.*, *B*, 7, 225 (1972). Reactivity Modulation of Organic Sulfur Compounds through Alkylation.
   l. G. Scorrano, *Acc. Chem. Research*, **6**, 132 (1973). Equilibria and Reactions of Organic Sulfoxides in Moderately Concentrated Acids.
   m. C. R. Johnson, *Acc. Chem. Research*, **6**, 341 (1973). The Utilization of Sulfoximines and Derivatives as Reagents for Organic Synthesis.

n. J. B. Lambert, "Pyramidal Atomic Inversion", Topics in Stereochemistry Vol. 6, N. L. Allinger and E. L. Eliel, Eds., Wiley-Interscience, New York, N.Y., 1972, pp. 19.

o. S. Wolfe, *Acc. Chem. Research*, **5**, 102 (1972). The Gauche Effect. Some Stereochemical Consequences of Adjacent Electron Pairs and Polar Bonds.

p. C. J. M. Stirling, *Int. J. Sulfur Chem., B*, **4**, 277 (1971). The Sulfinic Acids and Their Derivatives.

q. D. Landini, F. Rolla, and G. Torre, *Int. J. Sulfur Chem., A*, **2**, 43 (1972). Neighboring-Group Participation by the Carboxyl Group in the Reduction and Racemization of Sulfoxides by Halide Ions.

r. R. F. Stoodley, "Recent Penicillin Chemistry", Progress in Organic Chemistry, Vol. 8, W. Carruthers and J. K. Sutherland, Eds., John Wiley and Sons, New York, N.Y., 1973, pp. 102.

s. D. H. R. Barton and P. G. Sammes, *Proc. Royal. Soc. London., B*, **179**, 345 (1971). Chemical Relationship between Cephalosporins and Penicillins.

t. J. A. Weber, Progress in the Chemistry and Biological Activity of Cephalosporin Antibiotics, Abstracts, Thirteenth National Medicinal Chemical Symposium, Iowa City, Iowa, June 1972, p. 99.

u. D. H. R. Barton, *Pure Appl. Chem.*, **33**, 1 (1973). Some Aspects of the Chemistry of Penicillin.

v. R. D. G. Cooper, L. D. Hatfield and D. O. Spry, *Acc. Chem. Research*, **6**, 32 (1973). Chemical Interactions of the β-Lactam Antibiotics.

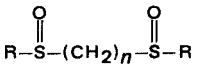
w. R. B. Morin and B. G. Jackson, "Chemistry of Cephalosporin Antibiotics", Progress in the Chemistry of Organic Natural Products, W. Herz, H. Grisebach, and A. I. Scott, Eds., Wien. Springer-Verlag, New York, N.Y., 1970, pp. 343.

x. E. H. Flynn, "Cephalosporins and Penicillins, Chemistry and Biology", Academic Press, New York, N.Y., 1972.

II. SULFOXIDES

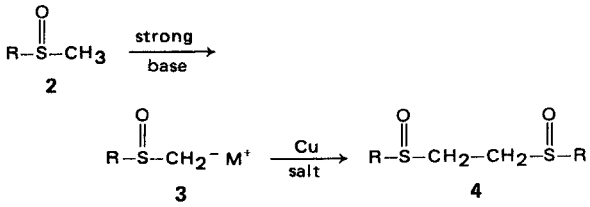
A. Stereospecific Synthesis

The procedure most commonly used for the stereospecific preparation of optically active sulfoxides is the Anderson synthesis (I-16). The method involves the preparation of (−)-menthyl (−)-(S)-*p*-toluene sulfinate and subsequent reaction with a Grignard reagent. An improved synthesis of the menthyl sulfinate has been reported by Estep and Travers,[2] where up to 90% of the desired crystalline diastereomer can be isolated. An extension of this procedure has been developed[3] whereby di-(−)-menthyl ethane-1,2-disulfinate is treated with the appropriate Grignard reagent to form the first reported aliphatic disulfoxide **1** showing high optical activity. Similar racemic disulfoxides where R is an aromatic ring were partially[4] resolved by chromatography on an activated lactose column.



1

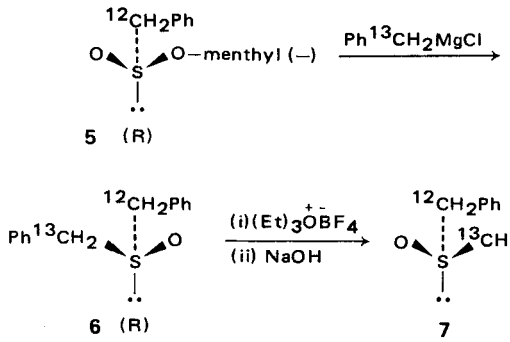
A versatile one-step synthesis of 1,2-ethano bis sulfoxides **4** which allows the preparation of either enantiomer in high optical purity has been developed by Mislow *et al.*[5] The process consists of the assembly of two subunits each containing a chiral sulfur center. The reaction is accomplished by a copper-catalyzed oxidative coupling of the α-carbonions derived from **2**



2 **3** **4**

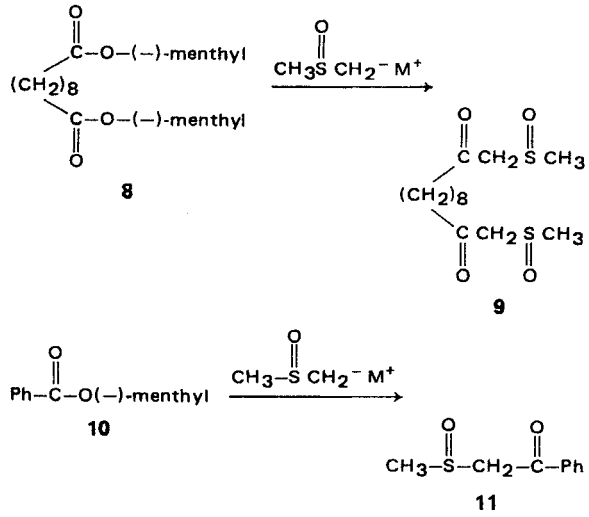
The reaction is highly stereospecific, and the products obtained were shown to be >97% optically pure by the use of the chiral shift reagent tris(3-heptafluoropropylhydroxy methylene-(+)-camphorato)europium (III). Other β-bis-sulfoxides partially resolved were prepared[6] by oxidation of the corresponding sulfides with optically active oxidizing agents.

The Andersen synthesis has also been used[7] in the preparation of the first example of chiral sulfoxides **6-7** where the molecular asymmetry stems from isotopic dissymmetry of carbon (I-224, 225).

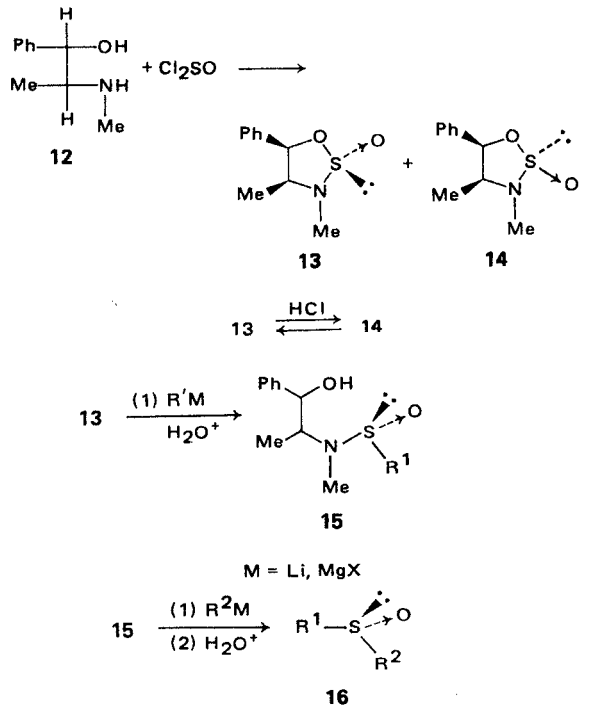


5 (R) **6** (R) **7**

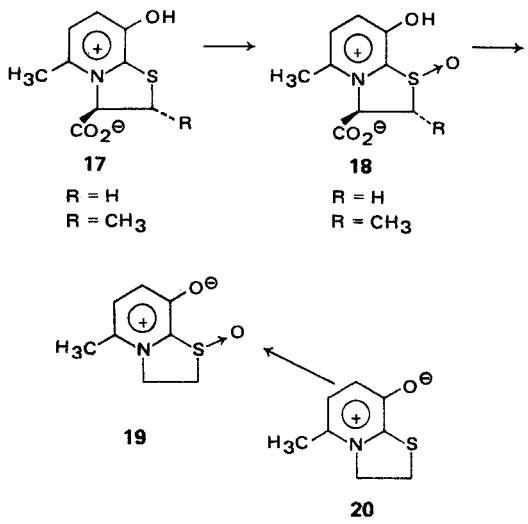
A variation[8] of this procedure has been used in the synthesis of optically active bis-β-ketosulfoxide, **9**, and β-ketosulfoxide, **11**.



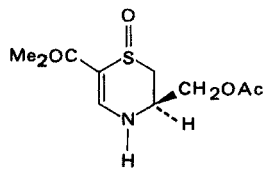
A novel procedure for the asymmetric synthesis of either enantiomer of an open chain chiral sulfoxide was developed by Wudl and Lee.[9] Optically active diastereomeric amidosulfites **13** and **14** are prepared from L-ephedrine, **12**, and thionyl chloride. Selective cleavage of the bonds to the S=O group afford chiral hydroxysulfinamides **15** which can be converted subsequently to the desired sulfoxides **16**. The order of introduction of R^1 and R^2 determines the enantiomeric composition of the product.



Additional[10] optically active sulfoxides **18** and **19** in the series of N-quaternary compounds have been prepared by Undheim *et al.* (I-38, II-22) and studies of their circular dichroism (cd) spectra were reported.[11]



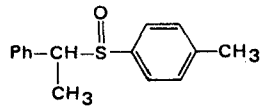
Stoodley *et al.*[12] has described the preparation of sulfoxide **21** by metaperiodate oxidation of the sulfide. Although an optical rotation is given no estimate of the degree of asymmetric induction obtained is presented.



Another stereospecific oxidation of a sulfide involves[13] the oxidation of methionine by means of gold trichloride ($AuCl_3$). The reaction takes place in quantitative yield with the formation of a single diastereomer.

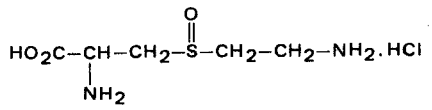
An additional example of a stereospecific synthesis of a sulfoxide has been described by Kexel and Schmidt.[14] Among the metabolites of *p*-thioanisidine fed to animals some R-(+)-*p*-thioanisidine sulfoxide was isolated. The authors attribute the formation of the R-isomer to selective destruction of its enantiomer (I-17).

In an extension of their previous work (I-26) Nishihata and Nishio[15] have confirmed the assigned absolute configuration of 1-phenylethyl *p*-tolyl sulfoxides **22**. Optical rotatory dispersion (ord) and cd spectra were the tools used, and the configurations thus obtained were found to be in agreement with those derived previously *via* chemical correlation.



22

In the course of their work on thio-analogs of the amino acid lysine, Hermann *et al.*[16] prepared sulfoxides **23-26** by oxidation of the corresponding sulfides. The individual diastereomers of **24** and **26** were separated by paper and ion exchange chromatography.



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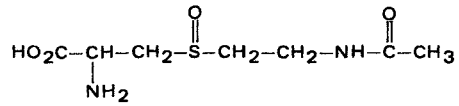

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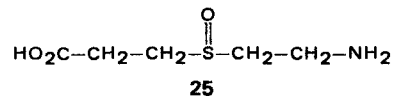

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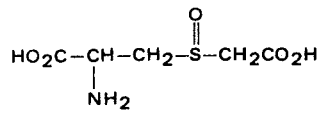
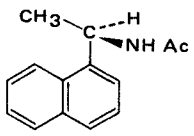


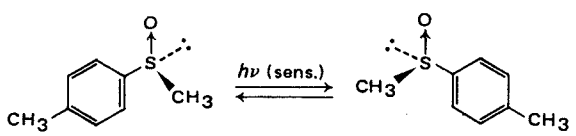
26

The optical photoactivation[17] of racemic **27** in the presence of optically active sensitizer **28** after 50 hrs of irradiation, gave sulfoxide with a rotation of $[\alpha]_D = +3.5°$ corresponding to a 2.25 ± 0.25% optical purity. It was further shown that the optical activity is derived from the photoequilibration of antipodes where

and did not stem from preferential decomposition of one enantiomer.



R(+) – **28**



S(–) **27** R(+) **27**

B. Racemization of Sulfoxides

A novel route[18] to racemization of sec- and tert-alkyl phenyl sulfoxides in aqueous perchloric acid has been observed (II-39). Several mechanistic differences between the tert-alkyl phenyl sulfoxides and other sulfoxides were detected. The reaction is independent of halide ion concentration and takes place in the absence of any nucleophile. Moreover, partial racemization of the chiral tert-alkyl group also takes place. Two possible mechanistic schemes are presented (Figures I and II).

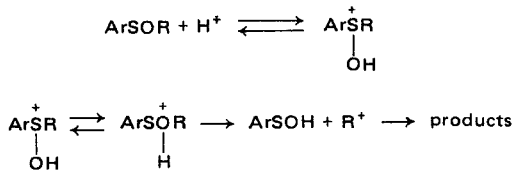


FIGURE I

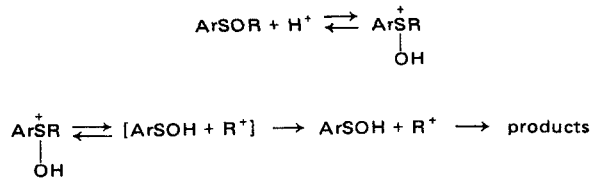
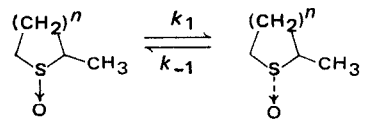


FIGURE II

The mechanism described in Figure II is preferred since the formation of an intimate ion-molecule pair would account for a certain degree of retention of configuration at carbon. The sulfur could racemize by rotation around the Ar–S bond or by formation of a sulfenate ester.

Scorrano and coworkers[19] have discussed the appearance of general acid catalysis with branching of the alkyl group, in relation to the general mechanism for the reduction and racemization of alkyl aryl sulfoxides. Fava *et al.*[20] studied the HCl-catalyzed stereomutation of cyclic sulfoxides, **29**. The data obtained indicate that the ring size affects the rate



29a **29b**

of stereomutation in the order $5 > 6 < 7$ while the opened chain (+)-methyl 2-butylsulfoxide racemizes at a rate comparable to that of the seven-member ring sulfoxide.

The mechanism of oxygen exchange and racemization of sulfoxides in hydrochloric acid,[21] sulfuric acid[22] and sulfuric acid in the presence of potassium chloride[23] have been investigated by Oae and coworkers. Intramolecular catalysis has been observed by Landini and Rolla[24] in the reduction and racemization of *O*-methylsulfinylbenzoic acid (II-35-38). The HCl-catalyzed oxygen-18 exchange between *p*-substituted phenyl methyl sulfoxides and water has been examined by Ookuni and Fry.[25] Four distinct mechanisms for the ^{18}O-exchange have been detected. In the presence of hydrogen chloride the mechanism described in Figure III is proposed.

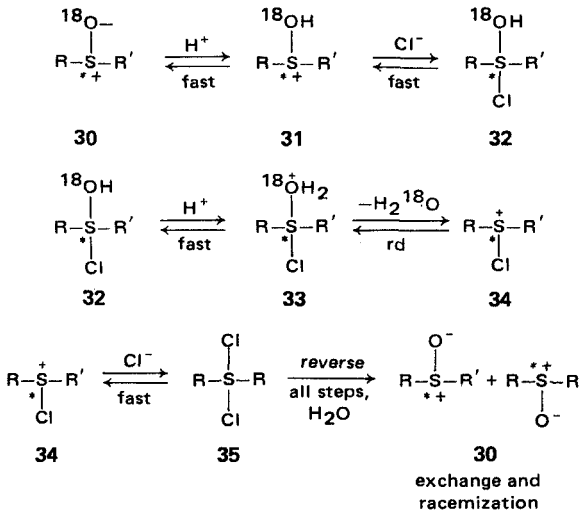


FIGURE III

Since **35** is symmetrical and leads to both exchange and racemization then k_{ex} and k_{rac} are equal. When the reaction is carried out in sulfuric acid in acetic anhydride the $k_{ex}/k_{rac} = 0.5$. This mechanism (Figure IV) indicates that each exchange takes place with inversion and therefore the racemization rate is twice the exchange rate.

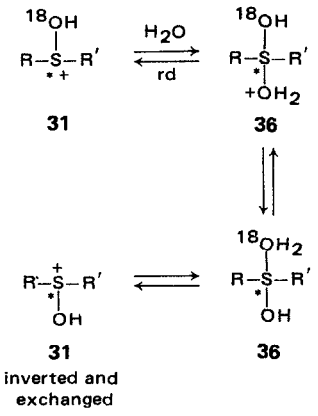


FIGURE IV

When the reaction is carried out in concentrated sulfuric acid (I-61), phosphoric acid (II-32) trichloroacetic acid (I-62) and N_2O_4 (II-40), the ^{18}O-exchange and racemization take place via formation of a dication $R - {}^{+}S^{+} - R$ or radical cation $R - S^{\ddagger} - R$. A base catalyzed reaction is also described where the $k_{ex}/k_{rac} = 0.5$ (Figure V).

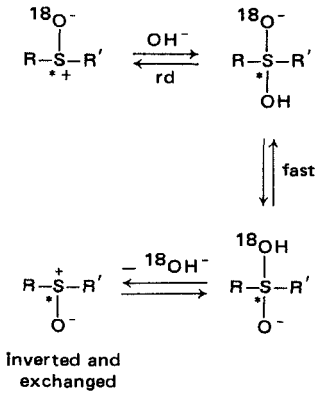


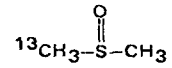
FIGURE V

In a related paper Kwart and Omura[26] studied the effects that result in cleavage rather than stereomutation of sulfoxides in the presence of hydrogen chloride. The influence of the solvent medium on kinetics, of added neutral salts on the cleavage product ratio, and the differing role of water in the two reactions was established. Mislow and coworkers[27] have found that linear relationships correlate the pyramidal inversion barriers of identically substituted amines, phosphines, arsines, carbanions, oxonium ions, silyl anions, sulfonium ions and sulfoxides. Thermal racemization of allylic sulfoxides and thermal rearrangement of allyl sulfenates were studied by Tang[28] (II-47).

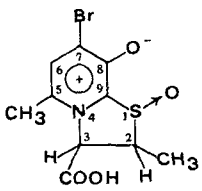
C. Spectral Studies

The optical purity of partially resolved sulfoxides may be determined with the aid of nmr shift reagents. Thus Fraser, Petit, and Saunders[29] studied the nmr spectrum of benzyl methyl sulfoxide whose optical rotation indicated 90% optical purity. The value obtained from the nmr spectrum using tris-(3-heptafluoropropylhydroxymethylene-(+)-camphorato) europium as shift reagent was 89%, indicating excellent agreement of optical purity between the two independent determinations. In a similar study Nozaki *et al.*,[30] measured the optical purity of partially resolved methyl *p*-tolyl sulfoxide using tris-[3-(tert-butylhydroxymethylene)-d-camphorato] europium-(III). Further work in this area by Pirkle *et al.*[31] has shown that the methyl groups of dimethyl sulfoxide

in chiral 2,2,2-trifluorophenyl ethanol are anisochronus. Furthermore, a sample of R-enriched



in this solvent shows non-equivalence in its pmr spectrum but equivalence in the cmr spectrum. However, in the presence of tris[3-trifluoromethylhydroxymethylene-*d*-camphorato] europium (III) or its ytterbium (III) analog the methyl resonances of dimethyl sulfoxide are anisochronus in both pmr and cmr spectra. The cd spectra of aryl alkyl and diaryl sulfoxides are strongly modified in going from aqueous to acidic solution.[32] In particular the extremum centered near 210-220 nm is shifted to shorter wavelengths. The intensity of this extremum is a function of the degree of protonation and from its value at various acidities, thermodynamic pK_{BH+} were obtained. This technique gives as good results



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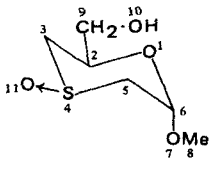

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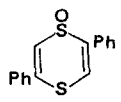

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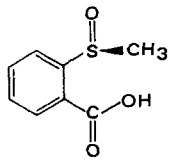

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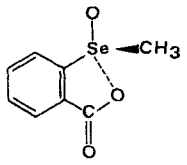


41

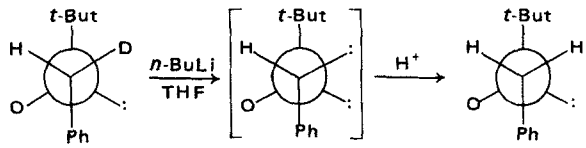
as ultraviolet (UV) and nmr methods in evaluating ionization ratios of weak bases. Others[33] have studied the cd spectra of arylthioglycoside sulfoxides in particular those substituted by an *o*-nitro group in order to determine possible interaction of the *o*- substituent and the sulfur chromophore.

X-Ray crystallographic studies of sulfoxides **37**[34] (II-22), **38**[35] (I-22), **39**,[36] **40**, and **41**[37] have been reported. In the case of **40** no intramolecular hydrogen bonds exist between carboxyl hydrogens and the S=O group of adjacent molecules, whereas, in the selenoxide **41** all the oxygens are in the same plane of the benzene and the carboxyl hydrogen has migrated to the Se=O group.

D. Reactions

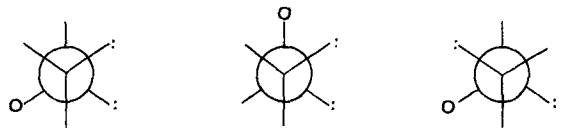
The reaction of sulfoxides may be divided roughly into two groups; those reactions where stereoselectivity at the α-positions has been observed and all other reactions including oxygen exchange reduction, stereomutation and others. Some of the pertinent reactions are included in the section of racemization.

When tetrahydrofuran solutions of (RR/SS)- and (RS/SR)-α-deuteriobenzyl *t*-butyl sulfoxides[38] are treated with one equivalent of *n*-butyllithium followed by quenching with excess water, the products isolated show that the (RR/SS)- diastereomer **42** gives non-deuterated sulfoxide **43**, whereas the (RS/SR)-diastereomer remains unchanged. This indicates that



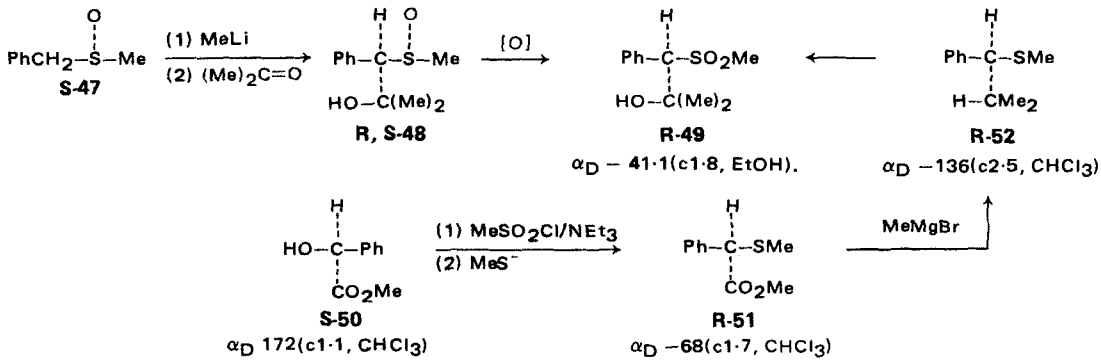
(RR/SS)–42 43

the pro-(R)-hydrogen (and-deuterium) in (R)-sulfoxide is more acidic than the pro-(S)-hydrogen and that the carbanion where the lone pair of electrons is trans to the S=O bond and gauche to the sulfur lone pair **44** is more stable than the conformations **45** and **46.**

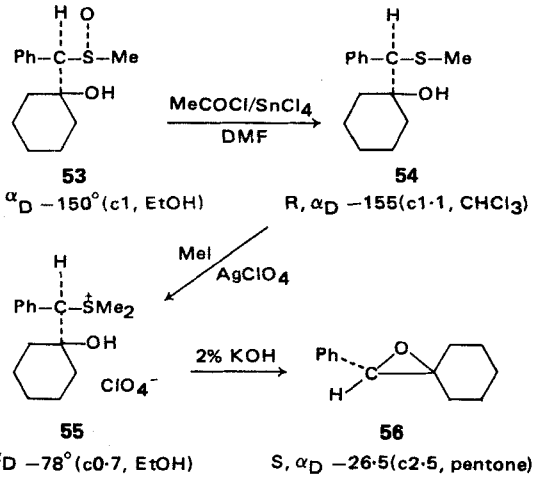


44 45 46

These observations appear to resolve the controversy discussed previously (II-66, 67) between Nishihata and Nishio on one hand and Durst *et al.* on the other. The earlier observation by Nishihata



and Nishio where it was concluded that conformer **46** is of greater stability than **44** was erroneous since the assignment was made on the basis of the diastereotopic protons of benzyl *p*-substituted phenyl sulfoxides. Similar results have been obtained by Brauman *et al.*[39] during hydroxide ion catalyzed proton removal from methyl 1-phenethyl sulfoxide where $k_{ex}/k_{ep} = 1.30$. Further work (II-66) by Durst *et al.*[40] has exploited the diastereotopic character of α-sulfinyl carbanions. Sulfone **49** was prepared by two alternative routes. It may be concluded on the basis of these reactions that the α-lithio sulfoxide of **47** had the R-configuration at carbon and the hydroxy-alkylation proceeded with retention of configuration. Furthermore, the reaction was used in the synthesis of optically active epoxide **56**.



