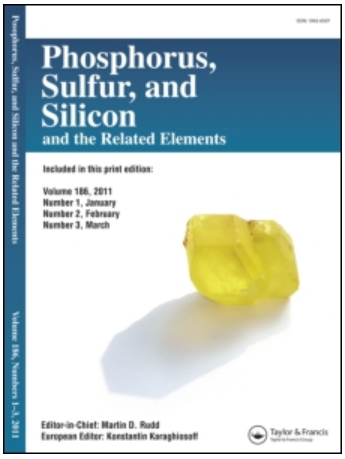

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The Chemistry of Optically Active Sulfur Compounds-Part IV

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REVIEW ARTICLE
The Chemistry of Optically Active Sulfur Compounds—Part IV

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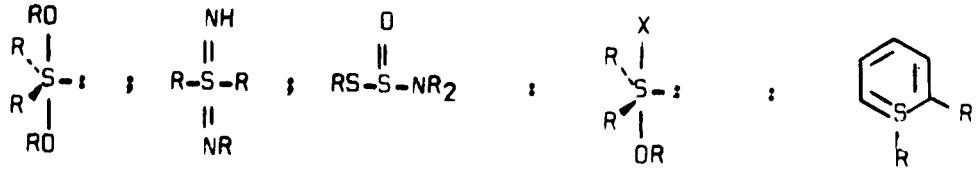
I INTRODUCTION

This paper constitutes the fourth part[1a,b,c] of a continuing series of reviews on the chemistry of optically active sulfur compounds. In addition to the chiral sulfur compounds described previously, five new classes of optically active sulfur compounds have been prepared:

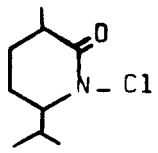


Sulfuranes; sulfodiimides, amidothiosulfites; halosulfuranes; thiabenzenes. Although intensive research continues on the various chiral sulfur compounds described thus far, the overwhelming effort has been devoted to chiral sulfur compounds derived from the penicillins and cephalosporins. It is expected that in the future these compounds will continue to constitute the single most active area of chiral sulfur research. This review covers articles published up to January 1977. Reference 1 lists general papers and review articles in this field.

II SULFOXIDES

A Stereospecific Syntheses

A novel stereoselective oxidation[2] of sulfides to optically active sulfoxides with *N*-bromo-ε-caprolactam (NBC) in the presence of optically active alcohols has been observed. The maximum optical yield obtained was 56%; however, this was only on a total overall yield of 4% sulfoxide. A decrease in optical yield is seen as the overall yield is increased. Subsequently it was shown[3] that optically active sulfoxides may also be obtained upon oxidation of the sulfides with *N*-chloroamide (**1**) prepared from 1-menthol. A second method for the



(**1**)

preparation of enantiomerically enriched sulfoxides (**3**), involved the α,β-dehydrohalogenation of sulfoxides (**2**) in the presence of chiral bases.[4] The enantiomeric excesses obtained were in the range of 8–15% when X was bromide and of 20–25% when X was fluoride. A series of optically active β-disulfoxides (**6**) have been prepared[5] by the reaction of sulfinates (**4**) and α-methylsufinyl carbanions (**5**) (Scheme 1). The stereochemical course of the reaction S_n2 displacement at sulfinate sulfur with inversion of configuration as shown in Scheme 2.

$$2(R,S)\text{-}p\text{-}MeC_6H_4SOCH_2CH_2X + B\text{-} \begin{cases} \rightarrow p\text{-}MeC_6H_4SOCH{=}CH_2 \\ \quad (\mathbf{3}) \\ \quad (\text{excess of } R \text{ or } S) \\ \quad +BH^+ + X^- \\ \rightarrow p\text{-}MeC_6H_4SOCH_2CH_2X \\ \quad (\text{excess of } S \text{ or } R) \end{cases}$$

(**2a**) X = Br
(**2b**) X = F
B = chiral base

A second family of β- and γ-disulfoxides were prepared and separated into *d*, *l* and *meso* forms.[6] The assignment of configuration was made through the stereospecific synthesis shown in Scheme 3, by partial chromatographic resolution of (**14**) on a lactose column, and by nmr analysis.

$$R_2\text{—}\overset{\overset{O}{\uparrow}}{\underset{\underset{O}{\downarrow}}{S}}\text{—}O\text{—}R_3 \xrightarrow[(2)\ H_3O^+]{(1)\ 2\ R_1\text{—}\overset{\overset{O}{\uparrow}}{S}\text{—}CH_2^-,\ (\mathbf{5})}$$