53 R, S $^{\alpha}D$ −150°(c1, EtOH)

54 R, α_D −155(c1·1, $CHCl_3$)

55 R, $^{\alpha}D$ −78°(c0·7, EtOH)

56 S, α_D −26·5(c2·5, pentone)

The course of halogenation of optically active aryl methyl sulfoxides[41] (Table I) indicates that one of the reactions either in the presence or in the absence

TABLE I

α-Halogenation of methyl *p*-tolyl sulfoxide

	Halogenomethyl sulphoxides		
Halogenating agent	$[\alpha]_D^{25}$(°)	Optical purity (%)	Yield (%)
$PhICl_2$	+ 92	43	75
$PhICl_2$–$AgNO_3$	−106	49	55
NCBTA	+104	48	77
NCBTA–$AgNO_3$	−134	62	50
Br_2	+153	73	86
Br_2–$AgNO_3$	−196	98	84

NCBTA, N-chlorobenzotriazole

of silver ions proceeded with inversion of configuration at sulfur. To elucidate the stereochemical course of the reaction (−)-halosulfoxides **58** and **59** were treated with sodium methoxide and with sodium toluene-*p*-thiolate to give **60** and **61**, and with zinc

p-MeC_6H_4·SO·CH_2X

57 X = H **60** X = OMe

58 X = Cl **61** X = S·C_6H_4Me-*p*

59 X = Br

to form **57**. All the compounds obtained showed Cotton effects of the same sign. Since reduction and nucleophilic displacement at the α-position do not involve the C–S bonds therefore, **57–61** having the same specific rotation must have the same configuration. Moreover, the halogenation in the presence of silver nitrate must proceed with inversion at sulfur. In the absence of the silver ion the mechanism formulated is described in Figure VI. In agreement with the retention of configuration in the absence of metal ions a simple 1,2-migration is proposed (Figure VII).

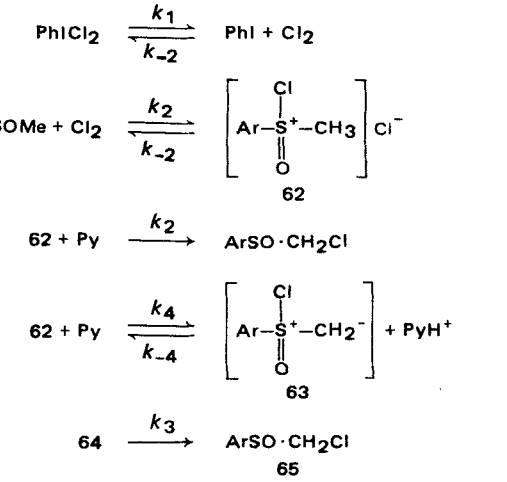


FIGURE VI

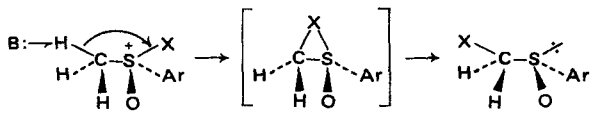


FIGURE VII

Whereas in the presence of the metal ion a mechanism involving polarization, **68**, opposite to the normally found is proposed (Figure VIII).

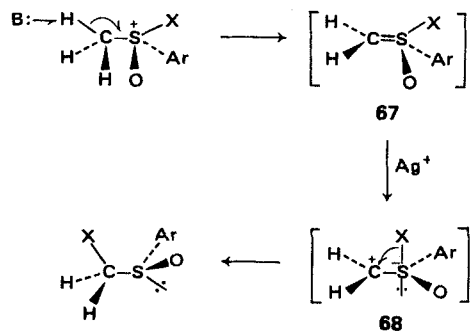
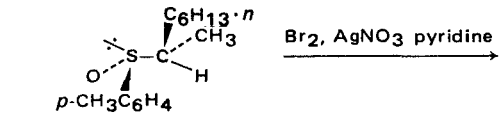
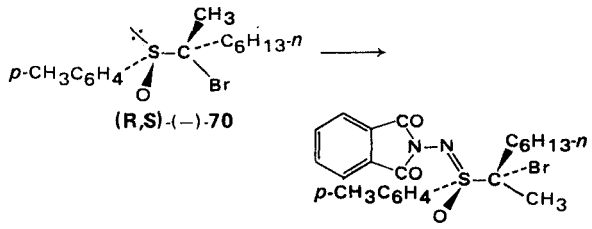


FIGURE VIII

The α-halogenation of aryl-ethyl and aryl-i-propyl sulfoxides contrary to the above discussed aryl-methyl sulfoxides proceeds with inversion of configuration at sulfur.[42] The degree of inversion depends on the complexity of the alkyl chain (i-Pr > Et) and on the nature of the halogen (Br > Cl), and is further increased in the presence of a molar excess of silver nitrate. In the case of the ethyl derivative where the α-hydrogens are prochiral, only one of the two possible diastereomers is obtained. To further ascertain the course of the reaction, the sequence involving halogenation of **69** and conversion of **70** to sulfoximine **71** was carried out.



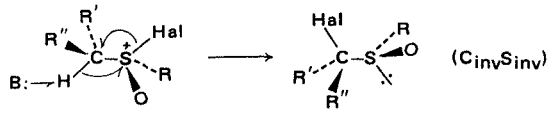
(R,S)-(+)-69, $[\alpha]^{25}D$ + 137°



(R,S)-(−)-70 **71**

FIGURE IX

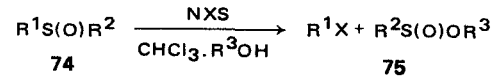
X-ray analysis of **71** shows that the halogenation indeed proceeds with inversion at both carbon and sulfur. The interdependence of the inversion at both centers is shown by the proposed mechanism (Figure IX).



72 **73**

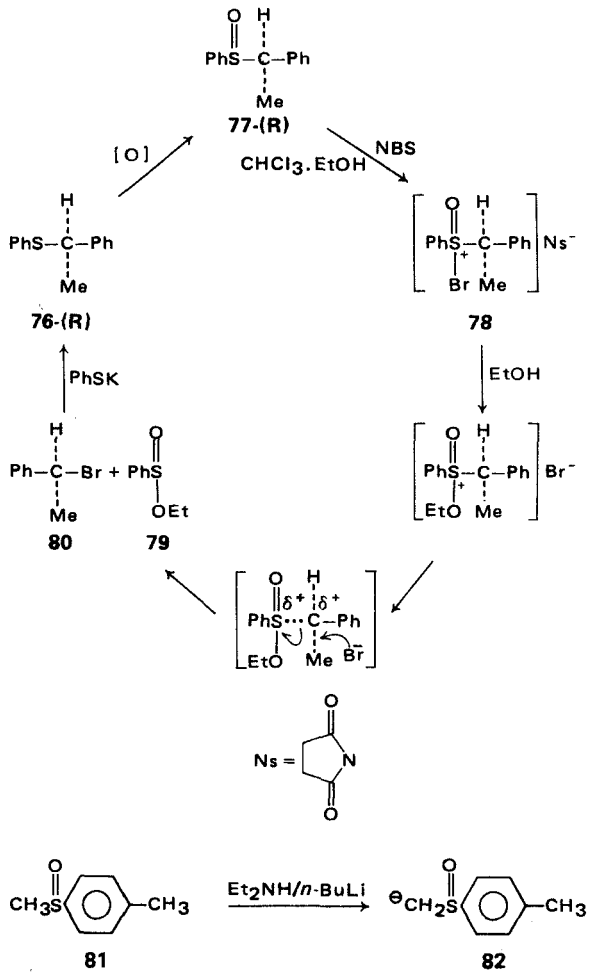
An antiperiplanar conformation **72** is preferred due to steric factors.

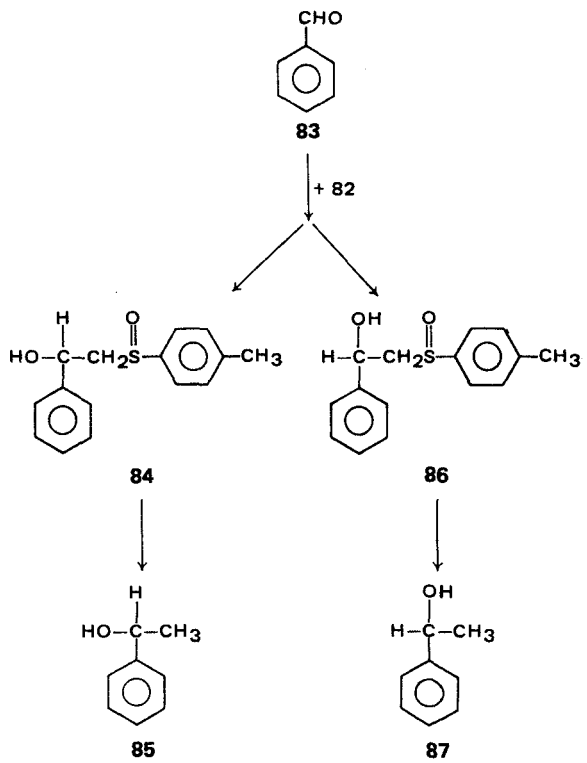
In contrast to the α-halogenation of sulfoxides with positive halogen species, Jung and Durst[43] observed C–S bond cleavage of sulfoxides **73** in the presence of N-bromo or N-chloro succinimide when such cleavage leads to relatively stable carbocations, *e.g.*, $PhMeCH^+$ or Me_3C^+.



74 **75**

The fragmentation mechanism was examined by studying the cleavage of optically active **77** obtained from **76**. Because of the ease of racemization of **80** the reaction mixture was treated with PhSK and the

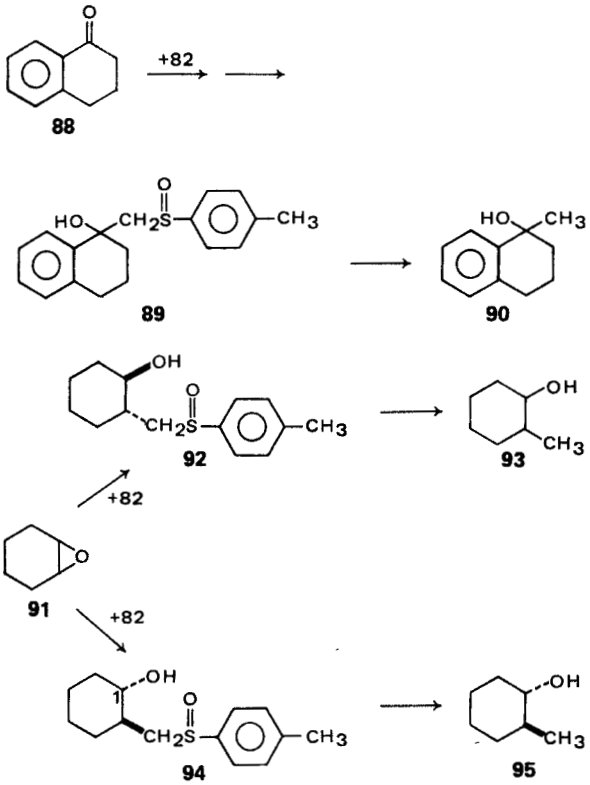




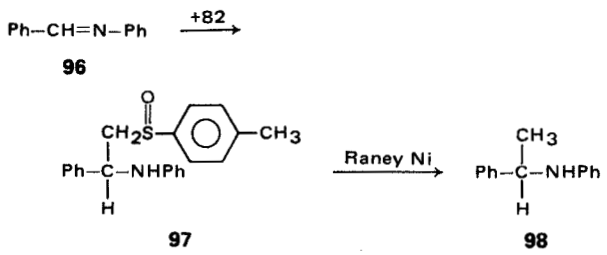
product **76** was then oxidized to sulfoxide **77**. The sign of the optical rotation of the product (6% optical yield) was the same as that of the starting sulfide indicating that the fragmentation must have occurred with net inversion at the benzylic carbon.

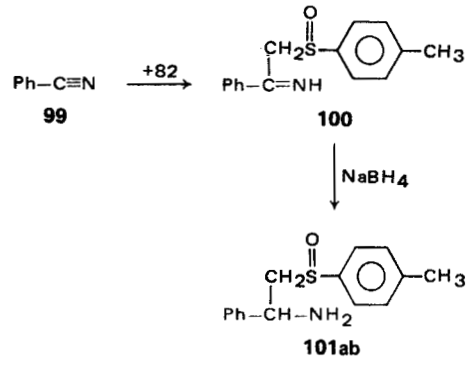
In view of the fact that **77** as obtained from **76** was a mixture of diastereomers the sulfinate **79** had to be racemic. However, it is conceivable that the present reaction might be used to prepare optically active sulfinates by carrying out the reaction with optically pure enantiomeric sulfoxides.

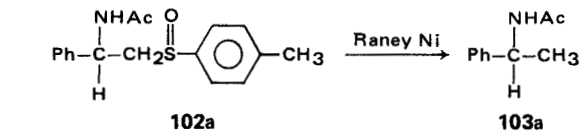
A number of alcohols obtained in high optical yield have been prepared by Tsuchihashi and coworkers[44] using optically active α-sulfinyl carbonions as reagents.

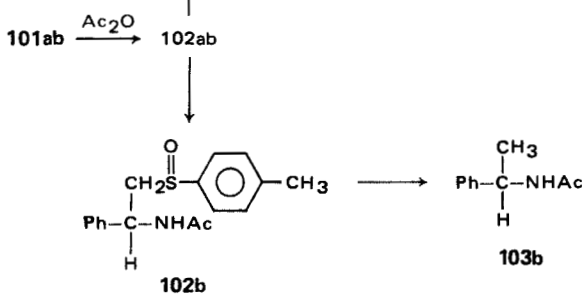


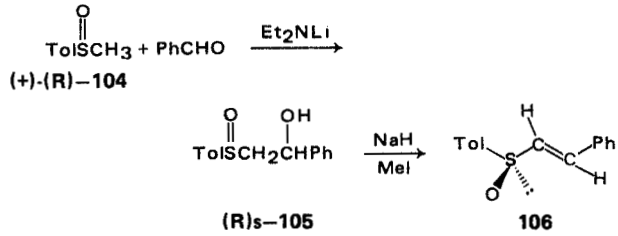
Alcohols **85, 87, 90, 93, 95** were obtained by reductive desulfurization of the diastereomeric sulfinyl alcohols **84, 86, 89, 92, 94** which were respectively separated by chromatography. In an extension of this work,[45] optically active amines **98** and **101** were prepared by the reaction of **82** with imine **96** and nitrile **99**.

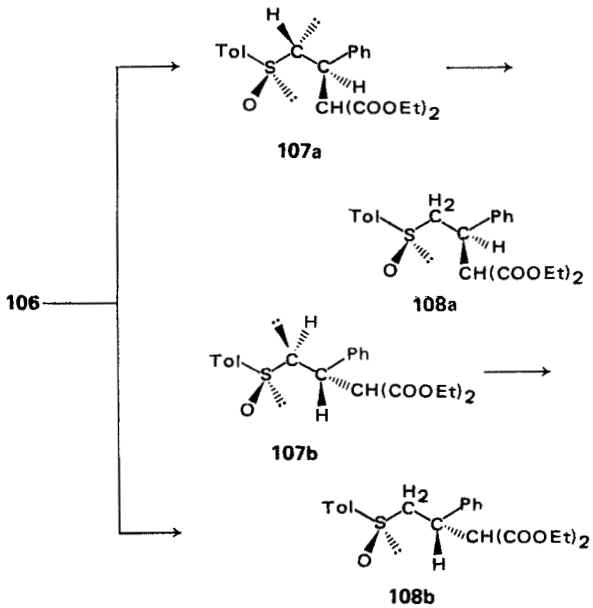




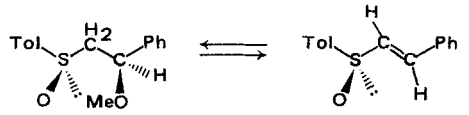




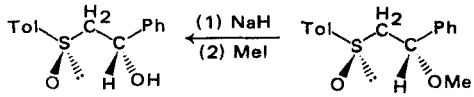




Further work by this group[46] has dealt with asymmetric synthesis using optically active α,β-unsaturated sulfoxides. The results obtained show that in anionic additions to these sulfoxides two types of results may arise depending on kinetic or thermodynamic control. When sulfoxide **106** is treated with diethyl malonate, the major product **107a** resulting from kinetic control is obtained, whereas, with sodium methoxide the major product is **107b** resulting from thermodynamic control.



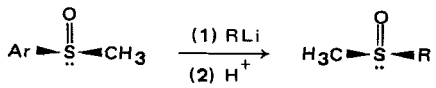
109 **110**



112 **111**

The structure of **111** was unambiguously established upon synthesis from **112**.

An additional[47] reaction of optically active aryl allyl sulfoxides has found synthetic utility in the preparation of optically active dialkyl sulfoxides. Treatment of arylmethyl sulfoxides **113** with alkyl lithium reagents gives dialkylsulfoxides **114** with inversion of configuration.

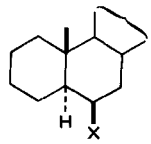


113 **114**

E. Steroidal Sulfoxides

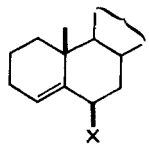
A number of recent papers have been published by Jones *et al.* in their continuing series on steroidal sulfoxides. In order to determine the chiroptical properties of β,γ-unsaturated sulfoxides,[48] compounds **115–118** were prepared, separated into R and S diastereomers, and their absolute configuration established.

On the basis of the ord spectra of these compounds it was concluded that the chiroptical properties are controlled by the relative orientations of the double bond and the lone electron pair at sulfur. Moreover, the configuration at the sulfur atom is not necessarily the predominant factor. The ord spectra of **115** R and S are almost mirror images despite the fact that the steroid skeleton is highly dissymmetric. In contrast **117** R and S give non-antipodal ord spectra.

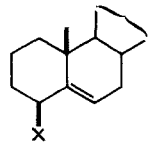


115 X = (l) – $SO{\cdot}CH_2{\cdot}CH{:}CH_2$; X = (s) – $SO{\cdot}CH_2{\cdot}CH{:}CH_2$

116 X = (l) – $SOPr^n$; X = (s) – $SOPr^n$

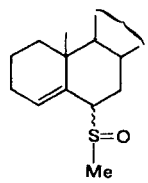


117 X = (l) – SOMe; X = (s) – SOMe



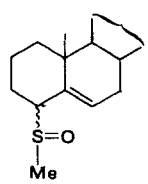
118 X = (s) – SOMe; X = (l) – SOMe

The influence of steric factors on the course of the acetic anhydride-induced Pummerer rearrangement of steroidal sulfoxides, indicates[49] that the reaction is independent of the sulfur configuration. In an analogous path to other sulfoxides, the 6β-steroidal sulfoxides underwent reorganization at sulfur under the reaction conditions, and no differences were found between the R- and S- isomers. The stereochemical aspects of the allyl sulfoxide-sulfenate rearrangement have also been examined by Jones and coworkers.[50] Sulfoxides **119–122** were prepared from the corresponding sulfides. A method which utilized the fact that allyl sulfoxides react rapidly with thiophiles to



119 (*R*)-6β; (*S*)-6β

120 (*R*)-6α; (*S*)-6α



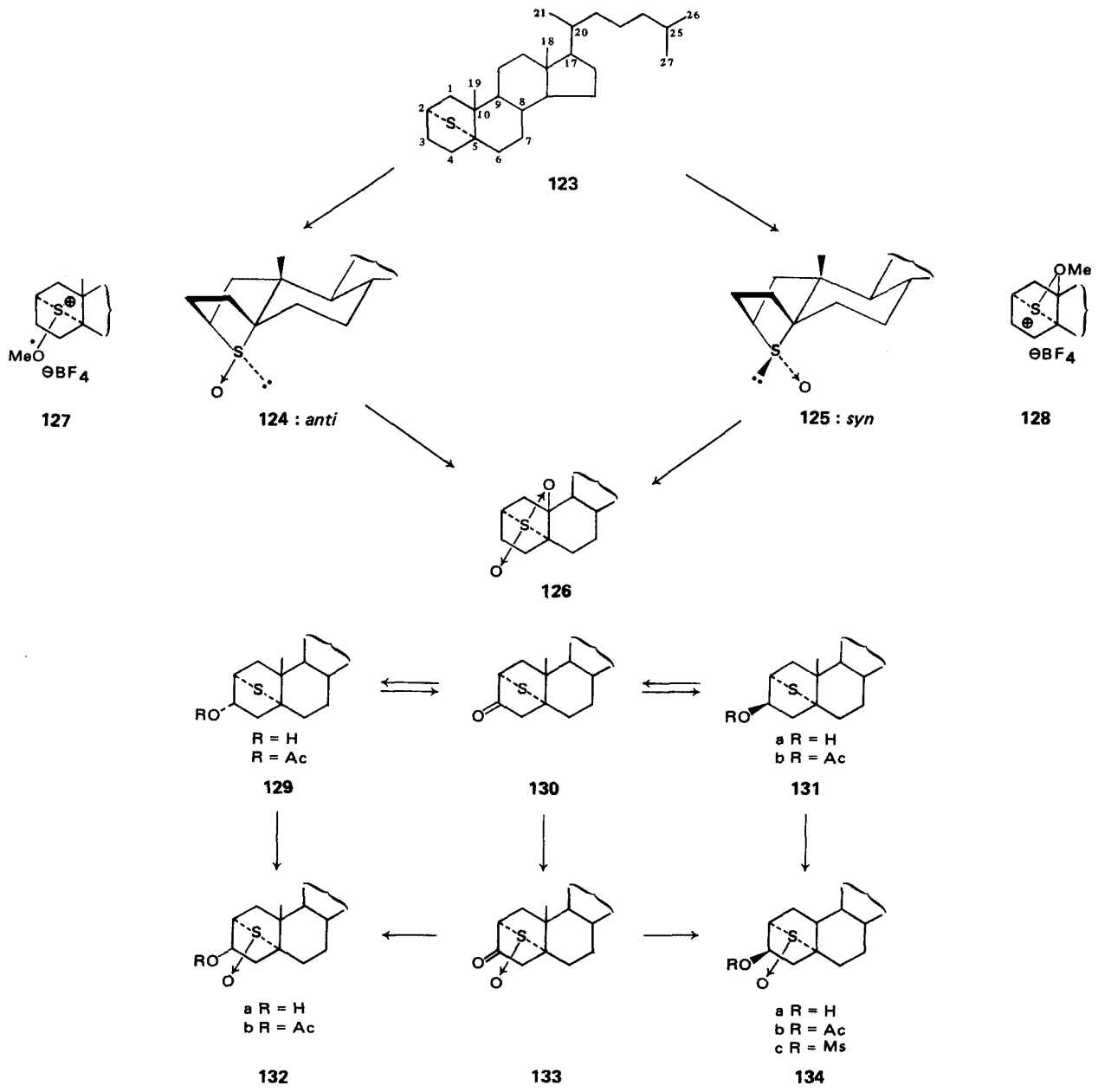
121 (*R*)-4β; (*S*)-4β

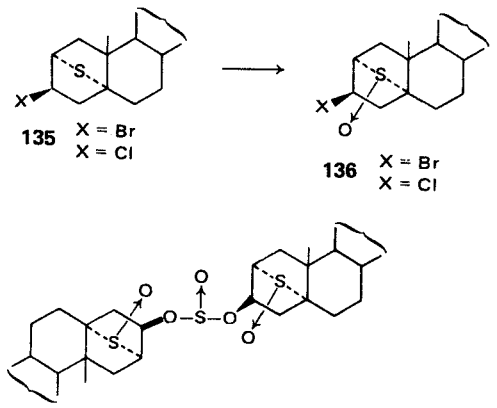
122 (*R*)-4α; (*S*)-4α

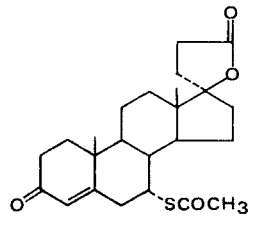
give allyl alcohols was used in the determination of the absolute configurations. The rates of the [2, 3] sigmatropic allyl sulfoxide-sulfenate rearrangement were shown to be influenced by the chirality at sulfur. The stereoselective synthesis of 5α-cholestan-2α,5-anti- and -syn-episulfoxides has been further (II-75) explored by Kishi *et al.*[51] The oxidation of episulfide **123** with a variety of oxidants gave various ratios of the anti-**124** and syn-sulfoxides-**125**, ranging from 98.5% **124** when *m*-chloroperbenzoic acid was used to 98.4% **125** when the oxidation was carried out with *tert*-butyl hypochlorite. The absolute configurations of the sulfoxides were assigned upon consideration of the chromatographic behaviour, selectivity

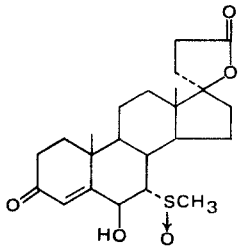
in oxidation of **123**, rate difference in oxidation to sulfone **126**, and nmr[52] data, especially with the aid of shift reagents. An interesting angular dependency of lanthanide-induced shift was observed whereby the C_{20} and C_{25} methyl signals of **124** were shown to be shifted to higher fields upon addition of the shift reagent. The corresponding alkyl sulfoxonium tetrafluoroborates **127** and **128** were prepared with retention of configuration, and were shown to be stable to alkoxy exchange, similar to the lack of reactivity of **124** and **125** under conditions where other sulfoxides undergo oxygen exchange reaction. In a subsequent paper[53] the preparation of a series of 3-substituted 5α-cholestan-2α,5-anti-episulfoxides was reported. Sulfoxides **132a** and **b**, **133**, **134a** and **b** were obtained in high yields as single products by *m*-chloroperbenzoic acid oxidation of the corresponding sulfides, whereas **134c** was obtained by mesylation of **134a**. Sulfoxides **135** and **136** are also reported. Attempted chlorination of **134a** with thionyl chloride afforded the bisulfite **137** as sole crystalline product. The determination of the sulfinyl configuration was based on chemical conversion, nmr and dipole moment studies.

The metabolic path of the aldosterone-antagonist diuretic spironolactone **138** was reported by Karim and Brown.[54] Among the six metabolites obtained, the steroidal sulfoxide **139** was isolated and identified.







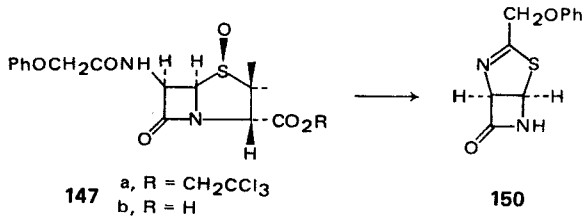


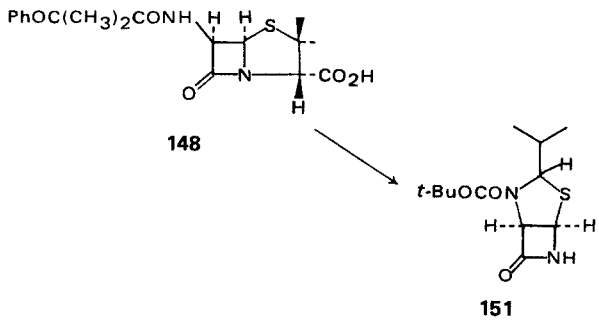
F. Penicillin and Cephalosporin Sulfoxides and Related Compounds

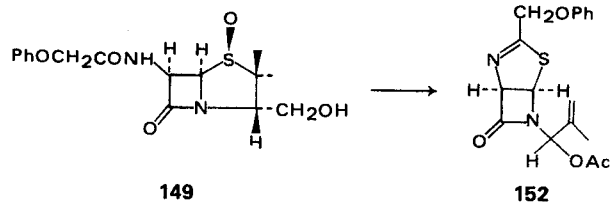
The elegant conversion (II-84) of penicillins to cephalosporins *via* the sulfoxides of the former, has brought about a considerable increase in the research related to the chemistry of both types of β-lactam antibiotics. Many of the published articles deal with sulfoxides of these compounds, all of which are chiral at sulfur. A number of the articles mentioned in this review have been dealt with by Flynn,[1x] however, many of the more recent publications have not been discussed. For the sake of completeness all pertinent articles published after Part II of this series are included.

The oxidation of penicillins and cephalosporins with ozone has been explored by Spry.[55] The degree of steric hindrance has great influence on the ratio of R- and S-sulfoxide product obtained (Table II).

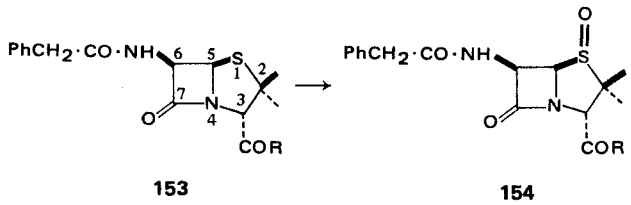
Treatment of Δ-3-cephems under similar conditions failed to produce sulfoxides as a result of competitive oxidation of the double bond. However the hydrogenated cephams **145** and **146** gave the desired sulfoxides. The stereochemistry of the products was determined on the basis of nmr chemical shifts. The structure of other sulfoxides was established[56] by means of lanthanide induced shifts. Vanderhaghe and coworkers[57] have prepared a number of 6-epi-penicillins by epimerization and deoxygenation of the corresponding sulfoxides. The process involves the silylation of the secondary amide side chain followed by base epimerization of the 6-H. The preferred reagents used are 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) as base and phosphorus tribromide as reducing agent. Cooper and Jose[58] have made use of sulfoxides **147**, **148**, and **149** in their preparation of thiazoline azetidinones **150**, **151**, and **152**, which serve as key intermediates in the synthesis of cephalosporins.







A series of articles entitled "Transformations of Penicillin" have been published by Barton and coworkers, and deals to a great extent with reactions of penicillin sulfoxides. In a detailed examination[59] of the mechanism of the penicillin-cephalosporin interconversion, the authors have shown that oxidation



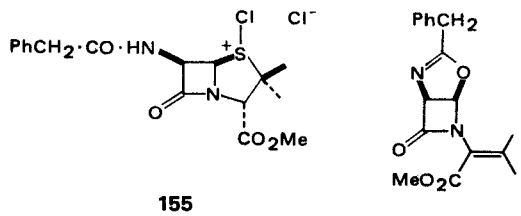
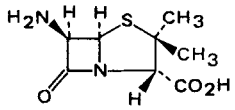
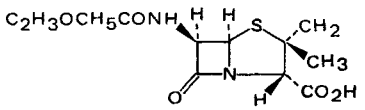
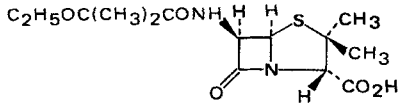
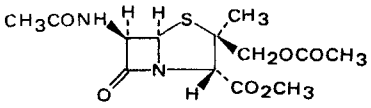
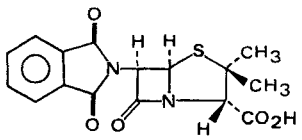
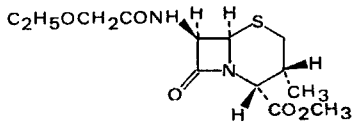
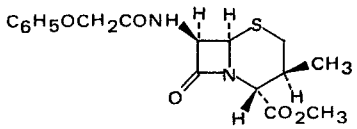
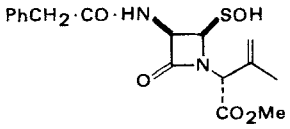


TABLE II
Oxidation of Penicillin and Dihydrodeacetoxycephalosporin Derivatives with Ozone

Derivative	Solvent	Yield of sulfoxide, %	*S/R* ratio
 **140**	H_2O	>95	4/1
 **141**	H_2O-acetone	>95	1/1
 **142**	H_2O-acetone	>95	1.4/1.0
 **143**	H_2O-acetone	70	1/2
 **144**	H_2O-acetone	>95	only R
 **145**	H_2O-acetone	91	1/7
 **146**	H_2O-acetone	>95	1/24

of **153** with iodobenzene dichloride or tert-butyl hypochlorite affords a mixture of R- and S-sulfoxides **154** with a preference for the former isomer (I-116). A halosulfonium intermediate **155** is proposed which undergoes hydrolysis with inversion of configuration. When an excess of oxidizing agent was used the oxazoline **156** was isolated. It had been previously shown (II-77, 78) that the thermal cleavage of the thiazoline ring of **153** proceeds via the sulfenic acid **157**. The reaction of **157** with acetic anhydride was studied in the hope of introducing an acetoxy group into the cephalosporin nucleus. The products isolated included the isothiazolinone **158** which isomerized to **159**; the major product was a mixture of **160** and **161** as predominant component, and a small amount of **162**.



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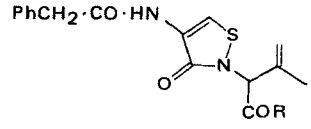

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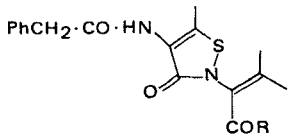

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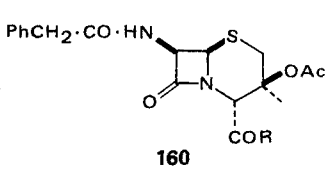

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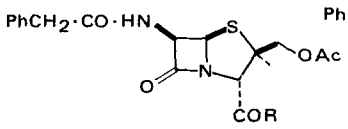

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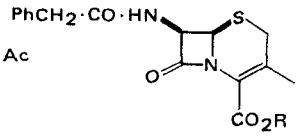
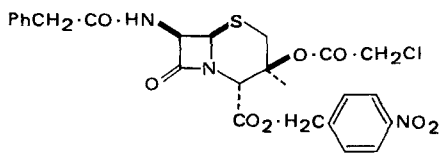


162

With chloroacetic anhydride the only product obtained was **163**. It was thus concluded that weak acids with strong conjugate anions favor the formation of penams which are products of kinetic control, whereas strong acids with weak conjugate bases prefer the formation of cephams that are the products of thermodynamic control. In order to ascertain the configuration of the cepham **160** which is isomeric and difficult to distinguish from the penam **161**, an X-ray study of the sulfoxide **164** was carried out indicating the assigned structure.



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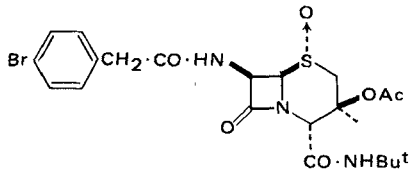
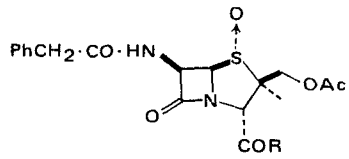


164

In contrast to the high selectivity in the course of oxidation of penicillins (I-114), the oxidation of cephalosporins is dependent on the oxidant giving rise to R- and S- sulfoxides. Three other novel sulfoxides **165–167** were also prepared.

A second paper[60] by Barton *et al.*, describes the rearrangement of penicillin sulfoxides **168** to a cephalosporin **169**. The acid group of the sulfoxide in this case was protected with the novel N,N-diisopropyl hydrazine which was subsequently removed by mild oxidation. However, when the protective group was the mono-isopropylhydrazide the rearrangement product obtained was the anhydro-penicillin **170**.



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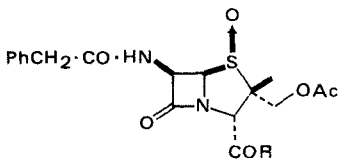

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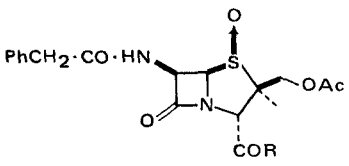
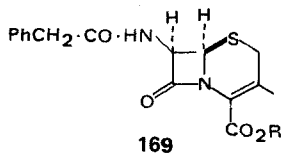


167

A novel method[61] for the decarboxylation of penicillin sulfoxides involved the oxidative thermal decomposition of the mixed anhydride **171** with the formation of the ester **172**. Reduction with sodium borohydride to alcohol **173** became feasible when Ar was 2,4-dinitrophenyl. When the reaction was carried out without observing strict anhydrous conditions the alcohol **174** was also obtained. Attempted basic hydrolysis of **172** with diethylamine resulted in epimerization at position 6 with the formation of



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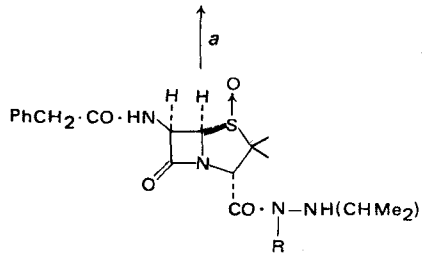

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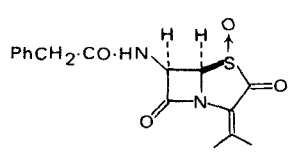

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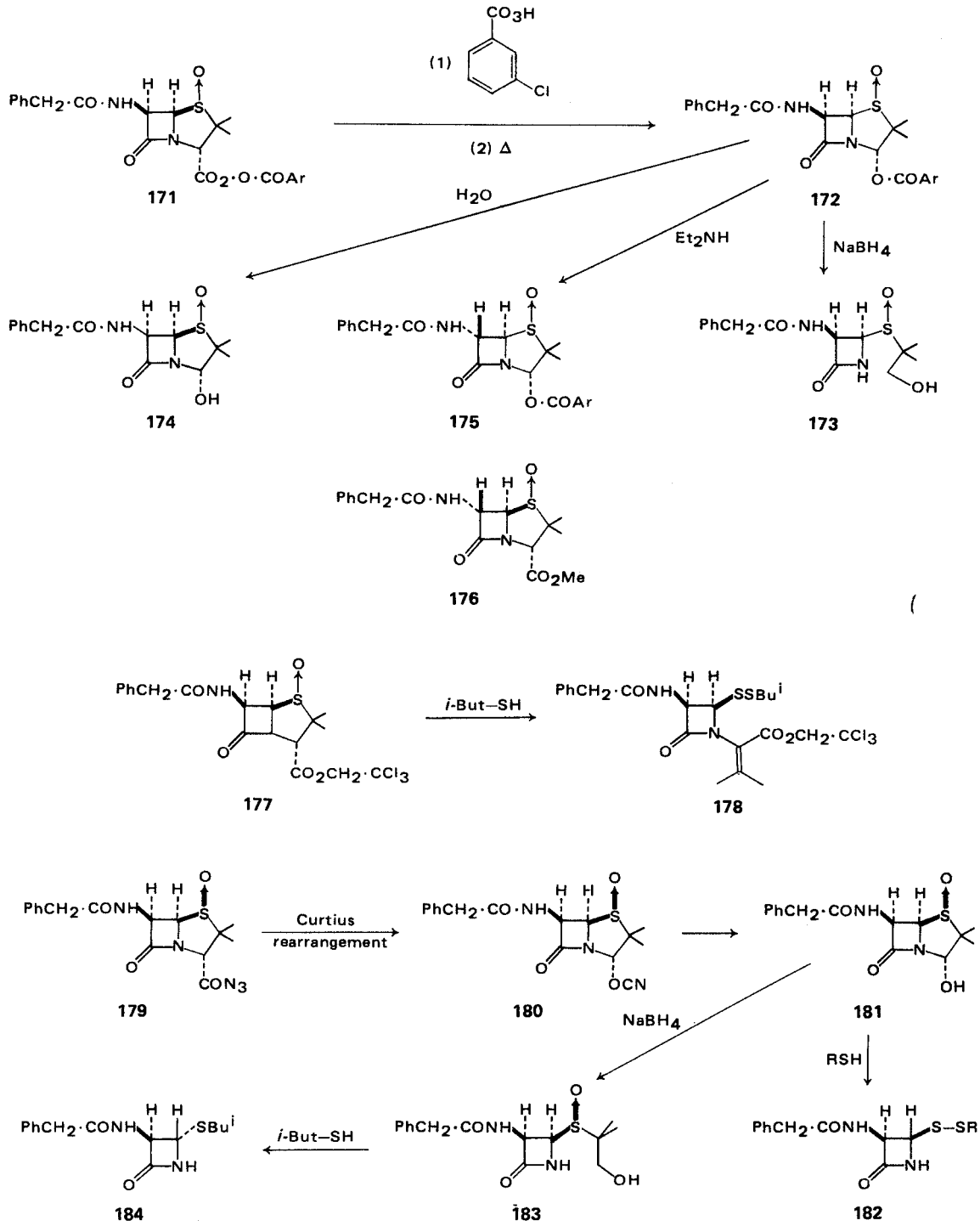
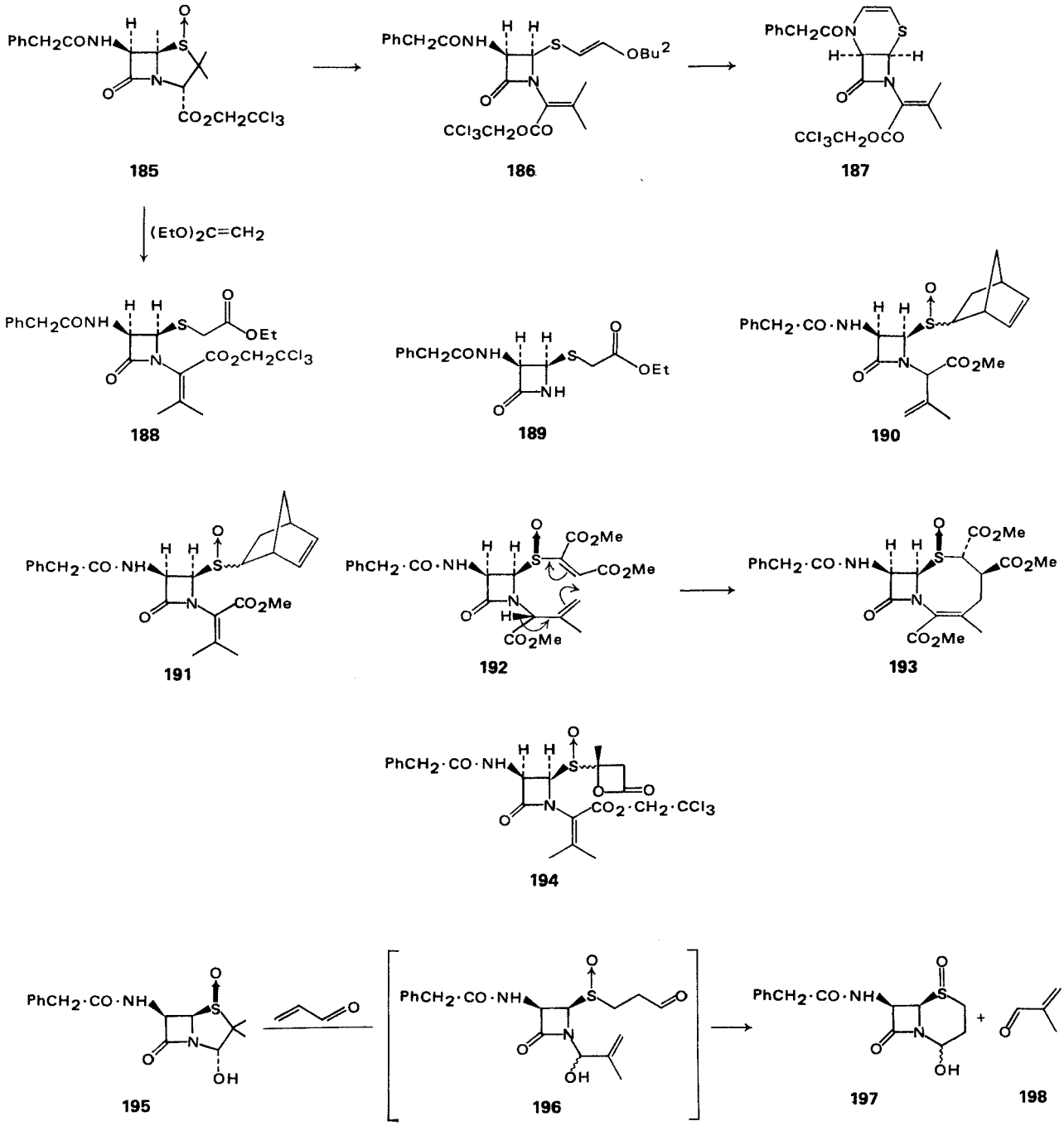
175. The use of this base enabled epimerization of other penicillins (**176**) containing a secondary amide group without the need of prior nitrogen silylation.



Other papers in this series by Barton *et al.* deal with the trapping of the sulfenic intermediate obtained in the course of rearrangements of penicillin sulfoxides. Several reactions whereby the intermediate sulfenic acid, obtained from thermal rearrangement of penicillin sulfoxides, has been trapped, have been mentioned earlier (II-90). Additional trapping experiments[62] with thiols have resulted in the formation of disulfides.

Heating **177** in thiols afforded **178**. Similar results were obtained with **181** obtained from **179**. However, **183** gave sulfide **184** where the configuration of the hydrogens on the β-lactam ring was trans. Other trapping experiments[63] yielded unstable vinyl ethers such as **186** which readily rearranged to **187**. Whereas treatment of the sulfoxide **185** with 1,1-diethoxyethane resulted in the formation of **188** that was

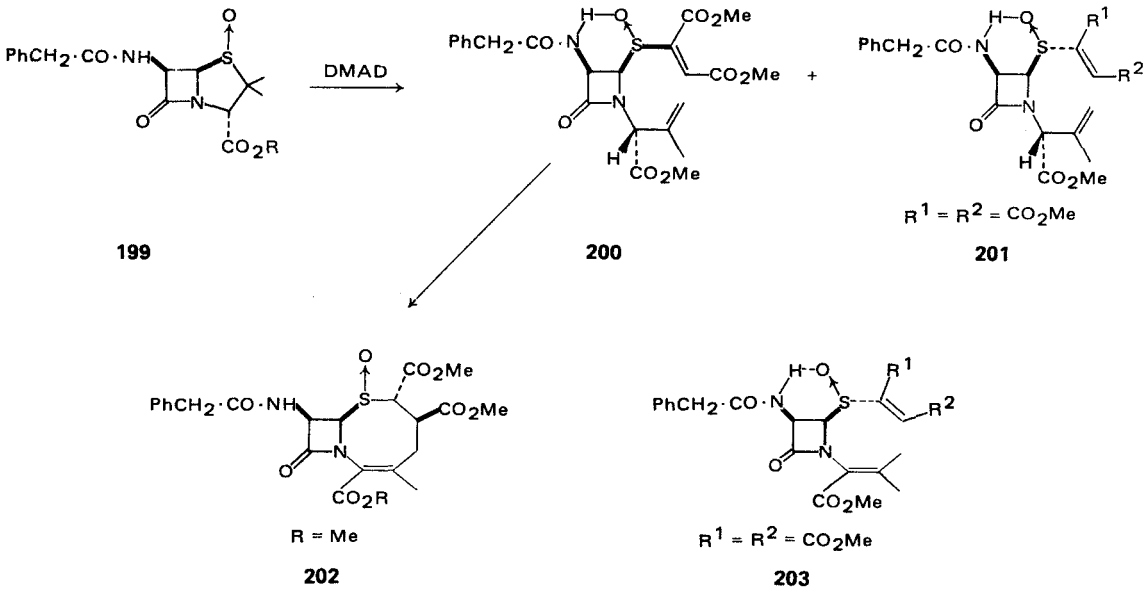


immediately converted to **189**. With norbornadiene a mixture of **190** and **191** was obtained. Other reagents used such as acetylenedicarboxylate produced **193** as main product. This compound probably arose *via* the adduct **192**. Condensation with diketene gave **194**.

The hydroxy penam **195** when treated with acryaldehyde gave a mixture of stereoisomers **197**.

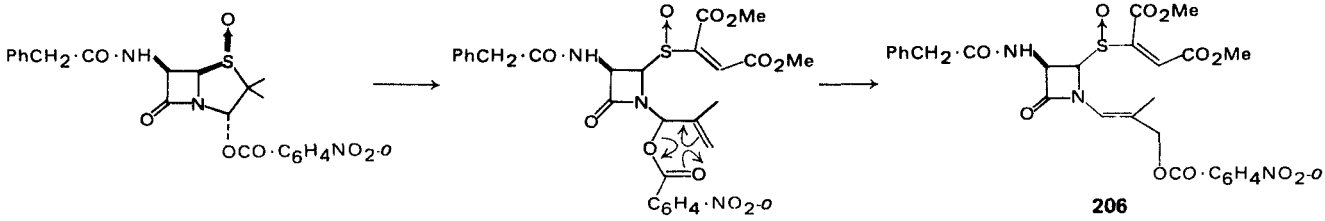
A novel trapping experiment[64] which provides a method for the introduction of a two-carbon fragment to the sulfur atom in penicillins bearing potential carboxy-group has been reported. Treatment of **199** with dimethylacetyldicarboxylate (DMAD) afforded a 1 : 1 mixture of **201** and unstable **200** which isomerized to **202**. Heating the mixture of **200** and **201** with a catalytic amount of triethylamine gave **202** and the conjugated isomer **203**. Furthermore, the reaction of **204** with DMAD gave **206** resulting from the allylic rearrangement of **205**.

The oxidative trapping of the sulfenic acid intermediate has been studied by Kukolja and Lammert.[65] Heating of **207** with sulfuryl chloride gives a mixture of diastereomeric sulfinyl chlorides **210** that in the

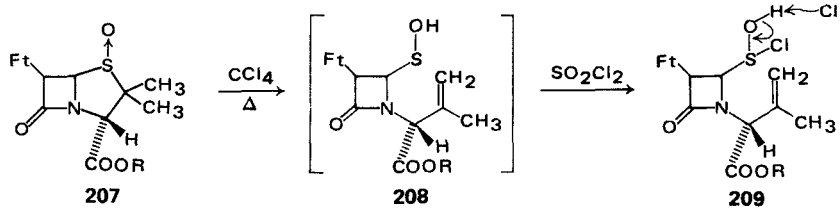


199 200 201

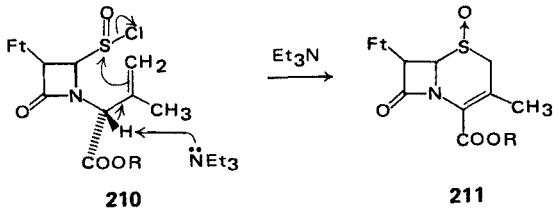
202 203



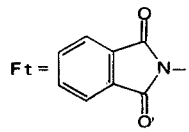
204 205 206



207 208 209



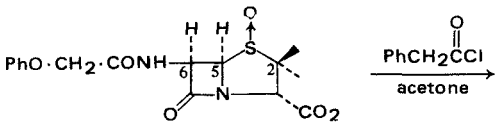
210 211



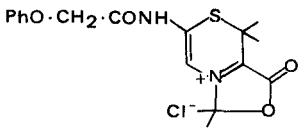
(*a*), R = CH_3; (*b*), R = *p*-NO_2–$C_6H_4CH_2$

presence of one equivalent of triethylamine gave sulfoxide **211**. The mechanism proposed involves an electrophilic and/or free radical attack by chlorine on the nucleophilic sulfur of the sulfenic acid **208** giving an intermediate **209**, that after elimination of hydrogen chloride gives sulfinyl chloride **210**. Cyclization follows abstraction of the α-proton. This reaction is reported to be the first example of the preparation of sulfinyl chlorides by the oxidative trapping of a thermolytically formed sulfenic acid.

Other ring expansion reactions of penicillin sulfoxides involve the treatment[66] of penicillin V sulfoxide **212** with phenyl acetyl chloride giving rise to the formation of **213**. This reaction does not take place with the α-sulfoxide.

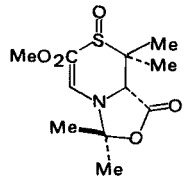


212

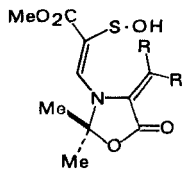


213

In related studies[67] the thermally induced racemization of **214** suggests the probable involvement of the intermediate sulfenic acid **215** formed by a sigmatropic hydrogen shift.

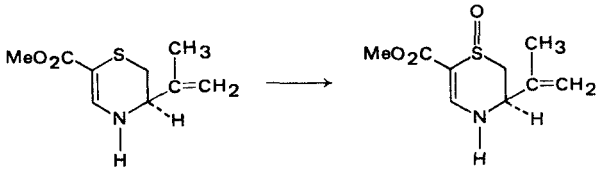


214

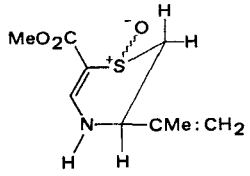


215

Oxidation of **216** with sodium metaperiodate gave a single sulfoxide **217**[68] whose conformation in solution was shown to be the sofa conformer **218**.