(**4**)

(**5**) { **a**: $R_1 = CH_3$; **b**: $R_1 = C_6H_5$; **c**: $R_1 = p\text{-}CH_3C_6H_4$

(**4**) { **a**: $R_2 = p\text{-}CH_3C_6H_4$, $R_3 = CH_3$; **b**: $R_2 = C_6H_5$, $R_3 =$ (−)-Menthyl; **c**: $R_2 = p\text{-}CH_3C_6H_4$, $R_3 =$ (−)-Menthyl

$$R_1\text{—}\overset{\overset{O}{\downarrow}}{S}\text{—}CH_2\text{—}\overset{\overset{O}{\downarrow}}{S}\text{—}R_2 + R_1\text{—}\overset{\overset{O}{\downarrow}}{S}\text{—}CH_3 + R_3OH$$

(**6**)

(**6**) { **a**: $R_1 = CH_3$, $R_2 = C_6H_5$; **b**: $R_1 = CH_3$, $R_2 = p\text{-}CH_3C_6H_4$; **c**: $R_1 = R_2 = C_6H_5$; **d**: $R_1 = p\text{-}CH_3C_6H_4$, $R_2 = C_6H_5$; **e**: $R_1 = R_2 = p\text{-}CH_3C_6H_4$

SCHEME 1

$$p\text{-}CH_3C_6H_4\text{—}\overset{\overset{*}{\downarrow}}{\underset{\underset{O}{\downarrow}}{S}}\text{—}CH_3 \xrightarrow{Br_2\text{-NBS-pyridine}} p\text{-}CH_3C_6H_4\text{—}\overset{\overset{*}{\downarrow}}{\underset{\underset{O}{\downarrow}}{S}}\text{—}CH_2Br$$

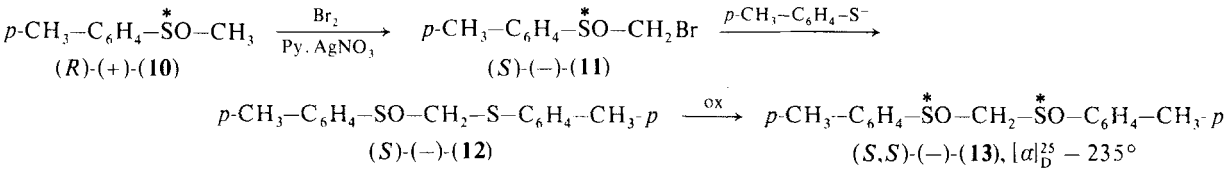
(+)-(*R*)-(**7**) (+)-(*S*)-(**8**)

$$(+)\text{-}(S)\text{-}(\mathbf{8}) \xrightarrow{p\text{-}CH_3C_6H_4SNa} p\text{-}CH_3C_6H_4\text{—}\overset{\overset{*}{\downarrow}}{\underset{\underset{O}{\downarrow}}{S}}\text{—}CH_2\text{—}S\text{—}C_6H_4CH_3\text{-}p$$

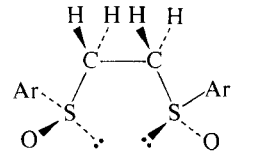
(+)-(*S*)-(**9**)

$$(+)\text{-}(S)\text{-}(\mathbf{9}) \xrightarrow[(2)\ \text{Fractional crystallization}]{(1)\ H_2O_2 \text{ in } CH_3COOH} (+)\text{-}(S,S)\text{-}(\mathbf{6e}) \text{ and optically inactive } (R,S)\text{-}(\mathbf{6e})$$