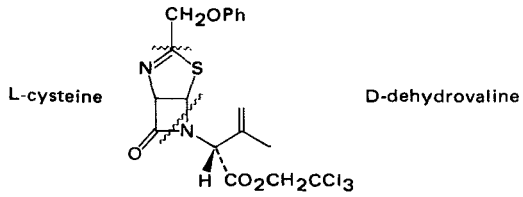


216 **217**

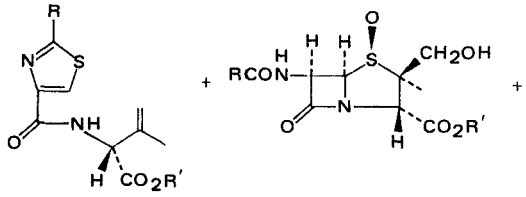


218

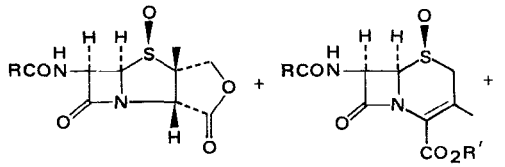
Since the initial conversion by Morin *et al.* (II-84) of penicillin sulfoxides into cephalosporins, much effort has been placed into further investigating this type of rearrangement. A variety of reaction conditions have shown this to be a feasible and diversified process. Moreover, Cooper[69] has studied the reactions of thiazoline-azetidinone **219** as a model for a possible intermediate in the biosynthesis of both penicillins and cephalosporins. Treatment of **219** with *m*-chloroperbenzoic acid in the presence of a catalytic amount of trifluoroacetic acid resulted in the formation of compounds **220-225**. Of these, compounds **221-225** are believed to arise from the acid catalysed opening



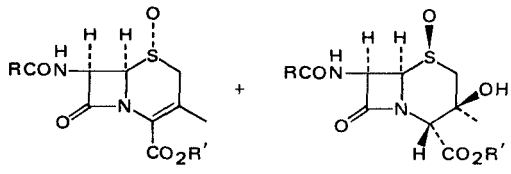
219



220 **221**



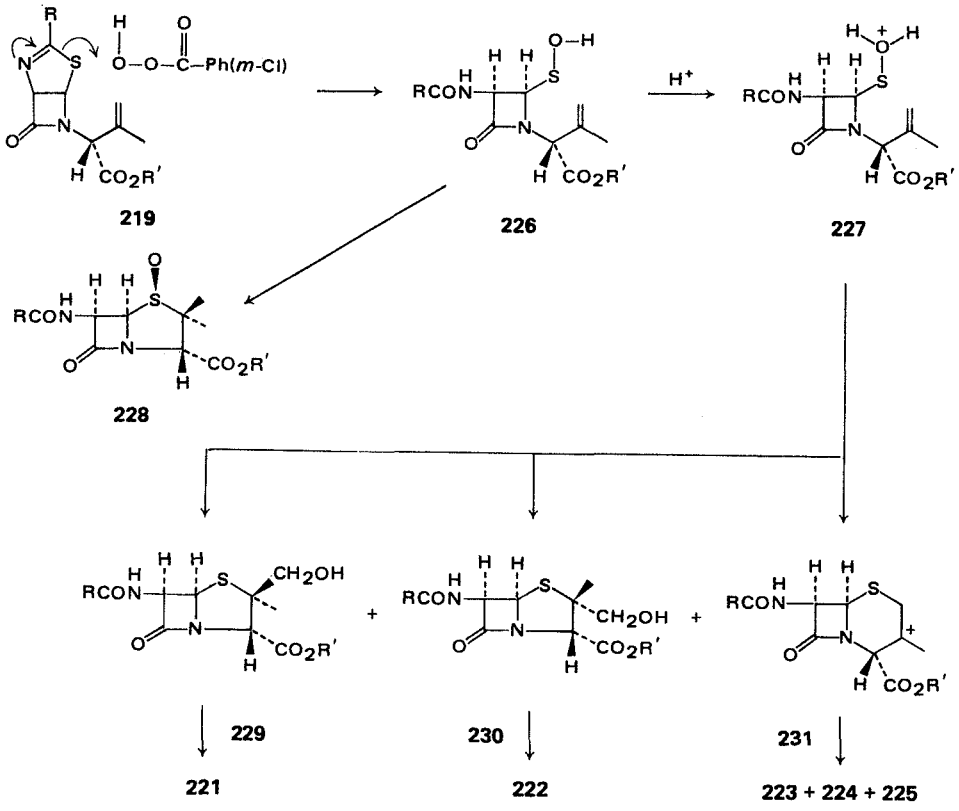
222 **223**



224 **225**

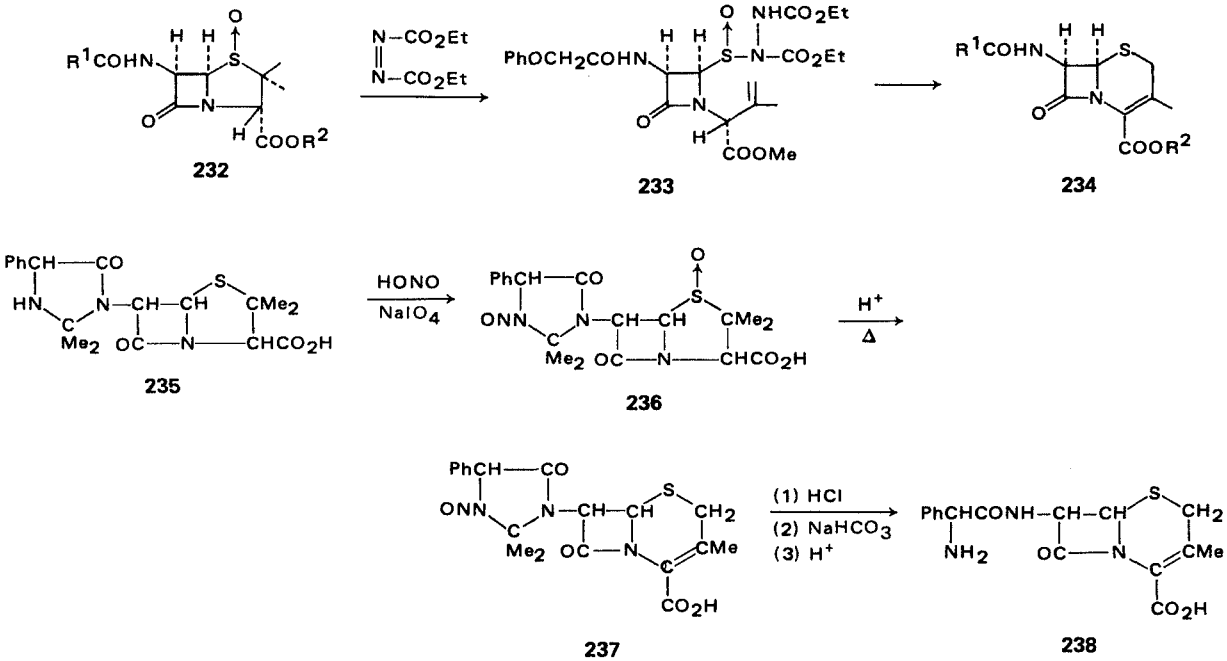
R = $PhOCH_2-$; R' = CCl_3CH_2-

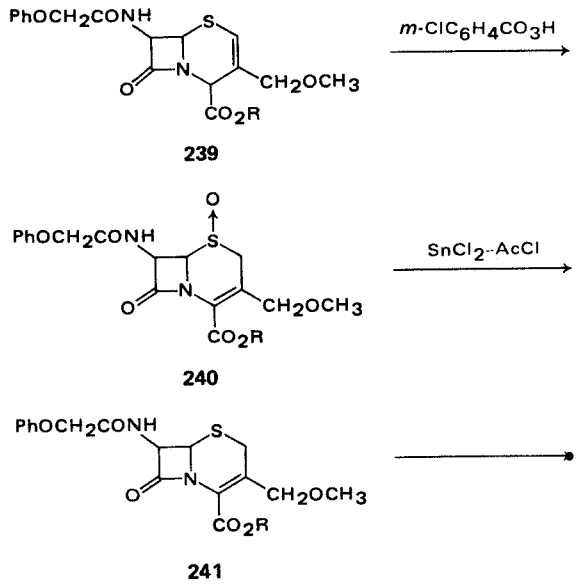
of the thiazoline ring to sulfenic acid. Alternatively the products **221-225** may derive from nucleophilic displacement at the sulfur of **227** by the double bond. Thus both penams and cephams may be obtained from a common starting material such as **219**.



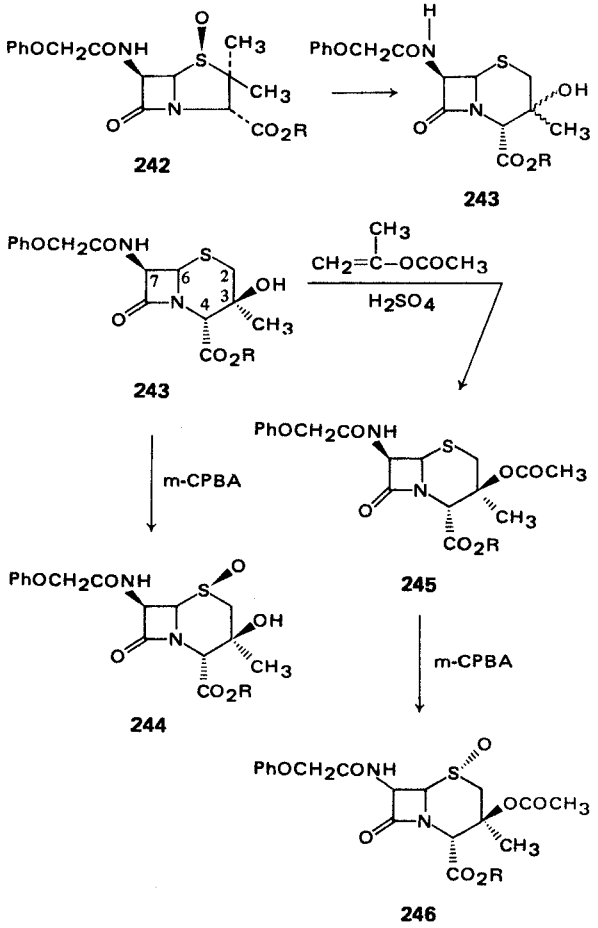
It has been shown[70] that penicillin sulfoxides **232** are converted into cephalosporins **234** under non-acidic conditions by azo compounds *via* the postulated intermediate **233**. The conversion of hetacillin **235** into the orally active broad spectrum antibiotic cephalexin **238** *via* the sulfoxide **236** has been reported.[71]

The cephalosporin sulfoxide **240** was prepared by Webber *et al.*[72] as an intermediate in the $\Delta-2\rightarrow\Delta-3$ isomerization step in the course of the synthesis of 3-methoxymethyl derivative **241**.

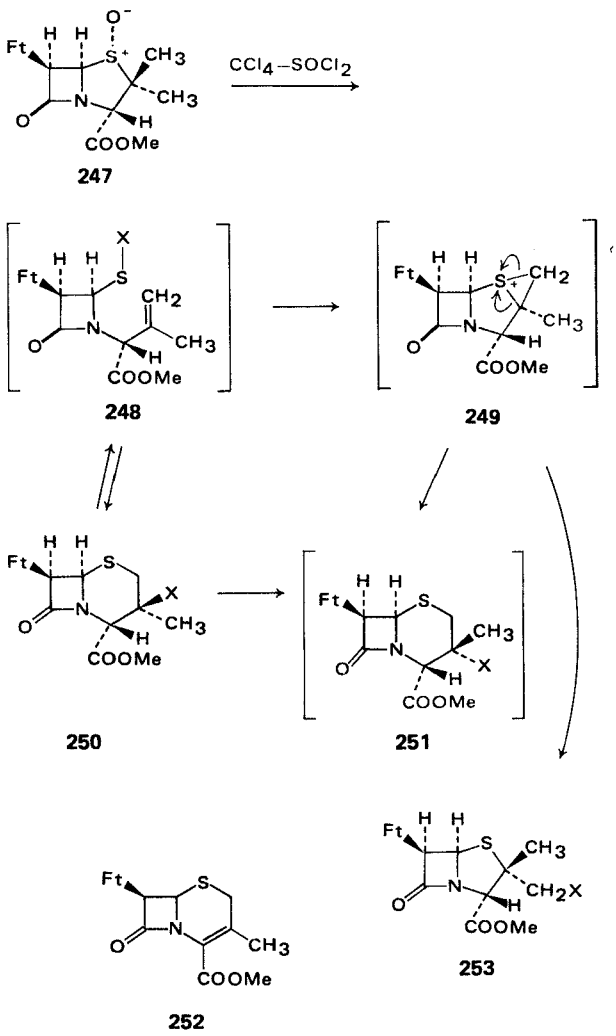




The isolation of 3-substituted cephams in addition of Δ-3-cephems has been described by a number of authors in the course of pencillin-cephalosporin rearrangements. Gutowski *et al.*[73] isolated compound **243** which was subsequently shown to have an *S* configuration at the 3-carbon.[74] Oxidation gave the corresponding β-sulfoxide **244**, whereas the oxidation product of the acetylated derivative **245** gave the α-sulfoxide **246**.



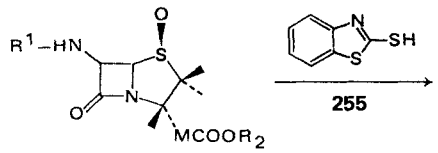
The 3-chloro cepham **250** was obtained[75] by treatment of sulfoxide **247** with thionyl chloride *via* the thiiranium ion **249**.



Similar 3-halo cepham derivatives **257** have been prepared[76] by halogenation of disulfides **256** which may be obtained by treatment of the **254** with 2-mercaptobenzothiazole **255**.

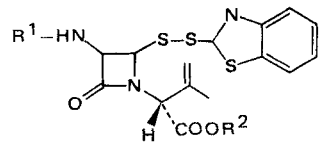
Novel penicillins have been prepared by Spry[77] *via* multiple sulfoxide rearrangements with acetic anhydride. Treatment of **260** with anhydride gave **261** which was further oxidized to **262**. The triacetylated **263** was obtained by subsequent treatment of **262** with additional anhydride.

Although penicillin sulfoxides have been shown to possess considerable chemical and thermal stabilities, the isoelectronic sulfonium ylides and sulfilimines

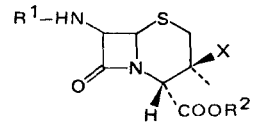


254

255



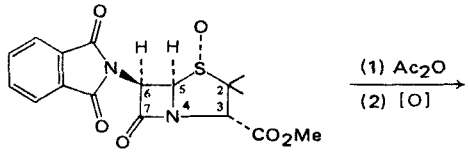
256



257

have not been isolated. However, the corresponding 2-azetidinones **265** and **266** have been prepared.[78] Treatment of penicillin **264** with dimethyl diazomalonate or *p*-nitrophenyldiazoacetate afforded **265**, whereas **266** was obtained from **264** and ethylazidoformate. That the original stereochemistry is retained was strongly indicated by the nmr spectra of **265** and **266** which suggest a six electron sigmatropic rearrangement (**268** and **269**) analogous to that reported in the formation of sulfenic acid from penicillin sulfoxides. A low yield of the cephalosporin **269** was isolated upon acid catalyzed cyclization of **267**.

The reverse reaction, namely, the rearrangement of the cephalosporin **270** to the penicillin **272** *via* the intermediate cephalosporin sulfonium ylide **271** has also been carried out.[79]



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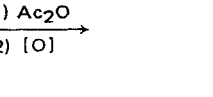
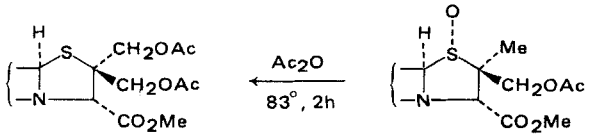
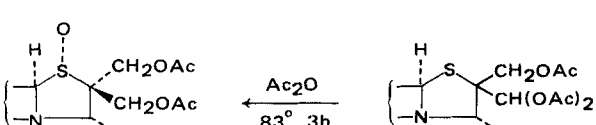


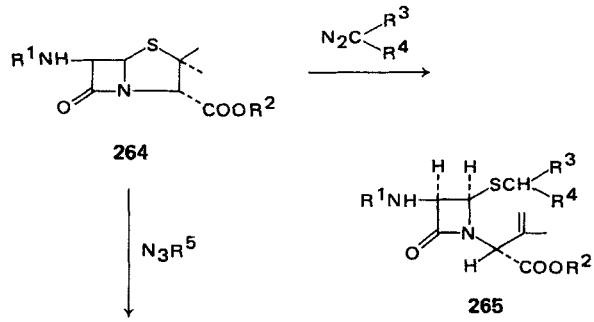
259



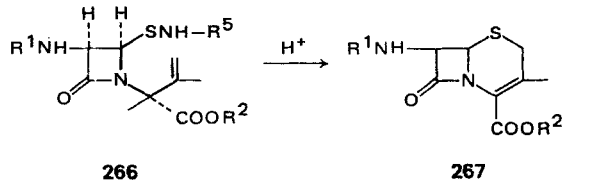
261 (19%) 260



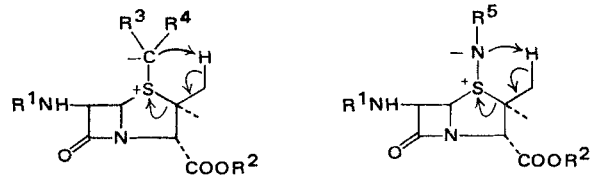
262 (84%) 263 (21%)



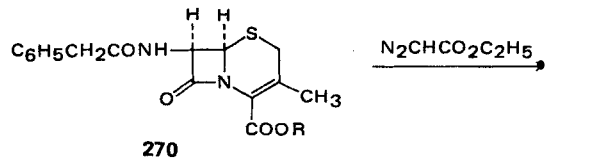
264 265



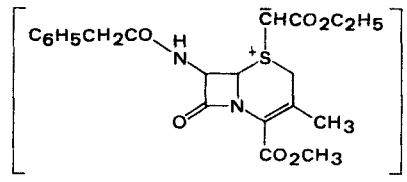
266 267



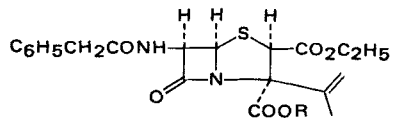
268 269



270

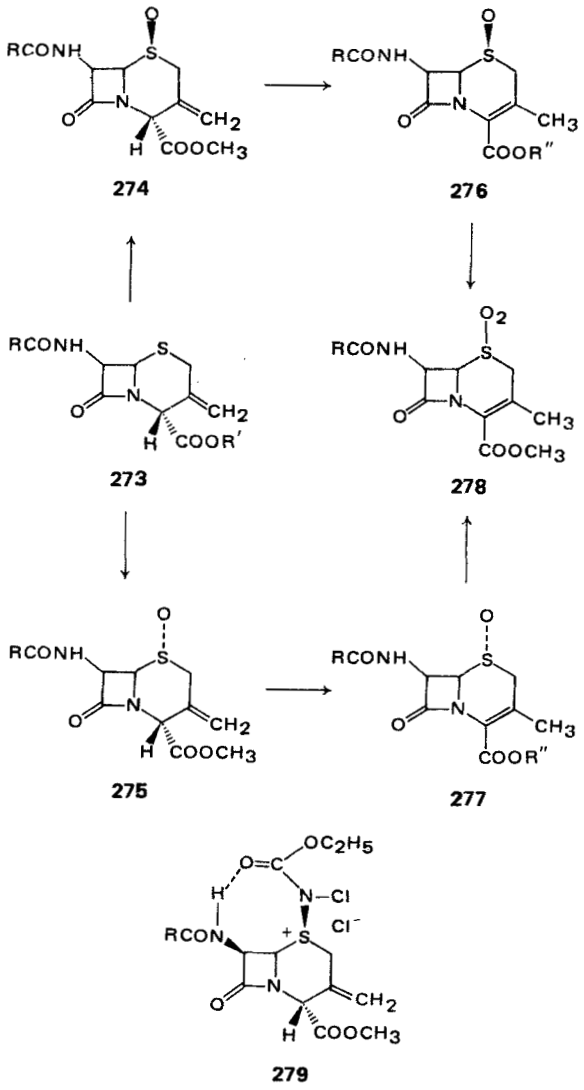


271



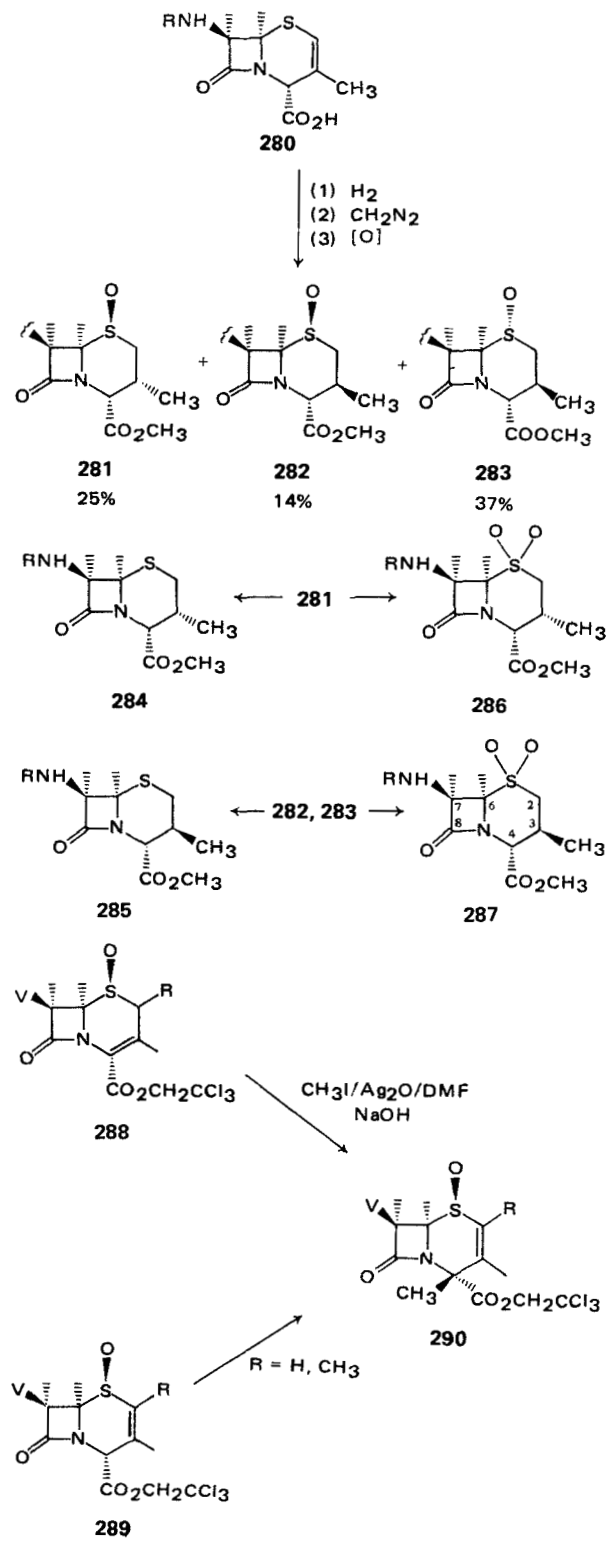
272

In the course of the oxidation of **273** to the α-sulfoxide **275**, a second cephalosporin sulfonium intermediate **279** has been postulated.[80] The usual course of oxidation affords β-sulfoxides **274**. The authors suggest that the initially formed β-sulfonium salt **279** subsequently hydrolyzes to the α-sulfoxide **275**, analogous to the formation of α-sulfoxides in the oxidation of penicillin with iodobenzene dichloride (I-116).



274 **276** **273** **278** **275** **277** **279**

A number of recent publications have reported the synthesis of cephalosporin sulfoxides and in some cases their use in the modification of the cephalosporin nucleus. Spry[81] upon oxidation of Δ-2-cephem-**280** obtained three isomeric sulfoxides **281**, **282**, and **283**. The sulfoxides were then reduced to the cephams **284** and **285** or further oxidized to the sulfones **286** and **287**. Two other cephem sulfoxides **288** and **289** were alkylated to a common product **290**, with the incoming group preferentially attacking from the β-face of the C_4-carbon.



280

281 25% **282** 14% **283** 37%

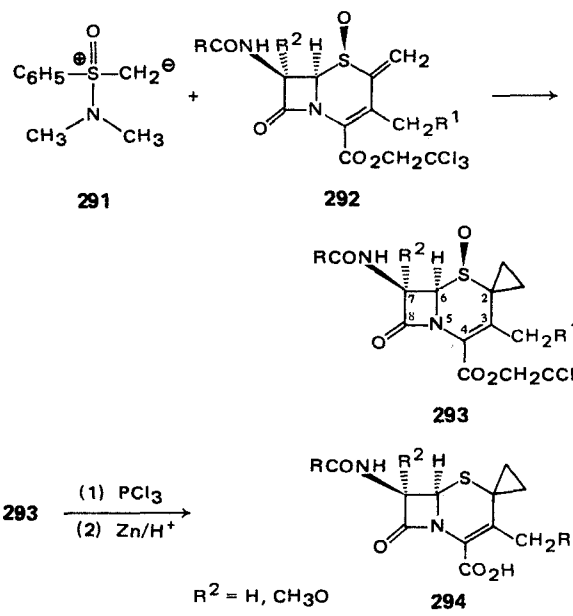
284 ← **281** → **286**

285 ← **282, 283** → **287**

288 **290**

289

Cephem sulfoxides **292** were also used[82] in the preparation of C-2 spiro derivatives **293** which in turn were reduced and hydrolyzed to sulfides **294**. Cephem **292** (R = H) proved[83] to be a versatile starting material in the synthesis of novel tricyclic derivatives, *i.e.*, **297**, **298**, **299**.

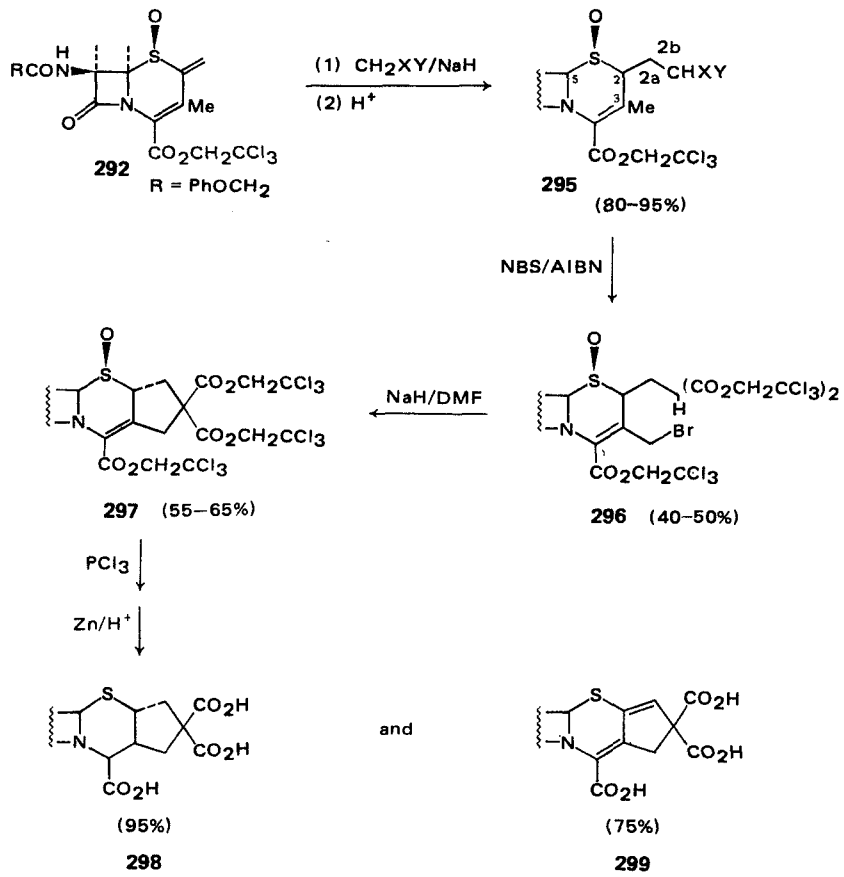


291 **292** **293** **294**

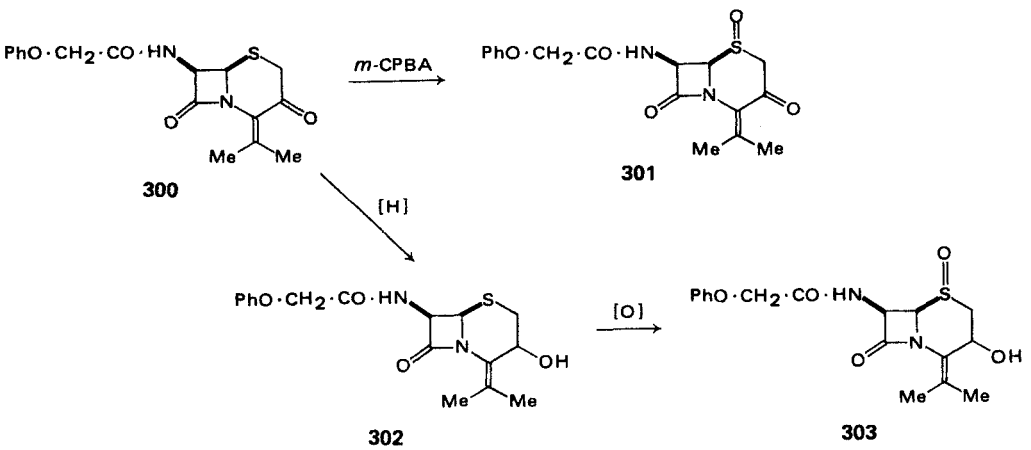
In an attempt to prepare analogues of penicillins and cephalosporins, Stoodley and Watson[84] examined the oxidation products of cephem **300**. Oxidation with *m*-CPBA resulted in the oxidation of the sulfur to a mixture of R and S sulfoxides **301** rather than epoxidation of the double bond. The stereochemistry of the sulfoxides was established by nmr. A single sulfoxide **303** was obtained upon attempted epoxidation of the alcohol **302**.

Comparative ord and cd spectra of phenoxymethylpenicillin and its sulfoxide and the corresponding methyl esters were obtained by Lisowski *et al.*[85] The sulfoxides showed a blue shift of a positive extremum (5–10 nm) in comparison to the sulfides. However, the shapes and amplitudes of the ord and cd curves were similar, suggesting that the character of the excitation expressed by the positive Cotton effect in the range of 227–228 nm (sulfoxide) and 233 nm (sulfides) is similar and probably of $n \rightarrow \sigma^*$ type.

Although optically active sulfur compounds whose chirality is derived from helicity along di- and polysulfide bond have been excluded from this review, two reports[86] dealing with the synthesis and stereochemical determination of novel disulfide analogues of penicillins are included. Chlorinolysis of **304** produced the sulfenyl chloride **305** which when treated with an alkanethiol afforded the disulfide **306**. Subsequent boiling of **306** with trifluoroacetic acid (TFA) gave a mixture of products **307–310**.



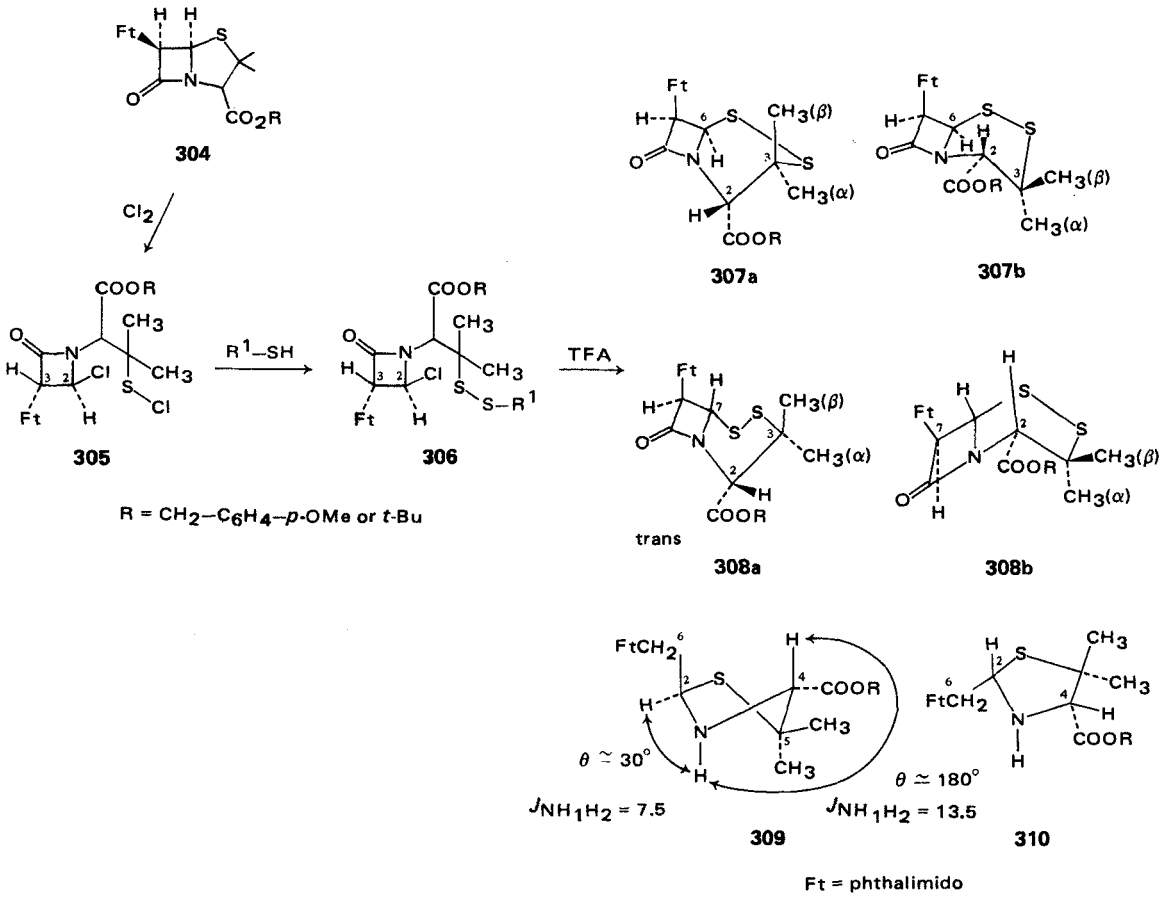
292 **295** **296** **297** **298** **299**

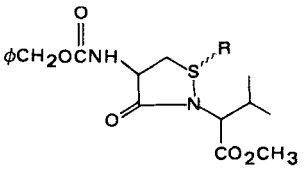


All the analytical data indicate that **307** and **308** contained the bicyclic azetidinone structure. The chiral disulfide function in turn created the possibility of four conformers for these isomers. The absolute configurations and conformations of these products were established with the use of nmr spectra, nuclear Overhouser effects and were further confirmed with X-ray analysis of **307a**.

Several papers related to the penicillin and cephalosporin antibiotic field have discussed interesting optically active sulfoxides. Morin *et al.*,[87] in their studies on the chemistry of dihydropeptides prepared the isothiazolidone monoxides **311a** and **b**, which upon treatment with thiol **312** produced the diastereomeric thiosulfinates **313**.

Stoodley and coworkers[88] in a series of papers on studies related to dihydro-1,4-thiazines have prepared a number of sulfoxides **314–319**, usually as a mixture of diastereomers. The absolute configurations of most of these compounds have not been rigorously established.





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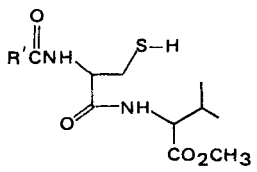

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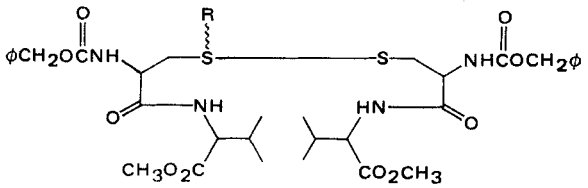
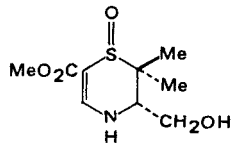


313

a, R =
b, R =



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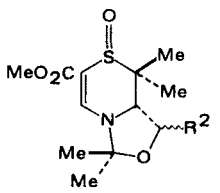
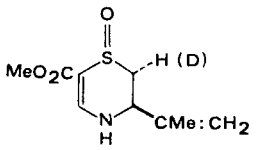
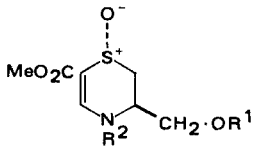


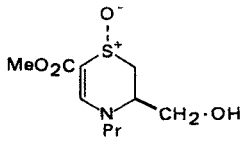
315 R^2 = SMe
316 R^2 = SO–ME



317

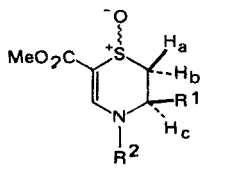


318



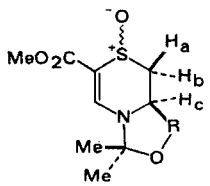
319

Tentative configurational assignments based primarily on nmr spectral evidence were made[89] for a number of sulfoxides **320** and **321** prepared in this series.



R^1 = CH_2OH, R^2 = H
R^1 = H_a, R^2 = H
R^1 = CO_2H, R^2 = H
R^1 = CH_2OAc, R^2 = H
R^1 = CH_2OMs, R^2 = H
R^1 = CH_2OH, R^2 = *i*-Pr

320

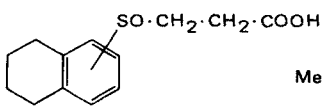


R = CH_2
R = CO

321

G. Sulfoxides with Handles for Resolution

Several new papers in the series of "Studies of the influence of the Chemical Structure on the Optical Properties of Sulfoxide Compounds" have been published by Janczewski and coworkers. The syntheses and resolutions of sulfoxides **322–325** are presented.[90]



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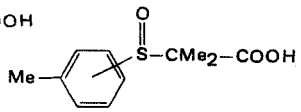

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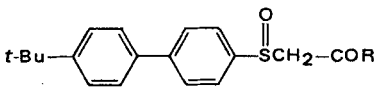

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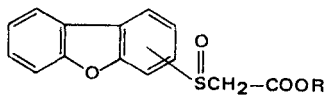

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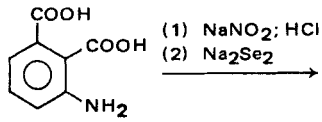

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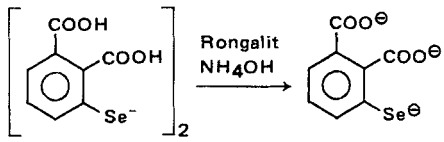
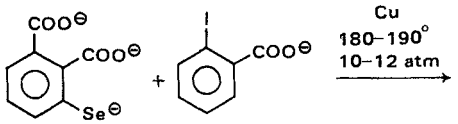
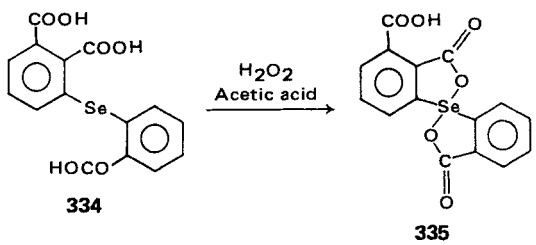


330 331



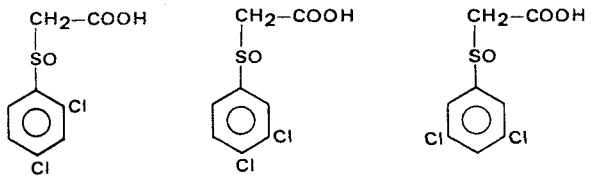
332 333



334 335

FIGURE X

In two earlier papers,[91] Stridsberg reported the synthesis and resolution of 2,4-, 3,4-, and 3,5-dichlorophenyl sulfinylacetic acids **326–328.**

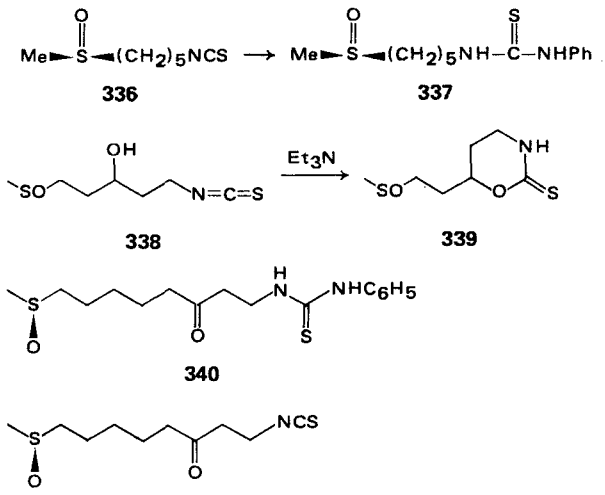


326 **327** **328**

In a related paper,[92] a novel spiro-selenium derivative **335** has been described as partially resolved *via* its quinine salt (Figure X).

H. Naturally Occurring Optically Active Sulfoxides

Kjaer and coworkers in their continuing work on naturally occurring glucosinates have isolated from *Erysimum hieracifolium* L.,[93] a number of novel compounds, some of which contain optically active sulfoxide groups. The sulfoxide **336** was obtained and was identified *via* the thiourea derivative **337**. A second sulfoxide **338** of unknown stereochemistry



336 **337**

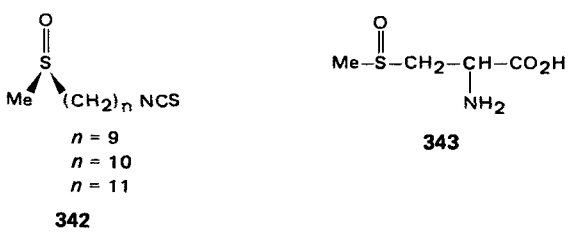
338 **339**

340

341

was identified *via* **339**. Another new sulfoxide[94] **340** identified *via* **341** was isolated from seeds of *Arabis hirsuta* (L.) *Scop.*

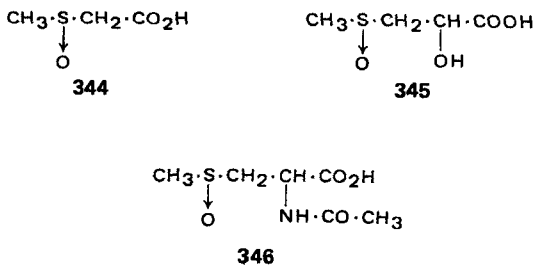
In a third paper[95] a group of homologous sulfoxides **342** isolated from seeds of *Neslia Paniculata*, have been described. The $n = 11$ compound represents a new member of this series of compounds which have been found in a variety of natural sources.



$n = 9$
$n = 10$
$n = 11$

342 **343**

Another sulfoxide found abundantly in members of Cruciferae and Liliaceae plants is S-methyl-L-cysteine sulfoxide, **343.** This amino acid[96] has been shown to possess potent anti-hypercholesterolemic properties. Metabolic studies[97] on the fate of S-methyl-L-cysteine in animals revealed the formation of several products **344–346.** A fourth sulfoxide-containing product was isolated but not identified. In the course of this work (−)-dicyclohexylammonium methylmercapturate sulfoxide was prepared by neutralization of (−)-methylmercapturic acid (**346**) with dicyclohexylamine.



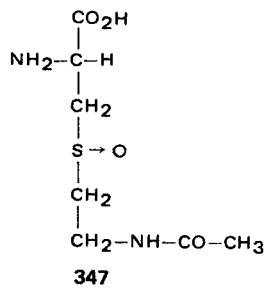
344 **345**

346

Microsomal preparations from rat liver have been used[98] to oxidize S-*n*-propyl-L-[^{35}S]-cysteine into its sulfoxide. Chromatography of the product showed that the (+)-sulfoxide was the predominant diastereomer.

The enzymatic specific reduction of one of the four diastereomers of methionine sulfoxide has been described by Black and coworkers.[99]

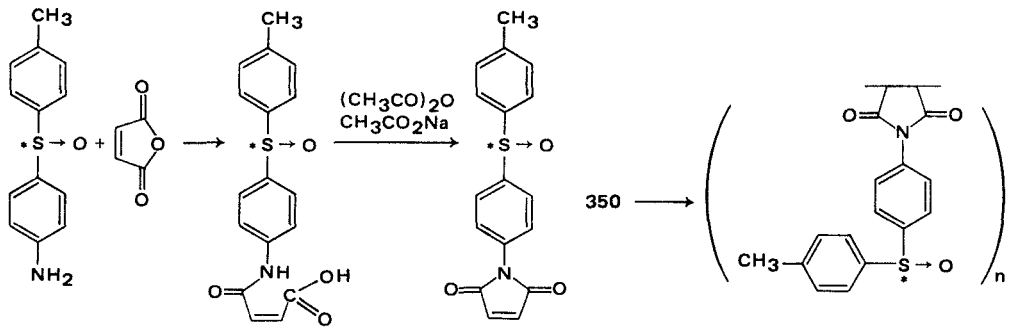
The absolute configuration of **347** was derived by comparison of its ord, cd, enzyme kinetic, chromatographic and ion exchange behavior with that of **343** of known sulfur configuration.[100]



347

I. Polymer-Containing Sulfoxides

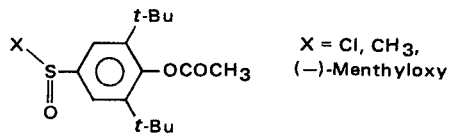
A novel optically active polymer **351** containing a chiral sulfoxide group has been prepared by polymerization of the monomeric optically active sulfoxide **350.**[101]



348 349 350 351

III. SULFINATES

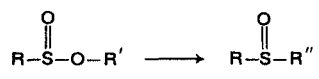
The sulfinate **352** has shown[102] magnetic non-equivalence of the aryl protons and the methyl protons of the tert-butyl groups, indicating slow rotation of the acetoxy group as well as slow inversion at sulfur. Since the resolved sulfoxide (X = Me) is optically stable after heating to 100°C it appears that the faster rate process is the rotation.



X = Cl, CH_3, (−)-Menthyloxy

352

Optically active sulfinate esters where the alkoxy moiety is devoid of an asymmetric center have been obtained[103] *via* β-cyclodextrin inclusion compounds. Optical purities of up to 70.2% were obtained for **353** (R = Me, R′ = i-Pr). The absolute configuration and optical purities were obtained by conversion of the sulfinates to known sulfoxides **354**.

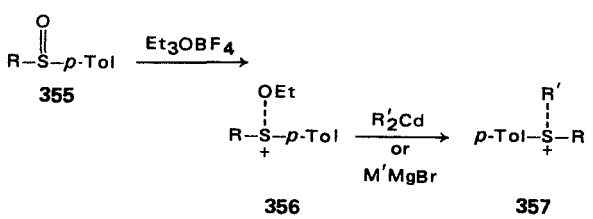


353 **354**

IV. SULFONIUM COMPOUNDS

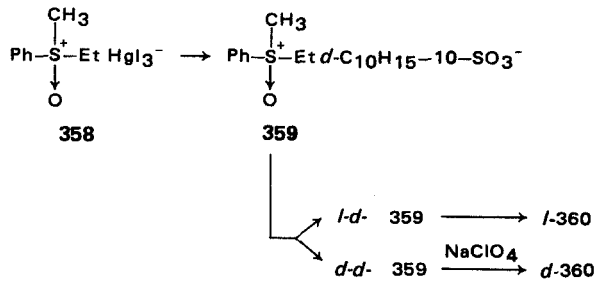
Sulfonium Salts, Oxosulfonium Salts and Sulfonium Ylides

Optically active sulfonium salts have been previously obtained by resolution of the racemates. A novel method for the direct preparation of optically active sulfonium salts (**357**) from the corresponding optically active sulfoxides has been reported by Andersen *et al.*[104] The procedure involves ethylation of the sulfoxides (**355**) to the oxosulfonium salts (**356**) followed by treatment with dialkyl cadmium or alkyl magnesium bromide. The isolated sulfonium salts **356**, were shown to be partially racemic. The diarylcadmium reagents lead only to racemic sulfonium salts.



355 **356** **357**

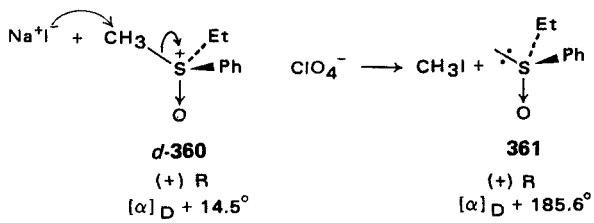
Subsequent studies on optically active oxosulfonium salts have been reported by Kobayashi *et al.* Racemic ethylmethylphenyloxosulfonium mercuritriiodide



358 **359**

l-d- **359** → *l-360*

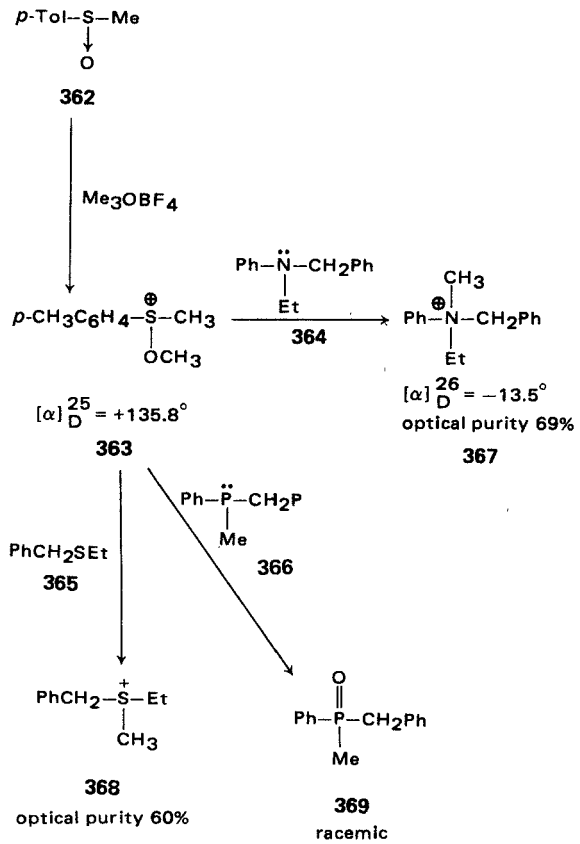
d-d- **359** $\xrightarrow{NaClO_4}$ *d-360*

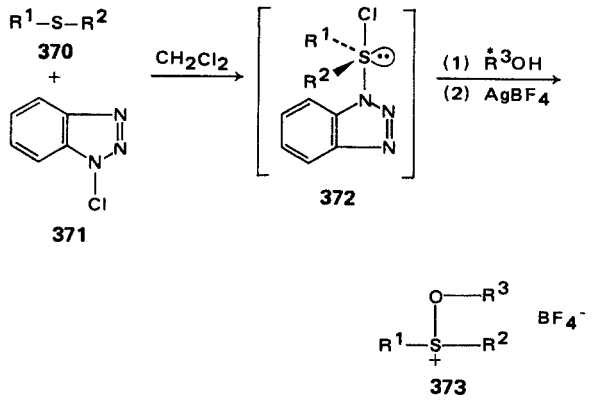


d-**360** (+) R $[\alpha]_D$ + 14.5° **361** (+) R $[\alpha]_D$ + 185.6°

358 was converted[105] to the diastereomeric *d*-camphor-10-sulfonated **359** and separated by repeated recrystallizations. Treatment of **359** with sodium perchlorate afforded the enantiomeric perchlorates **360**. The stereochemistry of **360** was determined by conversion into the corresponding sulfoxides **361** of known absolute configuration. Since the demethylation reaction proceeds by an S_N2 attack of iodide on the methyl group the reaction must proceed with retention of configuration. The reaction was shown[106] to be reversible allowing the formation of optically active oxosulfonium salts from optically active sulfoxides when treated with methyl iodide in the presence of mercuric iodide. This reaction also proceeds with retention of configuration at sulfur.

The optically active methoxy sulfonium salt **363** when treated[107] with amine **364** gave the ammonium salt **367** of 69% optical purity. With sulfide **365** it gave the sulfonium salt **368** of 60% optical purity. However, treatment with the phosphine **366** resulted in the formation of racemic phosphine oxide **369**. The authors suggest that the optical inactivity of **369** is the result of a more complex reaction than simple S_N2 attack of phosphorus on the oxygen atom of **363** since the product would then be expected to show some degree of optical activity.





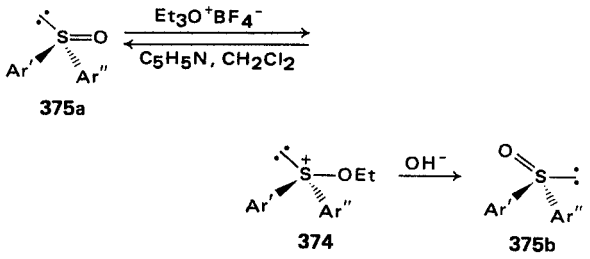
R^3OH represents an optically active alcohol

FIGURE X

A novel method for the preparation of optically active diastereomeric alkoxysulfonium salts **373** has been described by Johnson *et al.*[108] (Figure X).

The stereochemical course and the influence of structural factors on the reaction of diarylalkoxysulfonium salts with pyridine have been studied by Cinquini and coworkers.[109] Both enantiomers of the sulfoxide **375** may be obtained from a single optically active alkoxysulfonium salt **374**.

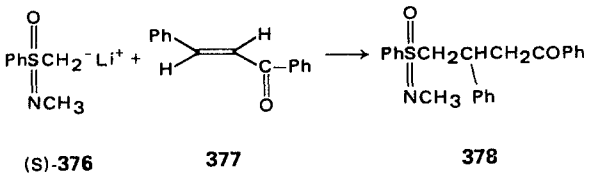
The enantiomer with the same configuration (a) is formed by nucleophilic attack of pyridine on the ethyl group, whereas the enantiomer with opposite configuration (b) is formed by nucleophilic attack of hydroxide on the sulfur atom.