SCHEME 2

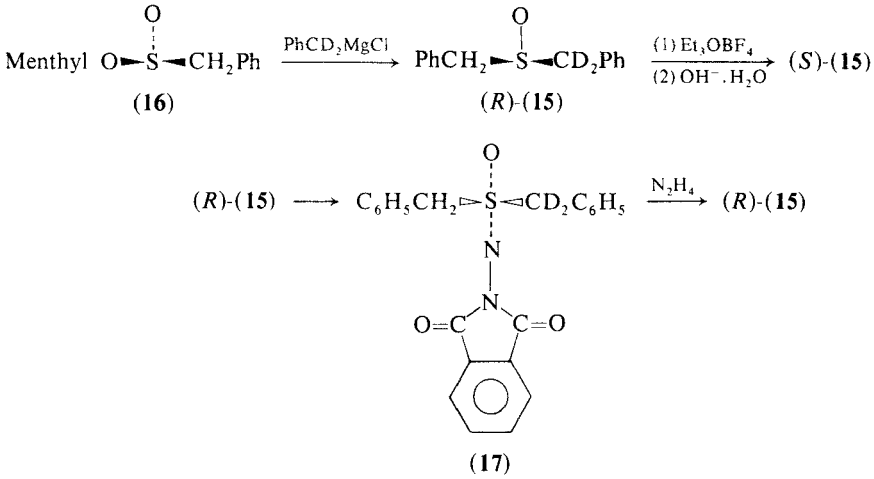


SCHEME 3



(14) Ar = p-CH_3O–C_6H_4

The first example of chiral sulfoxides whose asymmetry is derived solely from isotopic differences at the α-position of the sulfoxide group has been reported.[7] Compound *R*-(**15**) was prepared in 96% optical purity and was converted to its enantiomer *S*-(**15**). The appreciable rotatory strength observed for compound (**15**) is attributed to significant vibronic interaction differences of the benzyl and dideuterio benzyl groups. The sulfoximine (**17**) which is not racemic, since it was hydrazinolyzed to optically active sulfoxide, did not show optical activity due to the formation of strongly absorbing yellow solutions.



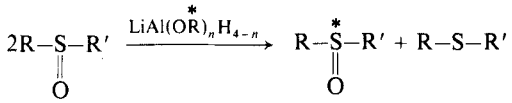
(17)

An example of an asymmetric anodic oxidation describes[8] the synthesis of optically active sulfoxides by electrolytic oxidation of sulfides using a modified DSA electrode.

A novel stereoselective oxidation of sulfides to optically active sulfoxides has been shown[9] to take place upon treatment of sulfides with t-butylhydroperoxide catalyzed by vanadyl and molybdanyl acetylacetonates in the presence of optically active alcohols used as solvents. The enatiomeric excesses obtained, of up to 9.8%, compare well with asymmetric oxidations of sulfides with chiral peroxy acids.

An improvement in the synthesis of optically active sulfoxides has been reported[10] when methyl sulfinates are treated with organocopper–lithium reagents of the type R_2CuLi. The use of these reagents gives sulfoxides in high optical yields and in higher degree of purity than the corresponding Grignard reagents.

Asymmetric reduction of racemic sulfoxides (**18**) with alkoxylithium aluminium hydrides derived from optically active alcohols such as quinidine gave optically active sulfoxides in low optical yield.[11] Optically active



(18)

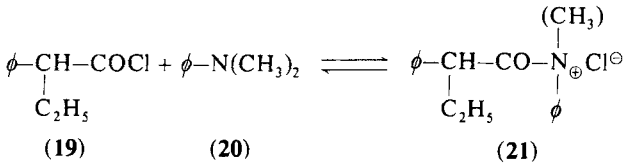
sulfoxides may be obtained[12] upon incubation of thioethers in the presence of Aspargillus niger. The optical yields vary in the range of 4–100%, depending on the structures of the thioether and on the extent of subsequent oxidation of the obtained sulfoxide to sulfone.

B Resolution and Racemization

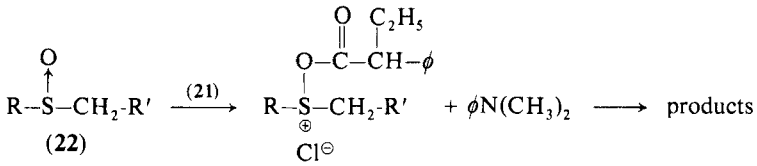
A novel method[13] for the determination of the absolute configuration of sulfoxides has been described by Juge and Kagan, whereby treatment of a racemic sulfoxide with an optically active acid chloride in the presence of a tertiary base, results in the asymmetric destruction of one of the enantiomers (Scheme 4). A constant correlation between the substituents on the sulfoxide group and the absolute configuration of the acid chloride has been obtained based on the steric sequence

$$C_6H_5 > CH(CH_3)_2 > C_2H_5 > CH_3 \quad \text{and} \quad C_6H_5CH_2 > CH_3$$

When the (+)-phenylbutyryl chloride is used, the recovered optically active sulfoxide of configuration (**24**) is recovered (L > M).

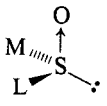


(19) (20) (21)



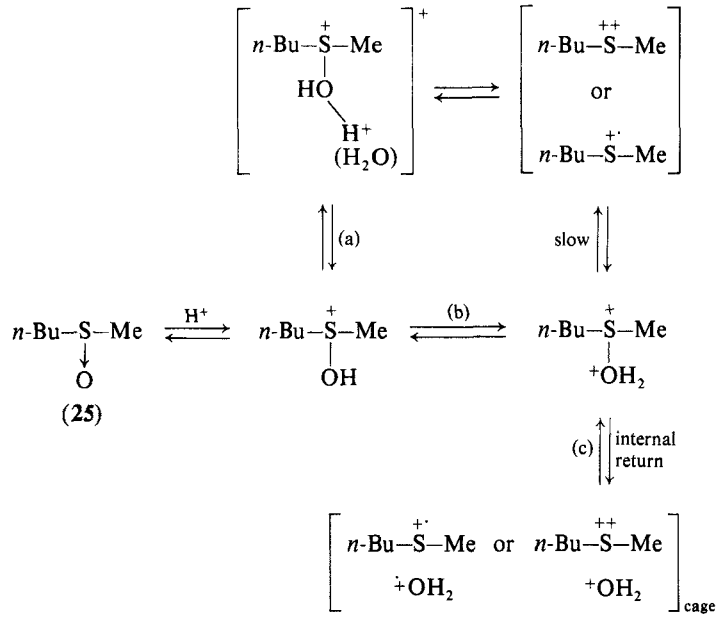
(22) (23)

SCHEME 4

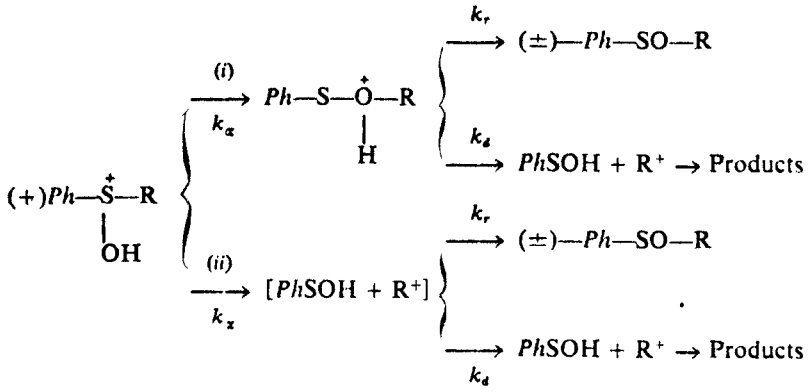


(24)

Mechanistic studies on the acid catalyzed racemization of sulfoxides have been carried out by Oae *et al.*[14] and Bonvicini *et al.*[15] The former group investigated the concomitant oxygen exchange and racemization reaction of ^{18}O-labelled optically active *n*-butyl methyl sulfoxide in sulfuric acid. The course of the reaction follows the formation of a radical cation or a dication intermediate followed by fast nucleophilic attack of water to give the starting sulfoxide. (Scheme 5). The latter group measured the β-deuterium isotope effect on the protonation equilibrium on rates of racemization and fragmentation of t-butyl phenyl sulfoxide. Evidence has been found indicating the formation of an alkyl cation–sulfenic acid ion-molecule pair leading to C–S bond cleavage (Scheme 6).



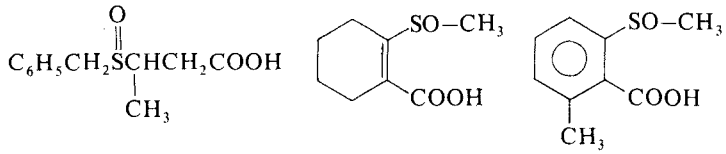
SCHEME 5



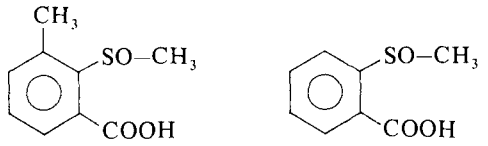
SCHEME 6

The course of racemization of sulfoxides anchimerically assisted by α-carboxy groups, with halide ions has been studied by Landini *et al.*[16] The reactivity ratios of k_{Br}/k_{Cl} found, are much higher than those observed in normal sulfoxides. The authors suggest that attack by halide ions in the halosulfonium intermediate proposed, occurs at sulfur or at halogen depending on the nature of the halide ion.