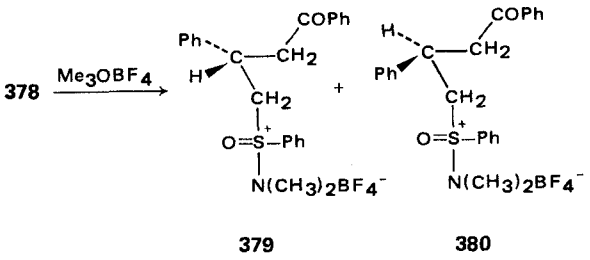
Johnson and Schroeck[110] have shown that betaine intermediates are present in nucleophilic methylene transfer ylides. When (S)-**376** was added to **377** a mixture of diastereomeric **378** was obtained. Subsequent methylation of the individual diastereomers with trimethyloxonium fluoroborate gave **379** and **380**. Betine **381** was obtained from **379** upon treatment with potassium tert-butoxide, and collapsed to optically pure cyclopropane **382**. The enantiomer of **382** was analogously obtained from **380**. Treatment of (S)-**376** with benzaldehyde gave a mixture of diastereomers from which pure **383** was obtained.

When **383** was reacted with potassium *tert*-butoxide a 71% yield of 22% optically pure styrene oxide **384** was isolated. It was shown that the low optical activity of **384** may be attributed to an equilibrium reaction with **385** and benzaldehyde. The enantiomeric styrene oxide **390** was also prepared as described on Figure XI.

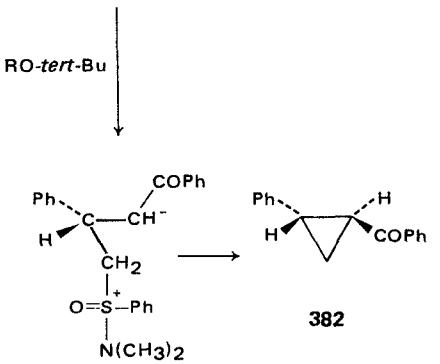
Trost and Hammen[111] have examined the feasibility of transfer of chirality from sulfur to carbon. Three types of reactions of optically active ylides were studied: (a) carbonyl addition, (b) conjugate addition and (c) [2,3] sigmatropic rearrangement. Sulfonium salt **392** was resolved *via* its l-malate salt and was converted to sulfurane **393** with *n*-butyl lithium. The first example of configuration retention at a simple sulfonium ylide was shown when **393** was treated with deuteriofluoroboric acid to give **394** with essentially no loss of optical activity. Condensation of **393** with benzaldehyde gave racemic styrene oxide **395** and the cyclopropane **396** which showed only a very low degree of optical activity. However, the [2,3] sigmatropic rearrangement proved to be a very promising approach to the transfer of chirality. The sulfonium salt **397** was resolved with dibenzyl tartaric acid.



(S)-376 377 378



379 380



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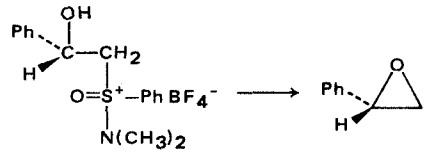
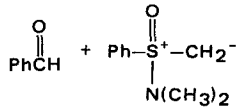


383 384



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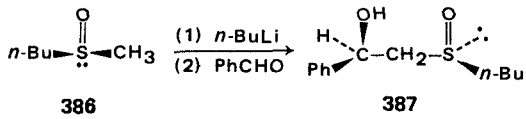
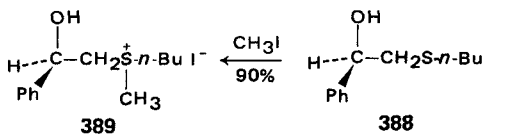
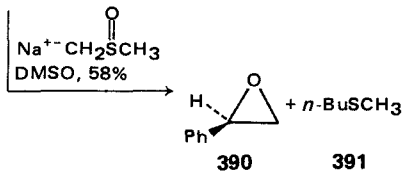


386 387



389 388

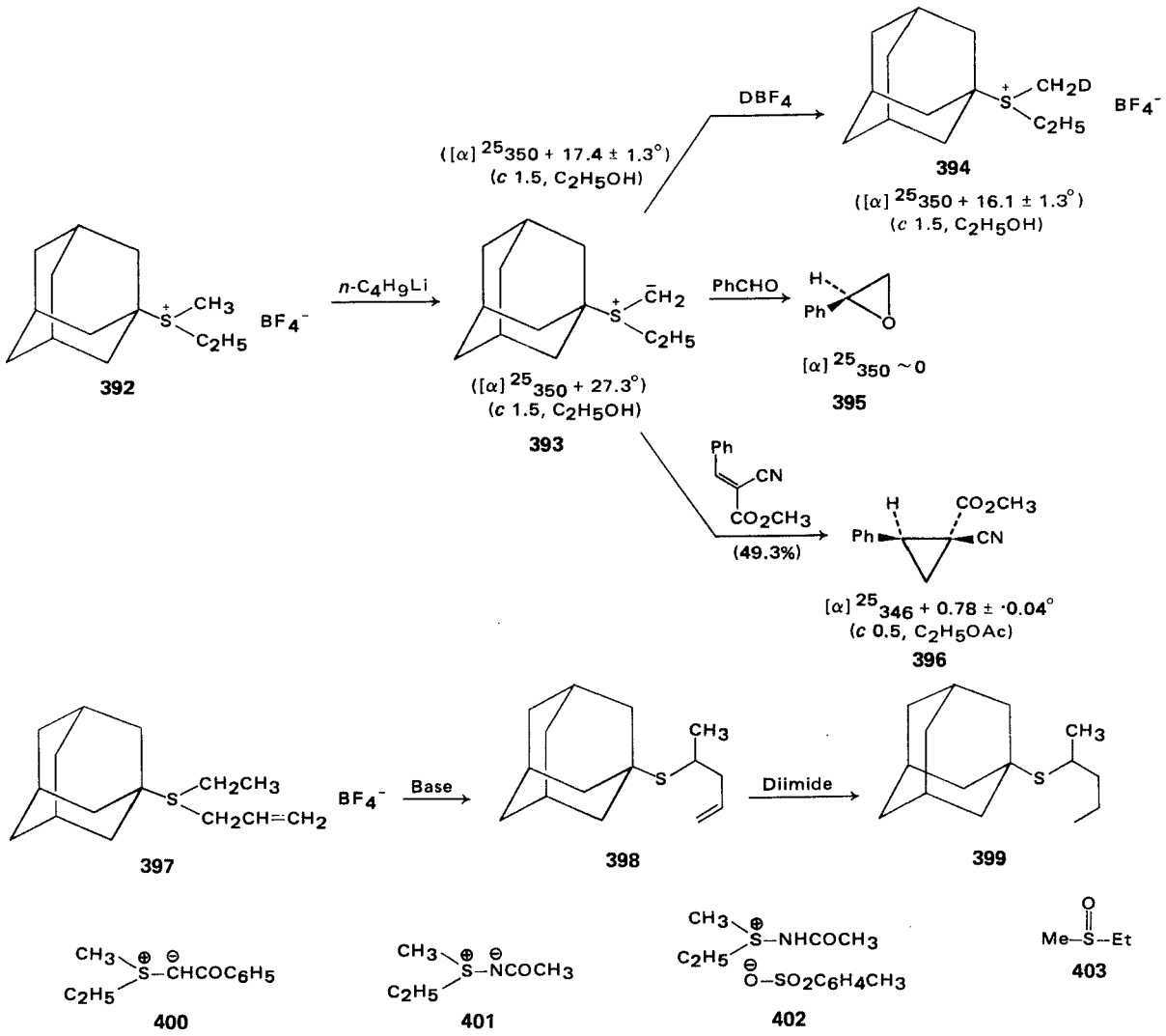


390 391

FIGURE XI

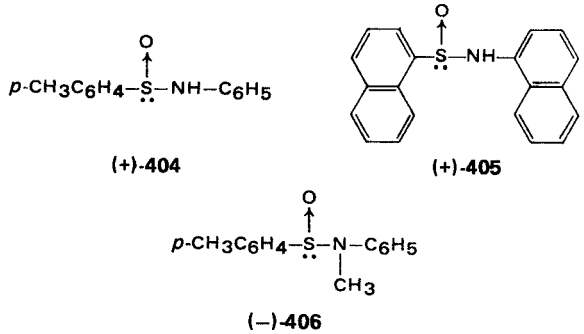
Treatment of **397** with potassium tert-butoxide gave sulfide **398** which was reduced to **399**. Independent synthesis of **399** from (S)-2-pentanol showed that the rearrangement of **397** to **398** proceeded with a minimum of 94% optical purity.

The facile thermal racemization of sulfonium ylide **400** (I-197) prompted the study[112] of the racemization of other sulfonium ylides. For this purpose ylides **401** and **402** were prepared in optically active form. Kinetic studies indicate that the rate of racemization is in the order **400** > **402** > **401** > **403**. The rates of racemization are discussed in terms of electron pair delocalization, electron repulsion and p-dπ stabilization.



V. SULFINAMIDES

The initial observations (I-200, 222) regarding the course of racemization of sulfinamides have been further investigated by Cram and Booms.[113] A novel racemization mechanism for an optically active sulfur compound in the sulfin oxidation state is reported.



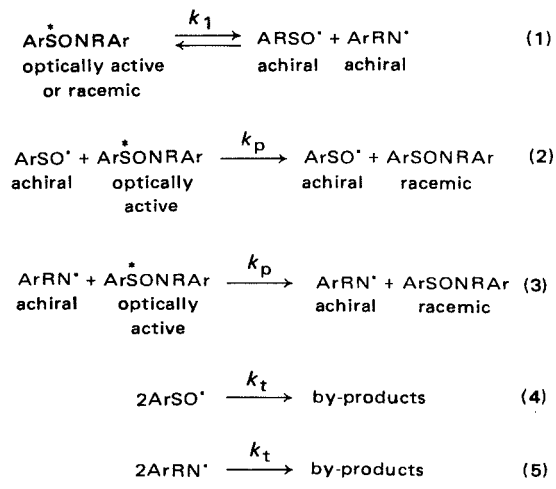


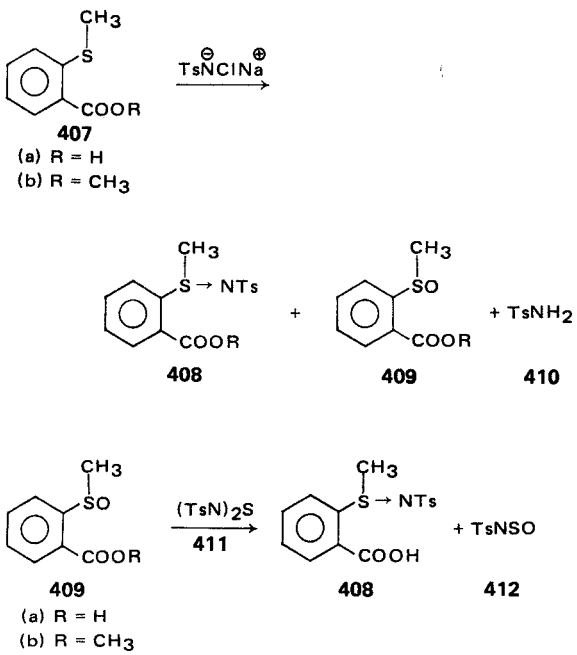
FIGURE XII

The racemization behavior of sulfinamides **404**, **405**, and **406** was studied by three methods: (a) kinetics of racemization, (b) crossbreeding experiments and (c) sulfinamide initiated polymerization. The following observations were made in the course of the reaction; (a) scission of S–N bond which leads to crossbred products when different sulfinamides are racemized jointly, (b) the racemization process is inhibited by the presence of catalytic amounts of di-tert-butyl nitroxide, (c) first order kinetics are observed, (d) the induction period may be reduced by the presence of 2,6-di-tert-butylphenol, (e) the rate is greatly influenced by the solvent. On the basis of these observations a radical chain mechanism is suggested (Figure XII).

VI. SULFILIMINES AND SULFOXIMINES

The chemistry of sulfilimines and sulfoximines continues to be one of the most prolific areas of investigation of optically active sulfur compounds. This work has led to the discovery of novel stereochemical cycles, new ring systems and synthetic applications have been found for some of these intriguing compounds. The nomenclature adapted here will be that of sulfilimines and sulfoximines even though these compounds are frequently named sulfimides and sulfoximides.

Bohman and Allenmark[114] prepared sulfilimine **408** from sulfide **407** and chloramine T. Resolution *via* the brucine salt afforded both enantiomers. Alternatively **408** was prepared in high optical yield from sulfoxide **409** and N,N′-bis-(*p*-toluenesulfonyl)sulfur diimide **411**. The reaction was shown to proceed with retention of configuration both in pyridine (97% stereospecificity) and in benzene (60% stereospecificity). The absolute configuration of **408**, was ascertained from the known configuration of **409a** as indicated in Figure XIII. Furthermore, the acid hydrolysis of **408** gives **409a** with retention of configuration and greater than 99% stereospecificity.



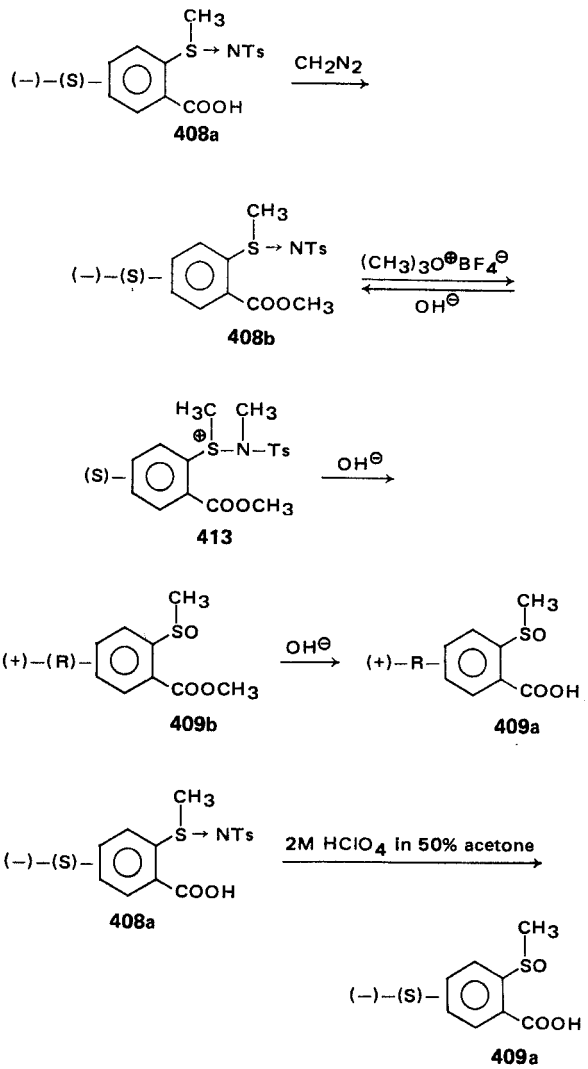
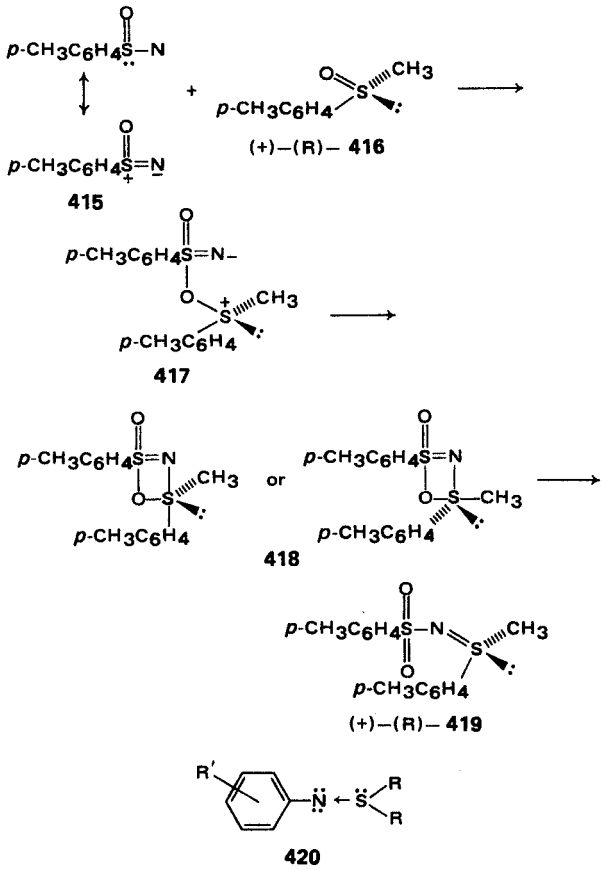


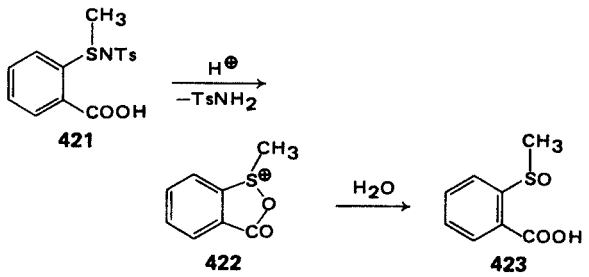
FIGURE XIII

Another example of nucleophilic substitution at sulfur with overall retention has been observed[115] in the conversion of sulfoxides **416** to sulfilimines **419** when treated with sulfinylnitrenes **415**, suggesting a four-membered cyclic sulfurane intermediate **418**.

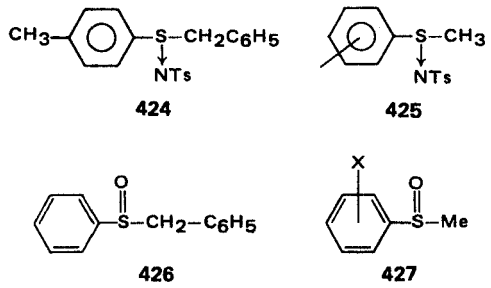
A number of optically active N-aryl-S,S-dialkylsulfilimines **420** have been prepared[116] by resolution and by synthesis from optically active sulfoxides.



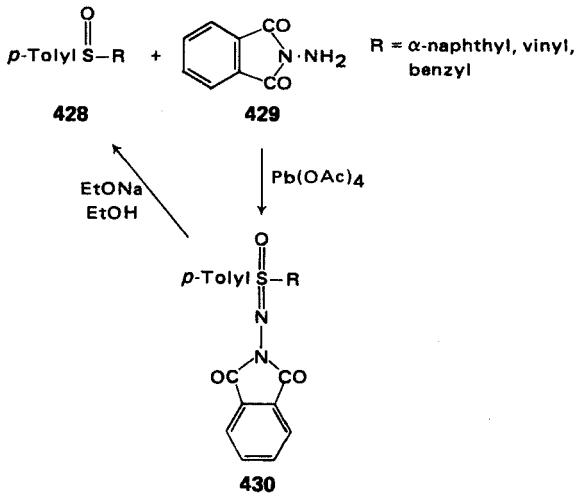
A mechanism involving a double inversion process and neighboring group participation has been proposed[117] in the hydrolysis of sulfilimine **421** giving rise to the formation of a sulfoxide **423** with predominant retention of configuration.



The thermal racemization of aryl methyl sulfilimines has been studied by Oae *et al.*[118] It was found that this process is a very facile one in a variety of solvents. Moreover, the reaction was found to be: (a) unimolecular, (b) independent of solvent polarity, (c) without correlation to Hammet parasubstituents, (d) the rate of racemization of **424** is similar to that of **425**, whereas the sulfoxide **426** racemizes much faster than **427**. It was concluded that the reaction proceeds by pyramidal inversion which when compared with similar processes falls in the order of sulfonium salt ≫ sulfilimine ≫ sulfoxide with relative rates $10^{12} : 10^{7} : 1$.



A stereospecific sulfoxide-sulfoximine-sulfoxide set of interconversions has been described by Colonna and Stirling.[119] N-Phthalimide sulfoximines **430** are easily prepared from optically active sulfoxides **428**. The sulfoxides in turn can be regenerated by treatment of **430** with sodium ethoxide. The recovered sulfoxides showed retained configuration. It was suggested that this two-reaction cycle occurs with retention at each step, with the formation of a nitrene intermediate at the first step.



A large number of reactions where stereospecific transformations at chiral sulfur take place, and involve stereochemical reaction cycles have been explored by Cram *et al.* and Johnson *et al.* The properties of these reaction cycles have been described by Garwood and Cram (II-6) with the use of the terms: (a) tri-, di-, mono- and a-ligostatic, referring to the number of static ligands in a cycle, (b) podal and apodal cycles and (c) ligand metathesis.

The interconversions reported by Cram and coworkers[120] were carried out on compounds **431–440** and were shown to be 90–100% stereospecific. The first example of a monoligostatic cycle is shown on Figure XIV, where the *p*-toly ligand is the only one common to all chiromers of the cycle.

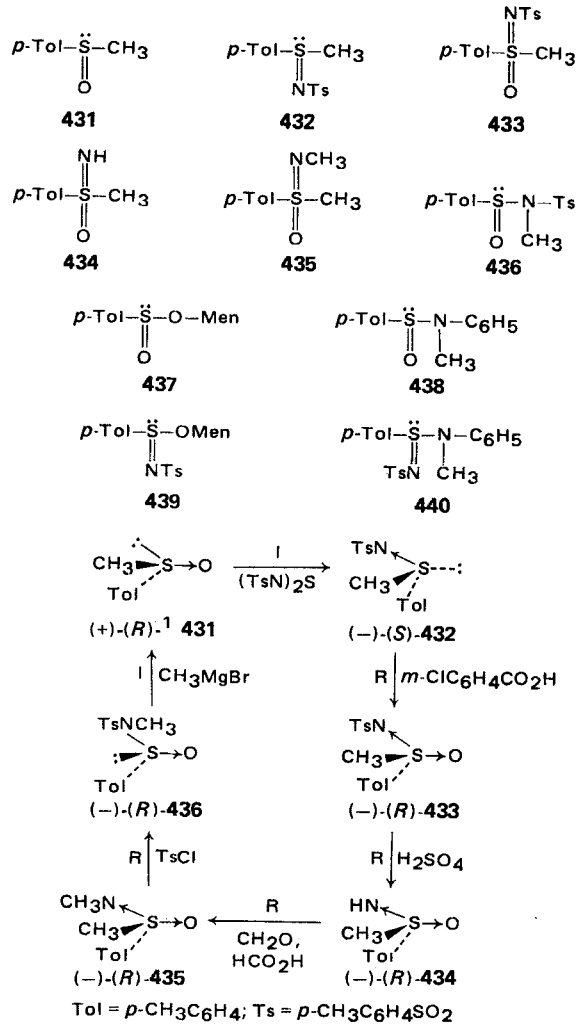
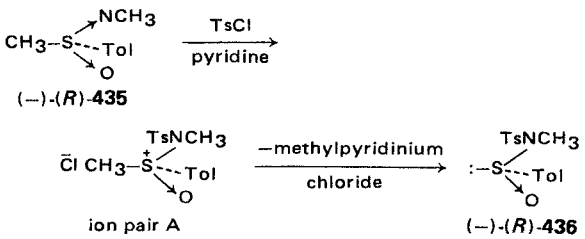


FIGURE XIV

Reaction (−)-(R)-434- → (−)-(R)-435 represents a novel method for the alkylation of sulfoximines. Reaction (−)-(R)-435 → (−)-(R)-436 is rather unusual and proceeded with a minimum of 94% stereospecificity, by a mechanism described as follows. The cycle is podal since none of the chiromers are enantiomerically related. Two reactions take place



with inversion, four with retention and no ligand metathesis is present. Treatment of (−)-(R)-434 with nitrosyl hexafluorophosphate (II-131) to give (+)-(R)-431 completed a podal, diligostatic cycle (Figure XV)

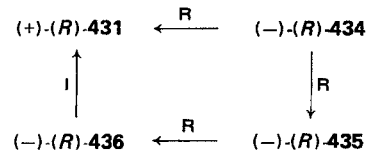


FIGURE XV

An example of an antipodal, triligostatic cycle is described on Figure XVI.

Treatment of (−)-(S)-437 with (+)-(R)-442 gave (+)-(R)$_c$-(S)$_s$-443 whereas (−)-(S)-442 and *p*-tolylsulfinyl chloride 444 gave a mixture of diastereomeric sulfiamides (+)-(S)$_c$-(S)$_s$-443. A dramatic solvent effect on optical rotation is reported for

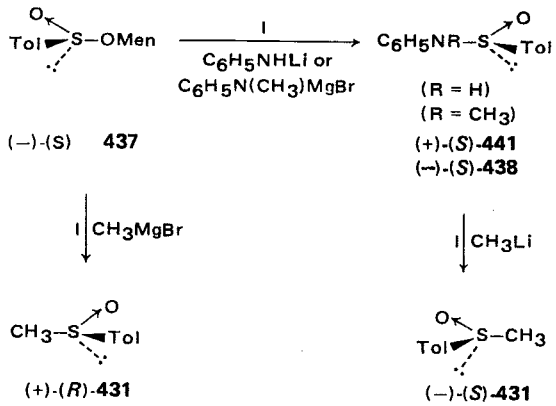
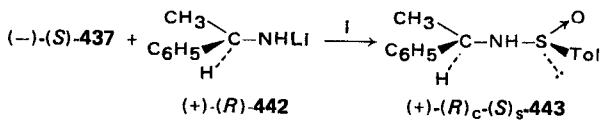
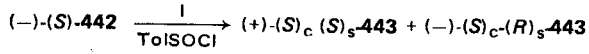


FIGURE XVI

(+)-(S)$_c$-(S)$_s$-443 which has $[\alpha]_D^{25}$ + 41.2° in chloroform and $[\alpha]_D^{25}$ − 64.2° in methanol.

A second antipodal, triligostatic cycle is described in Figure XVII. The diastereomeric (+)-(R)$_c$-(S)$_s$-449 and (+)-(R)$_c$-(R)$_s$-449 were obtained from the corresponding (+)-(R)-447 and racemic 448 and were easily separated by crystallization.





Tol = *p*-CH$_3$C$_6$H$_4$; Men = menthyl

Jonsson and Johnson[121] studying stereochemical interconversions of optically active sulfur compounds, reported two cycles, an antipodal diligostatic one (Figure XVIII) and an antipodal, diligostatic with one ligand metathesis (Figure XIX). Compounds (−)-(R)-451 and (+)-(S)-453 are the first reported examples of optically active sulfoximidoates.