The mechanism of HBr induced racemization of compounds (**26**)–(**30**), of which (**26**)–(**29**) are novel optically active sulfoxides, has been studied by Hagberg and Allenmark.[17] The halide ion dependence in the racemization is sensitive to the nature of the substrate, the nature of the halide and the reaction medium as well as the halide concentration.



(26) (27) (28)

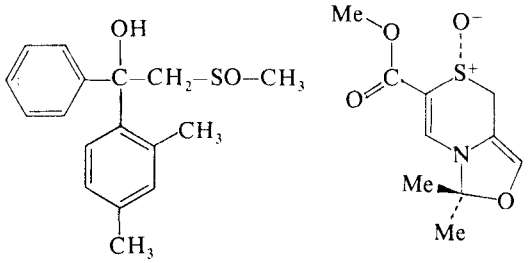


(29) (30)

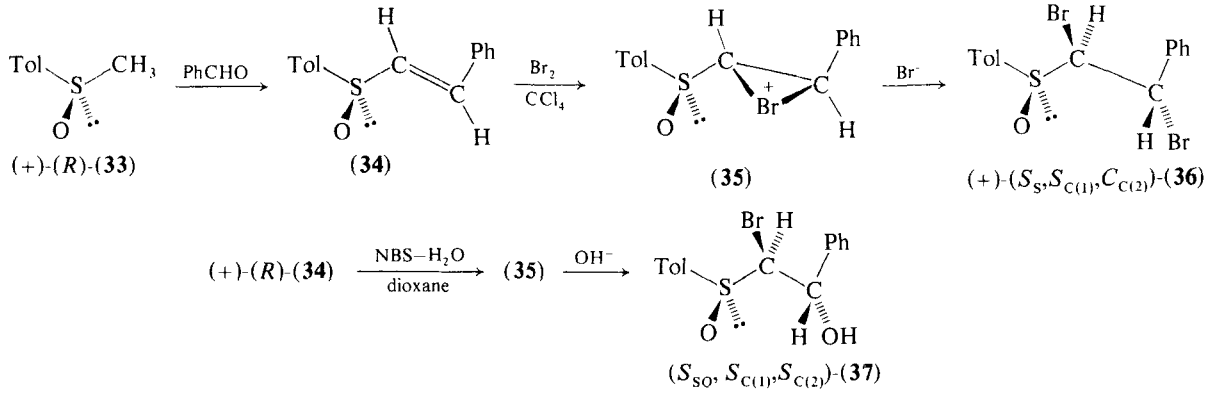
C *Spectral Studies*

The absolute configurations of sulfoxides (**31**)[18] and (**32**)[19] have been established by x-ray crystallography.

The structure of compound (**34**) prepared as described in Scheme 7, has also been obtained by x-ray crystallographic methods.[20,21] The same bromonium ion intermediate (**35**) was postulated in the formation of bromohydrin (**37**) whose absolute configuration was also subsequently obtained by x-ray crystallography.[22]



(31) (32)

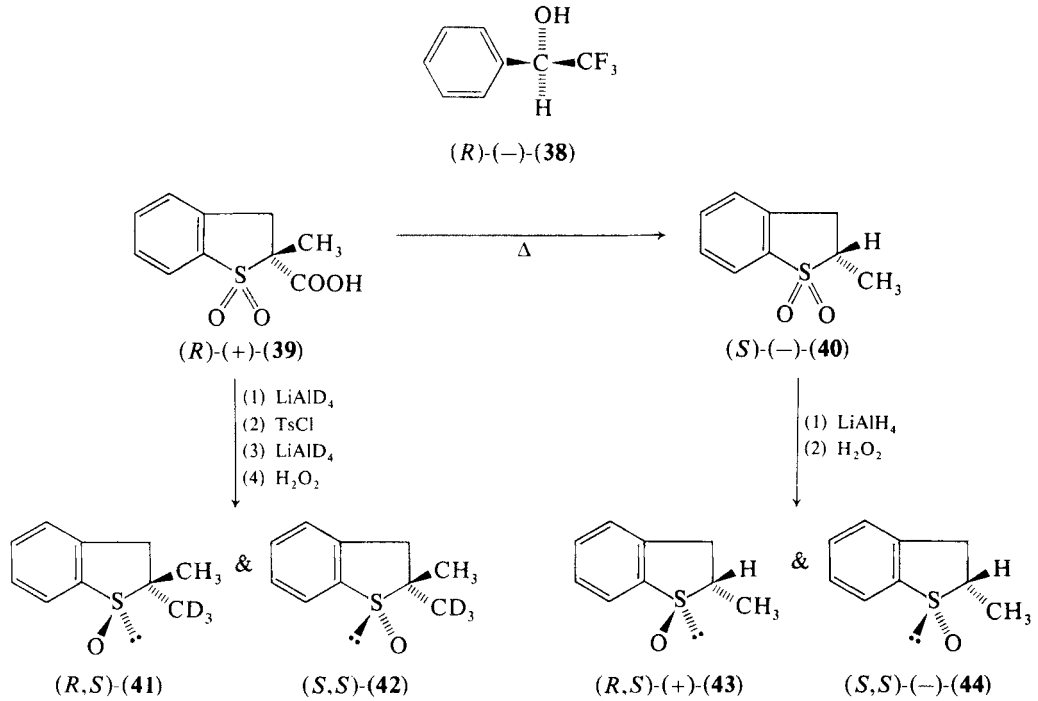


(+)-(*R*)-(**33**) (**34**) (**35**) (+)-(S_S,$S_{C(1)}$,$C_{C(2)}$)-(**36**)

(+)-(*R*)-(**34**) $\xrightarrow[\text{dioxane}]{\text{NBS}-H_2O}$ (**35**) $\xrightarrow{OH^-}$ (S_{SO}, $S_{C(1)}$,$S_{C(2)}$)-(**37**)

SCHEME 7

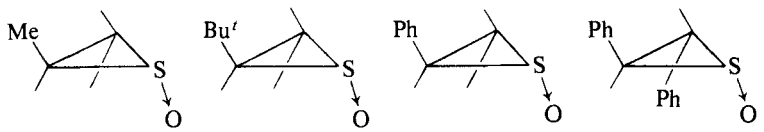
An unexpected observation has been made in the x-ray study of (α-*S*, *SS*/*R*, *SR*)-1-(*p*-bromophenyl)ethyl t-butyl sulfoxide and the diastereomeric pairs of 1-phenylethyl t-butyl sulfoxides.[23] It appears that the bulky t-butyl group orients itself in such a way that it is flanked by hydrogen and phenyl groups instead of hydrogen and methyl groups. Subsequent nmr, ord and cd data are best interpreted by these stereochemical assignments implying that these conformations prevail also in the solution state. The authors suggest that a flat hollow phenyl ring has a smaller van der Waals dimension than a methyl group.



SCHEME 8

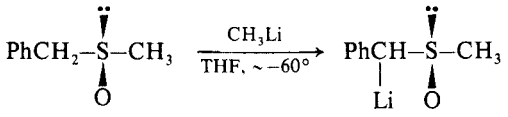
Several determinations of absolute configuration by means of nmr spectroscopic methods have been described. Pirkle and coworkers[24] have studied the solvent–solute interactions between (*R*)-(−)-1-phenyl-2,2,2-trifluoroethanol (**38**) and various sulfoxides. The solution model proposed is useful in the assignment of the absolute configuration of unknown sulfoxides. Whitney[25] prepared two pairs of diastereomeric sulfoxides (**41**)–(**42**) and (**43**)–(**44**) (Scheme 8) and used the chiral solvent (**38**) in the assignment of the absolute configurations. Further work by Pirkle[26] in this area has made use of an achiral lanthanide shift reagent Eu(fod)$_3$ which also alters the magnitude and sometimes the sense of non-equivalence in the nmr spectra of enantiomeric sulfoxides in chiral aryl perfluoroalkyl carbinols. In an analogous study Lett and Marquet[27] proposed nmr models for the assignment of configuration in a large number of sulfoxides. The proposed qualitative models are generally sufficient in solving the configurational assignment problems. In all the examples presented, examination of the nmr spectra according to the suggested model provides the correct configuration of the sulfoxides.

The circular dichroism of chiral episulfoxides (**45**)–(**48**) have been studied by a number of groups.[28,29] It was found that contrary to the case of the parent sulfides, the first transition in the sulfoxides has a prevalent σ–σ^* character.