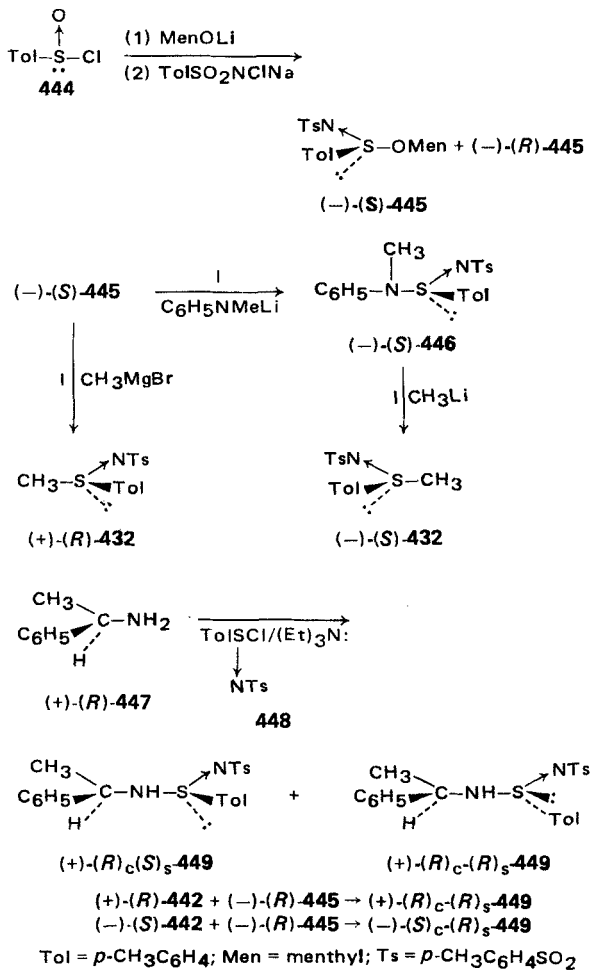


FIGURE XVII

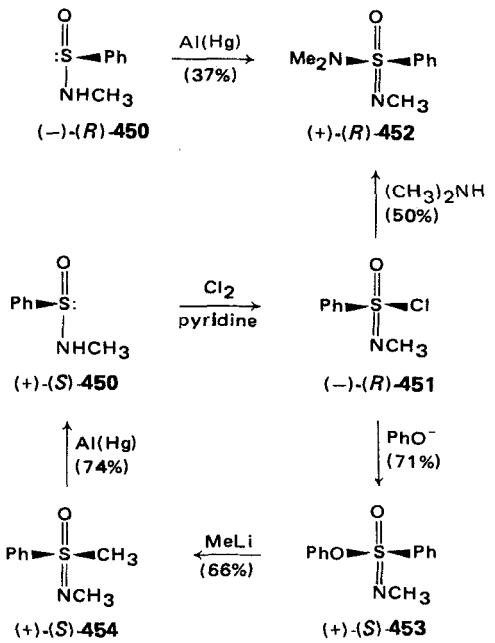


FIGURE XVIII

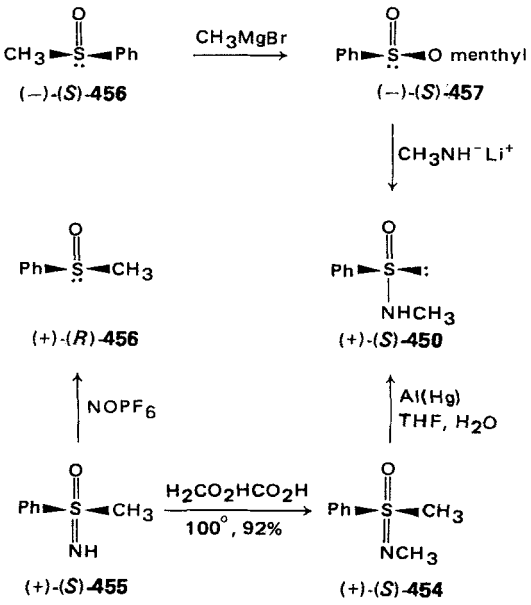


FIGURE XIX

Additional studies by Cram and coworkers[122] have focused on the effects of the constraints of five-membered ring systems on the course and rate of conversion of sulfoxides to sulfilimines. The reactions carried out are illustrated on Figure XX. The sulfoximine **461** was obtained in optically active form *via* treatment of the racemic material with (−)-*d*-10-camphorsulfonyl chloride. Nitrous acid has been found superior to nitrosyl hexafluorophosphate as a deimidation agent. From analogies and mechanistic considerations it is implied that reactions (+)-**461** → (−)-**458**; (−)-**458** → (−)-**460**; and (−)-**459** → (−)-**460** all proceed with retention. Reaction (−)-**458** → (−)-**459** in pyridine proceeds with inversion, however in benzene without pyridine the reaction follows a retention course. The reactions (+)-(R)-**462** → (+)-(R)-**463** and (−)-(R)-

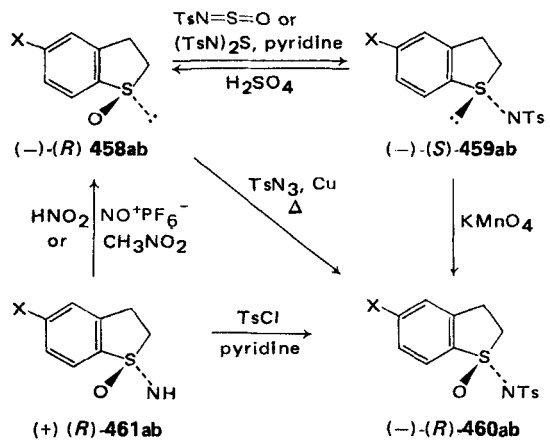
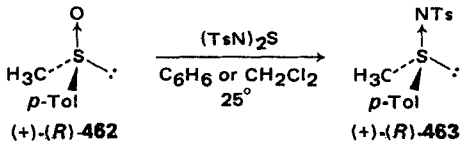
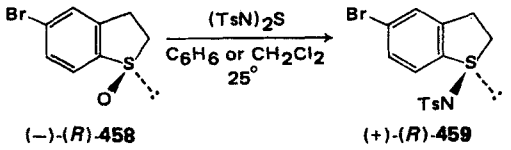


FIGURE XX

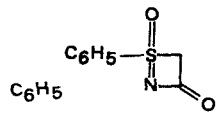
458b → (+)-(R)-**459b** were also carried out. An extensive discussion on the mechanisms of these reactions is presented.

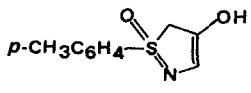


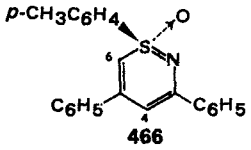


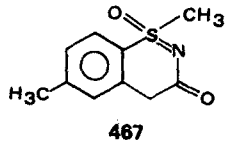
Subsequent studies[123] further explored the mechanism of sulfoxide-sulfilimine interconversion whereby (+)-(R)-**462** gave (−)-(R)-**463** upon treatment with *p*-toluenesulfonylisocyanate in acetonitrile.

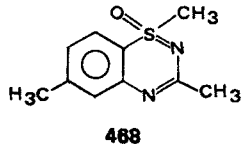
New ring systems of carbon, nitrogen and chiral sulfur where the sulfur is in the sulfoximine oxidation state have been prepared by Williams and Cram.[124] Six new heterocyclic ring systems, **464–469** were prepared by a variety of methods. The optically active **472**, obtained from sulfoximine **470**, showed as expected a much higher optical rotation than **470**. This was attributed to the higher degree of symmetry of **470** and to the similarity of the polarizabilities of the O and NH groups.

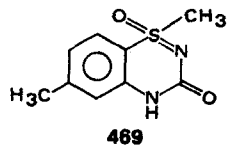




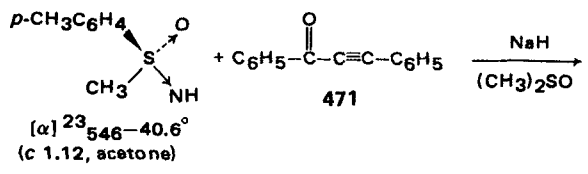


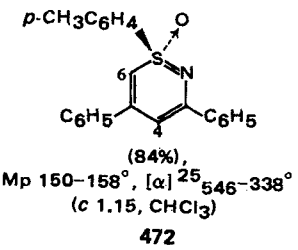




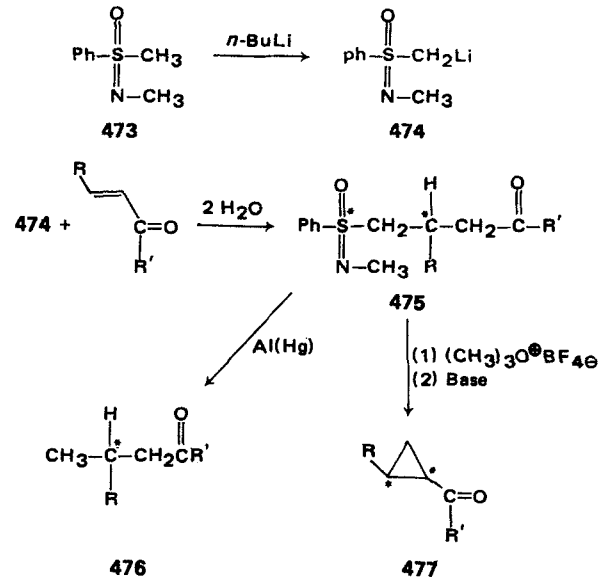


As an extension to their initial work (I-198), Johnson *et al.* have published a series of papers on the use of chiral sulfoximidic type compounds as nucleophilic alkylidene transfer agents for asymmetric synthesis. An efficient route has been found for the synthesis of optically pure **473**.[125] After treatment with *n*-butyl

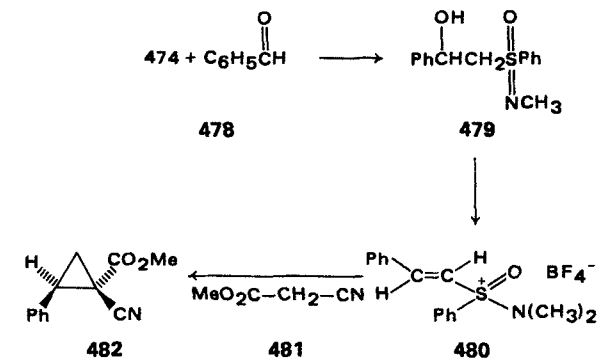




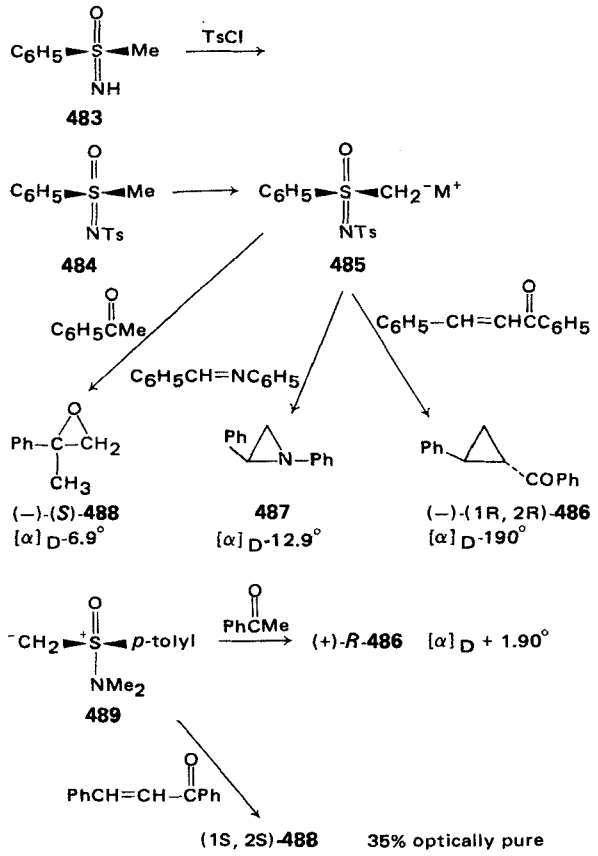
lithium, the product **474** was obtained and was used in the preparation of other optically active compounds, *i.e.*, **475–477**.



Optically active alcohols (**479**) are also obtained by treatment[126] of **474** with aldehydes and ketones. Subsequent dehydration and methylation gave **480**. This compound when treated with a variety of methylene activated compounds (*i.e.*, **481**) afforded optically active cyclopropanes.

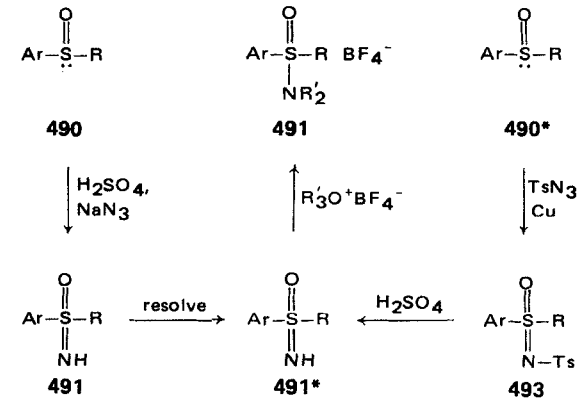


Similar reactions were carried out[127] with optically active **485**, which was obtained in 84% optical purity from the sulfoximine **473** and *p*-toluene sulfonyl chloride. Treatment of **485** with ketones gave oxiranes **486**, with imines it gave aziridines **487** and with olefines it gave cyclopropanes **488**. Compound **489** was also used in analogous reactions.



The reactions carried out with **489** were further expanded with a number of similar reagents (Figure XXI).[128] The optical purities of oxiranes and cyclopropane products obtained using compounds of type **494** as methylene transfer agents are the highest reported for any direct asymmetric synthesis. Optical yields of up to 43.2% were obtained. The absolute configurations of the salts **492** were established *via* the diligostatic cycle outlined in Figure XXII.

The mechanism of these nucleophilic alkylidene transfer reactions was shown[129] to involve betaine intermediates. Moreover, the addition of sulfurylides to carbonyl substrates led to the conclusion that sulfonium methylenes add "irreversibly" to the carbonyl group, whereas, with oxosulfonium ylides the addition is "reversible". However, the oxosulfonium methylide addition to electrophilic olefins was shown to be "irreversible". When (S)-**496** was treated with trans-



	Ar	(when shown on formula) R	R′	R″	Absolute config. (when opt. active)
a	*p*-tolyl	Me	Me	H	*R*
b	*p*-tolyl	Et	Me	Me	*R*
c	phenyl	Me	Me	H	*S*
d	2-mesityl	Me	Me	H	*R*
e	phenyl	Me	Et	H	*S*

Ts = *p*-$CH_3C_6H_5SO_2$; * indicates an optically active compound.

FIGURE XXI

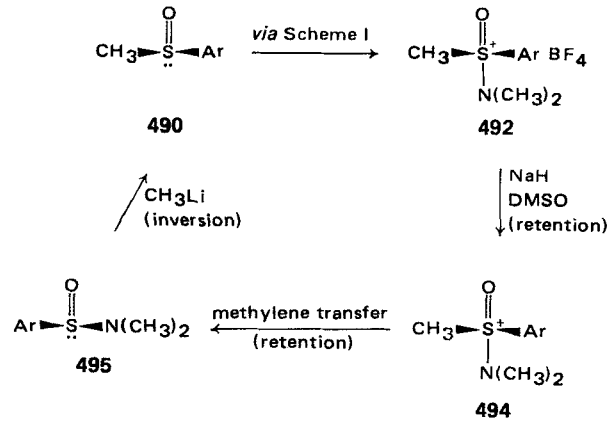
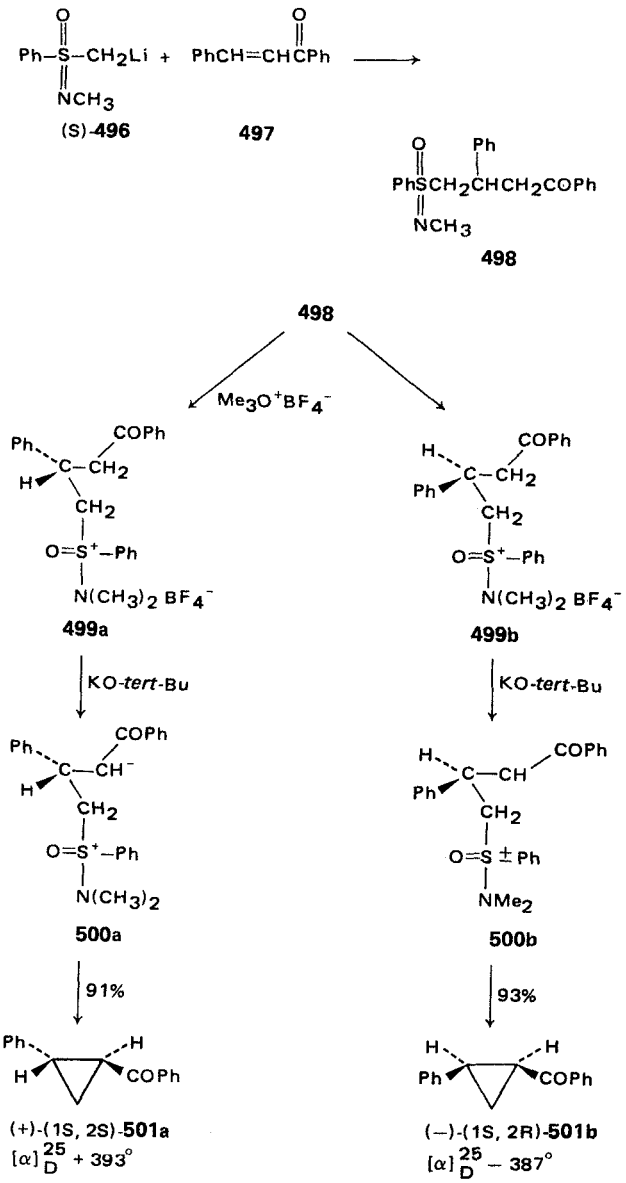


FIGURE XXII

benzalacetophenone in dimethyl formamide, a mixture of diastereomers **498** was obtained. Whereas, the same reaction in tetrahydrofuran resulted in 1,2-addition, indicating that 1,2-addition is thermodynamically preferred. Methylation of **498** gave **499** from which the optically active cyclopropanes **501** were obtained. Under these conditions, collapse of the betaines **500** is much faster than revision to ylide and olefin.



Alkylidene transfer agents derived from salts of sulfoximines have the advantage that they provide the only practical method for structural variation of the alkylidene group. Thus, Johnson and Janiga[130] have prepared three new agents **502-504**, of which **504** was synthesized in optically active form (Figures XXIII and XXIV).

Ylide **504a** gave extremely low yields of cyclopropylidene transfer whereas **504b** gave yields ranging from 41% to 89%.

A novel synthetic use for aluminum-amalgam has been found[131] in the reduction of sulfoximines **515** to sulfinamides **516**. The reaction is highly stereospecific with retention at sulfur. Moreover it provides a simple method for the preparation of optically active primary sulfinamides (*i.e.*, **516b**).

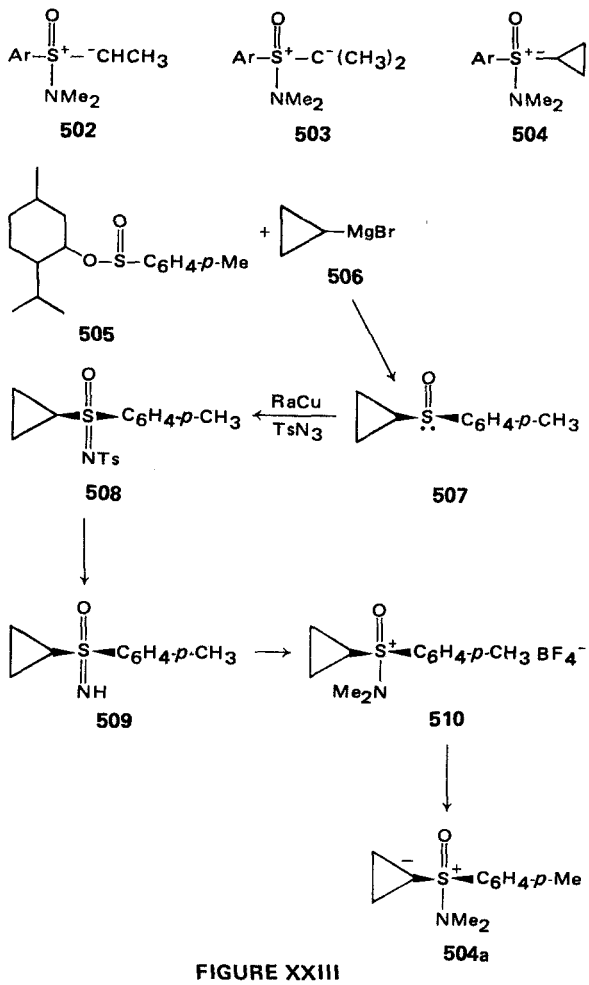


FIGURE XXIII

An alternative method for the nitrosyl hexafluorophosphate deimination of sulfoximines is the reduction of **517** to the sulfoxide **518** with aluminum-amalgam. The reaction proceeds with retention. A novel procedure[132] for the stereospecific deimination of sulfoximines involves the reaction with sulfur or diphenyl sulfide. The suggested mechanism involves the initial attack by the nitrogen on the sulfur atom

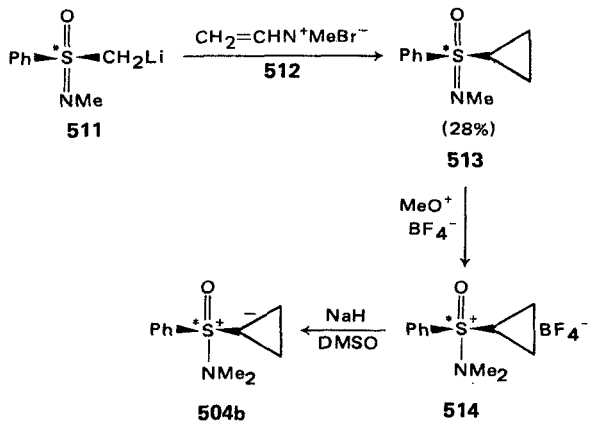
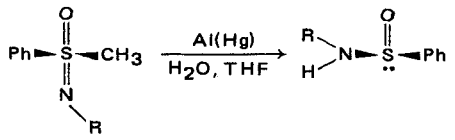


FIGURE XXIV

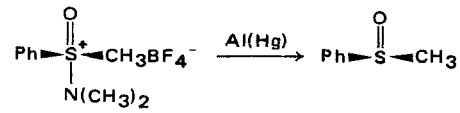
of the S–S bond followed by attack of thiolate anion on the nitrogen with eventual cleavage of the sulfoxide.

N-Halogeno aziridines possess barriers of inversion of high enough magnitude that permit their isolation in diastereomeric form. Optically active **524** has been prepared[133] by the reaction of aziridine **522** with optically active N-chlorosulfoximine **523**.



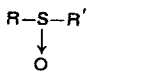
515 **516**

a = CH_3 a = CH_3
b = H b = H
c = p-$CH_2C_6H_4SO_2$



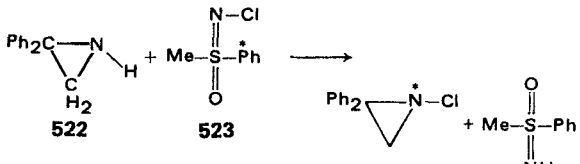
517 **518**

519 **520**



521

(a) R = p-$CH_3C_6H_4$-, R′ = CH_3-
(b) R = Ph-, R′ = CH_3-



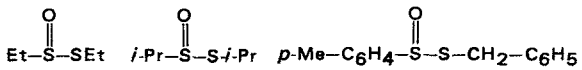
522 **523** **524** **525**

VII. THIOSULFINATES

The chemical and kinetic behavior of optically active thiosulfinate **526** toward ^{18}O-exchange and racemization has been studied by Kice and Cleaveland.[134] It was found that benzene sulfenic acid **527** is orders of magnitude more reactive than water as a nucleophile toward reactive sulfenyl derivatives such as **528**, **529**, and **530**.

526 **527** **528** **529** **530**

The complex nmr spectra obtained from thiosulfinates containing diastereotopic protons or methyl groups (**531-534**) have been shown[135] to be simplified by the use of the shift reagent Eu–FOD–d_{27}.

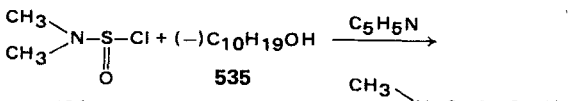


531 **532** **533**

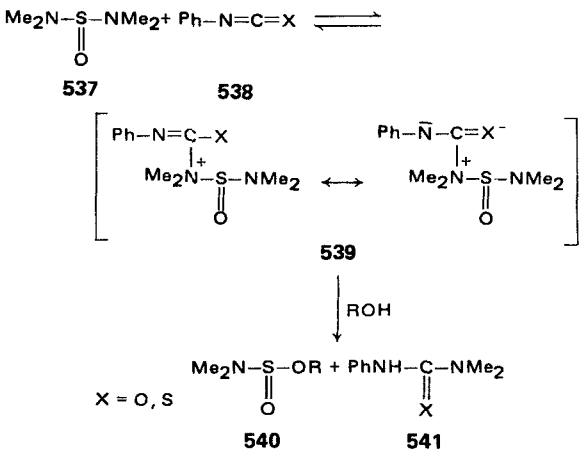
VIII. AMIDOSULFITES

The first reported optically active cyclic amidosulfite was used as described above for the synthesis of enantiomeric sulfoxides.[9]

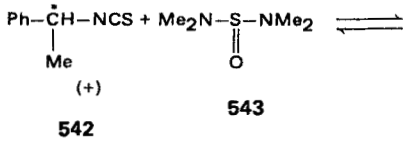
Diastereomeric mixtures of **536** with up to 10% diastereomeric purity were prepared[136] by the reaction of **534** and menthol **535** at −70°C. At higher temperatures the degree of asymmetric induction diminished.



534 **535** **536**



537 **538** **539** **540** **541**



542 543

By an alternative procedure (Figure XXV) amidosulfites with diastereomeric purities of 6% and 8% were prepared. This method was used for the synthesis of **545**, where only the sulfur is the center of chirality.

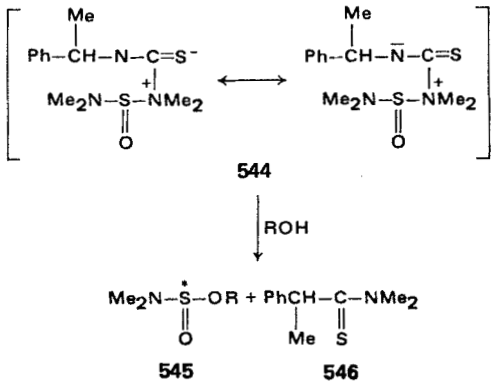
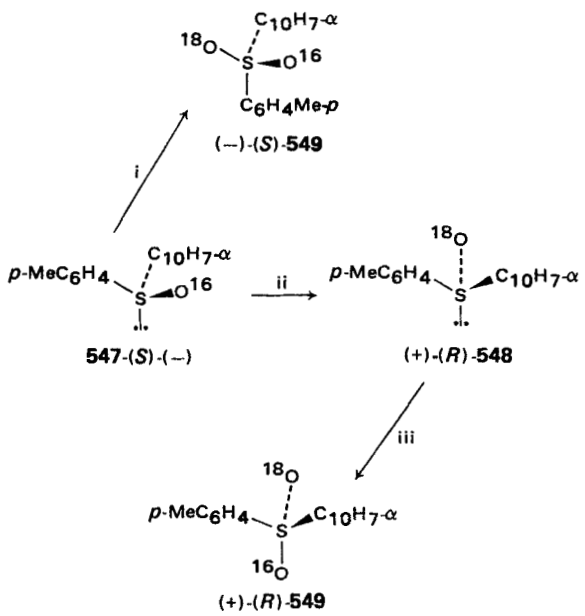


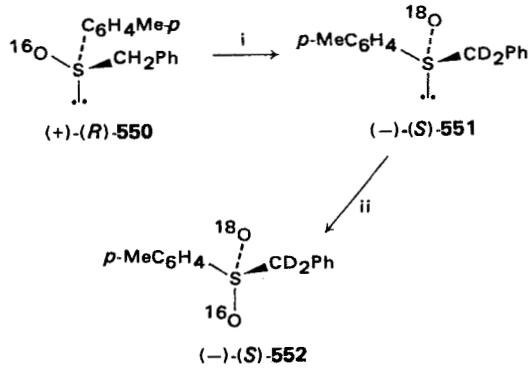
FIGURE XXV

IX. [^{16}O,^{18}O]-SULFONES

Two new methods for the synthesis of optically active [^{16}O,^{17}O]-sulfones have been reported by Cinquini *et al.*[137] Oxidation of sulfoxide **547** with



Reagents: i, $PhICl_2$–$H_2{}^{18}O$–$AgNO_3$; ii, $Et_3O^+BF_4^-$ and then $Na^{18}OD$–$D_2{}^{18}O$-dioxan; iii, *m*-ClC_6H_4·CO_3H.



Reagents: i, $EtO_3{}^+BF_4{}^-$, $Na^{18}OD$; ii, *m*-ClC_6H_4·CO_3H.

(dichloroiodo)benzene in aqueous (92% [^{18}O]-enriched water)-pyridine in the presence of silver nitrate, gave levorotatory sulfone **549**, 75% isotopically pure. The enantiomeric product was obtained by the sequence (−)-**547** → (+)-**548** → (+)-**549**.

This latter sequence of reactions was also used in the preparation of sulfone **552**. Since the stereochemical course of the reactions in this sequence has been established it can be concluded that the (dichloroiodo)-benzene oxidation proceeds with an overall inversion of configuration.

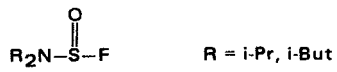
X. HALOSULFINYL COMPOUNDS

Although optically active tricoordinated sulfur compounds where one of the ligands is a halogen group have not been prepared, several papers have reported diastereomeric halosulfinyl compounds as detected by spectroscopic methods. Mikolajczyk and Drabowicz[138] have observed nuclear magnetic non-equivalence in the sulfinyl chlorides **553** and **554**.

553 **554**

Non-equivalence was also observed in the low temperature (−70°C) nmr of dialkylaminosulfinyl chlorides **555** (R = Me, Et, i-Pr).

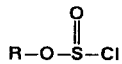
Similar observations have been made by Jackson and Kee[139] on compounds **556**.



556

The magnetic equivalence shown in the R groups of compounds **555** is attributed to rapid intermolecular halogen exchange with loss of sulfur configuration.

Earlier observations of non-equivalence by Seel *et al.*[140] were made on alkyl chlorosulfites **557**.



557

References*

2. R. E. Estep and D. J. Tavares, *Int. J. Sulfur Chem.*, in press.
3. H. Nieuwenhuyse and R. Louw, *J.C.S. Perkin I*, 839 (1973).
4. M. Cinquini, S. Colonna, and F. Taddei, *Boll. Sci. Fac. Chim. Ind. Bologna*, **27**, 231 (1969).
5. C. A. Maryanoff, B. E. Maryanoff, R. Tang, and K. Mislow, *J. Am. Chem. Soc.*, **95**, 5839 (1973).
6. T. M. Sutliff, *Diss. Abst.*, **31**, 3283B (1970).
7. K. K. Andersen, S. Colonna, and C. J. M. Stirling, *J.C.S. Chem. Comm.*, **645** (1973).
8. Y. Yamamoto and H. Nozaki, *Bull. Chem. Soc. Japan*, **45**, 1167 (1972).
9. *a.* F. Wudl and T. N. K. Lee, Abstracts of Papers, 162d National Meeting of the American Chemical Society, Washington D.C., Sept. 1971, ORGN 177.
   b. F. Wudl and T. B. K. Lee, *J.C.S. Chem. Comm.*, **61** (1972).
   c. F. Wudl and T. B. K. Lee, *J. Am. Chem. Soc.*, **95**, 6349 (1973).
10. T. Greibrokk and K. Undheim, *Acta Chem. Scand.*, **25**, 2251 (1971).
11. T. Greibrokk and K. Undheim, *Tetrahedron*, **28**, 1223 (1972).
12. J. Kitchin and R. J. Stoodley, *J.C.S. Chem. Comm.*, 959 (1972).
13. E. Bordignon, L. Cattalini, G. Natile, and A. Scatturin, *J.C.S. Chem. Comm.*, 878 (1973).
14. H. Kexel and H. L. Schmidt, *Biochem. Pharm.*, **21**, 1009 (1972).
15. K. Nishihata and M. Nishio, *J.C.S. Perkin II*, 758 (1973).
16. P. Hermann, K. Stalla, J. Schwimmer, I. Willhardt, and I. Kutschera, *J. Prakt. Chem.*, **311**, 1018 (1969).
17. G. Balavoine, S. Juge, and H. B. Kagan, *Tetrahedron Lett.*, 4159 (1973).
18. *a.* G. Modena, U. Quintily, and G. Scorrano, *J. Am. Chem. Soc.*, **94**, 202 (1972).
    b. G. Modena, *Int. J. Sulfur Chem.*, C, 7, 95 (1972).
19. D. Landini, G. Modena, U. Quintily, and G. Scorrano, *J. Chem. Soc.*, B, 2041 (1971).
20. L. Sagramora, A. Garbesi, and A. Fava, *Helv. Chim. Acta*, **55**, 675 (1972).
21. H. Yoshida, T. Numata, and S. Oae, *Bull. Chem. Soc. Japan*, **44**, 2875 (1971).
22. N. Kunieda and S. Oae, *Bull. Chem. Soc. Japan*, **46**, 1745 (1973).
23. N. Kunieda, T. Numata, and S. Oae, *Int. J. Sulfur Chem.*, in press.
24. D. Landini and F. Rolla, *J.C.S. Perkin II*, 1317 (1972).
25. I. Ookuni and A. Fry, *J. Org. Chem.*, **36**, 4097 (1971).
26. H. Kwart and H. Omura, *J. Am. Chem. Soc.*, **93**, 7250 (1971).
27. R. D. Baechler, J. D. Andose, J. Stackhouse, and K, Mislow, *J. Am. Chem. Soc.*, **94**, 8060 (1972).
28. T. H. Tang, *Diss. Abst.*, **32**, 6312B (1972).
29. R. R. Fraser, M. A. Petit, and J. K. Sauders, *Chem. Comm.*, 1450 (1971).
30. H. Nozaki, K. Yoshino, K. Oshima, and Y. Yamamoto, *Bull. Chem. Soc. Japan*, **45**, 3495 (1972).
31. M. Kainosho, K. Ajisaka, W. H. Pirkle, and S. D. Beare, *J. Am. Chem. Soc.*, **94**, 5924 (1972).
32. *a.* P. Bonvicini, A. Levi, and G. Scorrano, *Gazz. Chim. Ital.*, **102**, 621 (1972).
    b. G. Scorrano, P. Bonvicini, and A. Levi., *Int. J. Sulfur Chem.*, A, **2**, 199 (1972).
33. P. Laur and J. C. Østergaard, *Int. J. Sulfur Chem.*, A, **2**, 199 (1972).
34. N. Thorup, *Acta Chem. Scand.*, **25**, 1353 (1971).
35. D. J. Watkin and T. A. Hamor, *J. Chem. Soc.*, B, 1692 (1971).
36. G. Bandoli, C. Panattoni, D. A. Clemente, E. Tondello, A. Dondoni, and A. Mangini, *J. Chem. Soc.*, B, 1407 (1971).
37. S. Abrahamsson, B. Dahlen, and A. Fredga, *Int. J. Sulfur Chem.*, A, **2**, 212 (1972).

* Ref. 1 is on p. 52

38. *a.* R. Viau and T. Durst, *J. Am. Chem. Soc.*, **95**, 1346 (1973).
    b. K. Nishihata and M. Nishio, *J.C.S. Perkin II*, 1730 (1972).
    c. K. Kishihata and M. Nishio, *Tetrahedron Lett.*, 4839 (1972).
39. M. B. D'Amore and J. I. Brauman, *J.C.S. Chem. Comm.*, 398 (1973).
40. T. Durst, R. Viau, R. Van Den Elzen, and C. H. Nguyen, *Chem. Comm.*, 1334 (1971).
41. *a.* M. Cinquini and S. Colonna, *J.C.S. Perkin I*, 1883 (1972).
    b. M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J.C.S. Perkin I*, 1886 (1972).
    c. M. Cinquini and S. Colonna, *Synthesis*, **5**, 259 (1972).
42. *a.* M. Cinquini, S. Colonna, D. Landini, and F. Montanari, *Int. J. Sulfur Chem.*, A, **2**, 206 (1972).
    b. P. Calzavara, M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Am. Chem. Soc.*, **95**, 7431 (1973).
43. F. Jung and T. Durst, *J.C.S. Chem. Comm.*, 4 (1973).
44. G. Tsuchihashi, S. Iriuchijima, and M. Ishibashi, *Tetrahedron Lett.*, 4605 (1972).
45. G. Tsuchihashi, S. Iriuchijima, and K. Maniwa, *Tetrahedron Lett.*, 3389 (1973).
46. *a.* G. Tsuchihashi, S. Mitamira, S. Inoue, and K. Ogura, *Tetrahedron Lett.*, 323 (1973).
    b. G. Tsuchihashi, S. Mitamura, and K. Ogura, *Tetrahedron Lett.*, 2469 (1973).
47. J. P. Lockard, C. W. Schroeck, and C. R. Johnson, *Synthesis*, 485 (1973).
48. D. N. Jones, E. E. Helmy, and R. J. K. Taylor, *Chem. Comm.*, 1401 (1971).
49. D. N. Jones, E. Helmy, and R. D. Whitehouse, *J.C.S. Perkin I*, 1329 (1972).
50. D. N. Jones, J. Blenkinsopp, A. C. F. Edmonds, E. Helmy, and R. J. K. Taylor, *J.C.S. Perkin I*, 2602 (1973).
51. M. Kishi and T. Komeno, *Int. J. Sulfur Chem.*, *A*, **2**, 1 (1972).
52. M. Kishi, K. Tori, and T. Komeno, *Tetrahedron Lett.*, 3525 (1971).
53. T. Komeno, M. Kishi, H. Watanabe, and K. Tori, *Tetrahedron*, **28**, 2767 (1972).
54. A. Karim and E. A. Brown, *Steroids*, **20**, 41 (1972).
55. D. O. Spry, *J. Org. Chem.*, **37**, 793 (1972).
56. A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, *Tetrahedron*, **28**, 5977 (1972).
57. *a.* A. Vlietinck, E. Roets, P. Claes, and H. Vanderhaeghe, *Tetrahedron Lett.*, 285 (1972).
    b. P. Claes, A. Vlietinck, E. Roets, and H. Vanderhaeghe, *J.C.S. Perkin I*, 932 (1973).
    c. A. Vlietinck, E. Roets, P. Claes, G. Janssen, and H. Vanderhaeghe, *J.C.S. Perkin I*, 937 (1973).
58. R. D. G. Cooper and F. L. Jose, *J. Am. Chem. Soc.*, **94**, 1021 (1972).
59. D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc.*, C, 3540 (1971).
60. D. H. R. Barton, M. Girijavallabhan, and P. G. Sammes, *J.C.S. Perkin I*, 929 (1972).
61. D. H. R. Barton, I. H. Coates, and P. G. Sammes, *J.C.S. Perkin I*, 599 (1973).
62. *a.* D. H. R. Barton, P. G. Sammes, and M. V. Taylor, *Chem. Comm.*, 1137 (1971).
    b. R. D. Allan, D. H. R. Barton, M. Girijavallabhan, P. G. Sammes, and M. V. Taylor, *J.C.S. Perkin I*, 1182 (1973).
63. *a.* I. Ager, D. H. R. Barton, G. Lucente, and P. G. Sammes, *J.C.S. Chem. Comm.*, 601 (1972).
    b. I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, G. H. Hewit, B. E. Looker, A. Mowatt, C. A. Robson, and W. G. E. Underwood, *J.C.S. Perkin I*, 1187 (1973).
64. D. H. R. Barton, I. H. Coates, P. G. Sammes, and C. M. Cooper, *J.C.S. Chem. Comm.*, 303 (1973).
65. S. Kukolja and S. R. Lammert, *Angew. Chem., Int. Ed. English*, 67 (1973).
66. R. Thomas and D. J. Williams, *J.C.S. Chem. Comm.*, 226 (1973).
67. A. G. W. Baxter, J. Kitchin, R. J. Stoodley, and R. B. Wilkins, *J.C.S. Chem. Comm.*, 285 (1973).
68. J. Kitchin and R. J. Stoodley, *J. Am. Chem. Soc.*, **95**, 3439 (1973).
69. R. D. G. Cooper, *J. Am. Chem. Soc.*, **94**, 1018 (1972).
70. S. Terao, T. Matsuo, S. Tsushima, N. Natsumoto, T. Miyawaki, and M. Miyamoto, *J.C.S. Chem. Comm.*, 1304 (1972).
71. W. J. Gottstein, P. F. Misco, and L. C. Cheney, *J. Org. Chem.*, **37**, 2765 (1972).
72. J. A. Webber, G. W. Huffman, R. E. Koehler, C. F. Murphy, C. W. Ryan, E. M. Van Heyningen, and R. T. Vasileff, *J. Med. Chem.*, **14**, 113 (1971).
73. G. E. Gutowski, B. J. Foster, C. J. Daniels, L. D. Hatfield, and J. W. Fisher, *Tetrahedron Lett.*, 3433 (1971).
74. G. E. Gutowski, C. M. Daniels, and R. D. G. Cooper, *Tetrahedron Lett.*, 3429 (1971).

75. S. Kukolja and S. R. Lammert, *J. Am. Chem. Soc.*, **94**, 7169 (1972).
76. *a.* T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron Lett.*, 3001 (1973).
    b. T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *Fourth Intal. Cong. Heterocyclic Chem.*, Salt Lake City, Utah, July 1973, p. 97.
77. D. O. Spry, *J.C.S. Chem. Comm.*, 259 (1973).
78. *a.* M. Yashimoto, S. Ishihara, E. Nakayama, E. Shoji, H. Kuwano, and N. Soma, *Tetrahedron Lett.*, 4387 (1972).
    b. M. Numata, Y. Imashiro, I. Minamida, and M. Yamaoka, *Tetrahedron Lett.*, 5097 (1972).
79. M. Yashimoto, S. Ishahira, E. Nakayama, and N. Soma, *Tetrahedron Lett.*, 2923 (1972).
80. M. Ochiai, O. Aki, A. Morimoto, and T. Okada, *Tetrahedron Lett.*, 3241 (1972).
81. D. O. Spry, *Tetrahedron Lett.*, 165 (1973).
82. D. O. Spry, *Tetrahedron Lett.*, 2413 (1973).
83. D. O. Spry, *J.C.S. Chem. Comm.*, 671 (1973).
84. R. J. Stoodley and N. S. Watson, *J.C.S. Perkin I*, 2105 (1972).
85. J. Lisowski, I. Z. Siemion, and B. Tyran, *Rocz. Chem.*, **47**, 2035 (1973).
86. *a.* S. Kukolja, *J. Am. Chem. Soc.*, **94**, 7590 (1972).
    b. S. Kukolja, P. V. Demarco, N. D. Jones, M. O. Chaney, and J. W. Paschal, *J. Am. Chem. Soc.*, **94**, 7592 (1972).
87. R. B. Morin, E. M. Gordon, and J. R. Lake, *Tetrahedron Lett.*, 5213 (1973).
88. *a.* J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, 22 (1973).
    b. J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, 1985 (1973).
    c. J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, 2460 (1973).
    d. J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, 2464 (1973).
89. *a.* A. J. Anderson, J. Kitchin, and R. J. Stoodley, *Tetrahedron Lett.*, 3379 (1973).
    b. J. Kitchin and R. J. Stoodley, *Tetrahedron*, **29**, 3023 (1973).
90. *a.* M. Janczewski and S. Dacka, *Bull. Acad. Polon. Sci.*, **19**, 91 (1971).
    b. M. Janczewski and W. Janowski, *Rocz. Chem.*, **46**, 529 (1972).
    c. M. Janczewski and B. Dziurzynska, *Rocz. Chem.*, **47**, 453 (1973).
    d. M. Janczewski and H. Maziarczyk, *Rocz. Chem.*, **47**, 449 (1973).
    e. M. Janczewski and H. Maziarczyk, *Rocz. Chem.*, **47**, 2055 (1973).
91. *a.* B. Stridsberg, *Arkiv Kemi*, **32**, 9 (1970).
    b. B. Strisdberg, *Arkiv Kemi*, **32**, 295 (1970).
92. B. Lindgren, *Acta Chem. Scand*, **26**, 2560 (1972).
93. A. Kjaer and A. Schuster, *Acta Chem. Scand.*, **24**, 1631 (1970).
94. A. Kjaer and A. Schuster, *Acta Chem. Scand.*, **26**, 8 (1972).
95. A. Kjaer and A. Schuster, *Phytochem.*, **11**, 3045 (1972).
96. M. Fujiwara, Y. Itokawa, H. Uchino, and K. Inoue, *Experientia*, **28**, 254 (1972).
97. N. M. Sklan and E. A. Barnsley, *Biochem. J.*, **107**, 217 (1968).
98. G. P. Ebbon and P. Callaghan, *Biochem. J.*, **110**, 33p (1968).
99. S. Black, E. M. Harte, B. Hudson, and L. Wartofsky, *J. Biolog. Chem.*, **235**, 2910 (1960).
100. P. Hermann, I. Willhardt, K. Blaha, and I. Fric, *J. Prakt. Chem.*, **313**, 1092 (1971).
101. N. Kunieda, H. Wada, J. Shibatani, and M. Kinoshita, *Makromol. Chem.*, **172**, 237 (1973).
102. T. W. Wickersham and J. R. Cox, Jr., Abstracts of Papers, 162nd National Meeting of the American Chemical Society, Washington D.C., Sept. 1971, ORGN 145.
103. *a.* M. M. Mikolajczyk and J. Drabowicz, *Tetrahedron Lett.*, 2379 (1972).
    b. M. Mikolajczyk and J. Drabowicz, *Int. J. Sulfur Chem.*, *A*, **2**, 200 (1972).
104. *a.* K. K. Andersen, *Chem. Comm.*, 1051 (1971).
    b. K. K. Andersen, R. L. Caret, and D. L. Ladd, Abstracts of Papers, 163rd National Meeting of the American Chemical Society, Boston Mass., April 1972, ORGN 96.
    c. K. K. Andersen, R. L. Caret, and D. L. Ladd, *Int. J. Sulfur Chem.*, *A*, **2**, 196 (1972).
105. *a.* M. Kobayashi, K. Kamiyama, H. Minato, Y. Oishi, Y. Takada, and Y. Hattori, *Chem. Comm.*, 1577 (1971).
    b. M. Kobayashi, K. Kamiyama, H. Minato, Y. Oishi, Y. Takada, and Y. Hattori, *Bull. Chem. Soc. Japan*, **45**, 3703 (1972).
    c. M. Kobayashi and H. Minato, *Int. J. Sulfur Chem.*, *A*, **2**, 228 (1972).
106. K. Kamiyama, H. Minato, and M. Kobayashi, *Bull. Chem. Soc. Japan*, **46**, 3895 (1973).
107. K. Tsumori, H. Minato, and M. Kobayashi, *Bull. Chem. Soc. Japan*, **46**, 3503 (1973).
108. C. R. Johnson, C. C. Bacon, and W. D. Kingsbury, *Tetrahedron Lett.*, 501 (1972).
109. R. Annunziata, M. Cinquini, and S. Colonna, *J.C.S. Perkin I*, 1231 (1973).

110. C. R. Johnson and C. W. Schroek, *J. Am. Chem. Soc.*, **93**, 5303 (1971).
111. B. M. Trost and R. F. Hammen, *J. Am. Chem. Soc.*, **95**, 962 (1973).
112. B. C. Menon and D. Darwish, *Tetrahedron Lett.*, 4119 (1973).
113. *a.* R. E. Booms and D. J. Cram, *J. Am. Chem. Soc.*, **94**, 5438 (1972).
b. R. E. Booms, *Diss. Abst.*, **32**, 3842B (1972).
114. O. Bohman and S. Allenmark, *Chem. Scripta*, **4**, 202 (1973).
115. T. J. Maricich and V. L. Hoffman, *Tetrahedron Lett.*, 5309 (1972).
116. P. K. Claus, W. Vycudilik, W. Rieder, and H. Schwarz, *Int. J. Sulfur Chem., A*, **2**, 218 (1972).
117. S. Allenmark, O. Bohman, and C. E. Hagberg, *Int. J. Sulfur Chem., A*, **2**, 191 (1972).
118. N. Furukawa, K. Harada, and S. Oae, *Tetrahedron Lett.*, 1377 (1972).
119. S. Colonna and C. J. M. Stirling, *Chem. Comm.*, 1591 (1971).
120. *a.* A. Nudelman, R. E. Booms, D. C. Garwood, and D. J. Cram, Abstracts of Papers, 162nd National Meeting of the American Chemical Society Washington D.C., Sept. 1971, ORGN 178.
b. T. R. Williams, R. E. Booms, and D. J. Cram, *J. Am. Chem. Soc.*, **93**, 7338 (1971).
c. T. R. Williams, A. Nudelman, R. E. Booms, and D. J. Cram, *J. Am. Chem. Soc.*, **94**, 4684 (1972).
121. E. U. Jonsson and C. R. Johnson, *J. Am. Chem. Soc.*, **93**, 5308 (1971).
122. F. G. Yamagishi, D. R. Rayner, E. T. Zwicker, and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 1916 (1973).
123. D. C. Garwood, M. R. Jones, and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 1925 (1973).
124. *a.* T. R. Williams, *Diss. Abst.*, **32**, 5120B (1972).
b. T. R. Williams and D. J. Cram, *J. Am. Chem. Soc.*, **93**, 7333 (1971).
c. T. R. Williams and D. J. Cram, *J. Org. Chem.*, **38**, 20 (1973).
125. C. R. Johnson, *Int. J. Sulfur Chem., A*, **2**, 227 (1972).
126. C. R. Johnson and J. P. Lockard, *Tetrahedron Lett.*, 4589 (1971).
127. C. R. Johnson, R. A. Kirchhoff, R. J. Reischer, and G. F. Katekar, *J. Am. Chem. Soc.*, **95**, 4287 (1973).
128. C. R. Johnson and C. W. Schroeck, *J. Am. Chem. Soc.*, **95**, 7418 (1973).
129. C. R. Johnson, C. W. Schroeck, and J. R. Shanklin, *J. Am. Chem. Soc.*, **95**, 7424 (1973).
130. C. R. Johnson and E. R. Janiga, *J. Am. Chem. Soc.*, **95**, 7692 (1973).
131. C. W. Schroeck and C. R. Johnson, *J. Am. Chem. Soc.*, **93**, 5385 (1971).
132. S. Oae, Y. Tsuchida, and N. Furukawa, *Bull. Chem. Soc. Japan.*, **46**, 648 (1973).
133. R. Annunziata, R. Fornasier, and F. Montanari, *J.C.S. Chem. Comm.*, 1133 (1972).
134. *a.* J. L. Kice and J. P. Cleveland, *J. Am. Chem. Soc.*, **95**, 104 (1973).
b. J. L. Kice and J. P. Cleveland, *J. Am. Chem. Soc.*, **95**, 109 (1973).
135. L. E. Legler, S. L. Jindal, and R. W. Murray, *Tetrahedron Lett.*, 3907 (1972).
136. M. Mikolajczyk and J. Drabowicz, *Int. J. Sulfur Chem.*, **8**, 349 (1973).
137. R. Annunziata, M. Cinquini, and S. Colonna, *J.C.S. Perkin I*, 2057 (1972).
138. M. Mikolajczyk and J. Drabowicz, *Z. Naturforsch.*, **26b**, 1372 (1971).
139. W. R. Jackson and T. G. Kee, *J.C.S. Chem. Comm.*, 1154 (1972).
140. F. Seel, J. Boudier, and W. Gombler, *Chem. Ber.*, **102**, 443 (1969).
141. *a.* B. Donzel, B. Kamber, K. Wuthrich, and R. Schwyzer, *Helv. Chim. Acta*, **55**, 947 (1972).
b. J. P. Casey and R. B. Martin, *J. Am. Chem. Soc.*, **94**, 6141 (1972).
c. D. Hauser, H. R. Loosli, and P. Niklaus, *Helv. Chim. Acta*, **55**, 2182 (1972).
d. R. Nagarajan and R. W. Woody, *J. Am. Chem. Soc.*, 7212 (1973).
e. R. Schwyzer, *Angew. Chem., Int. Edit.*, **11**, 854 (1972).