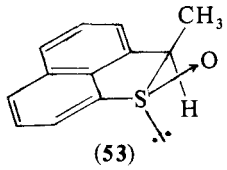
D Reactions

The reactions of sulfoxides will be divided into two groups, as was done in the previous report.[1c] Those related to reactions which take place specifically at the α-position of a chiral sulfoxide and later on, all other pertinent reactions. The protons in the α-position to the sulfoxide are somewhat acidic and may be removed with strong bases. The resulting carbanions upon subsequent treatment with various reagents give rise to diastereomeric products. The stereoselectivity of the reactions of these carbanions is frequently quite pronounced. α-Sulfoxide

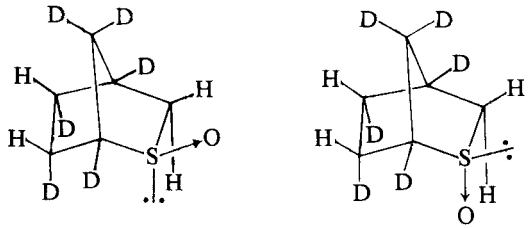


(49) (50)

(51) (52)



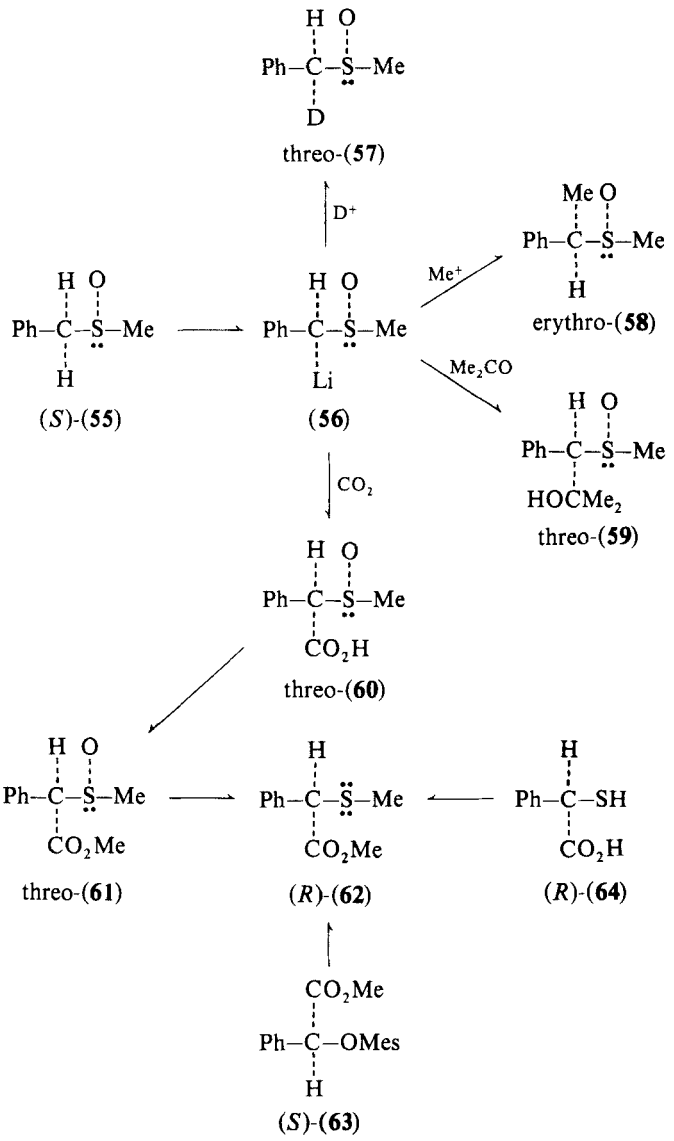
(53)



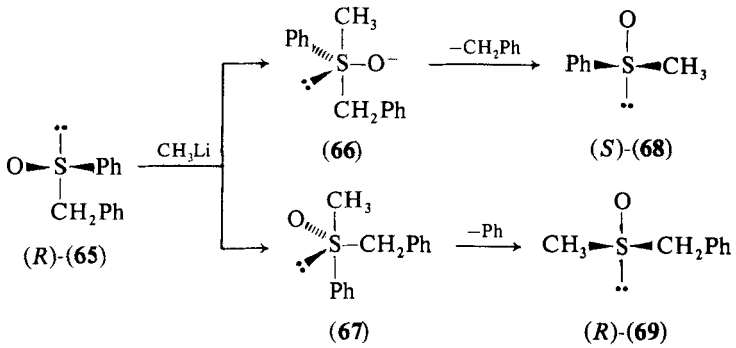
(54a) (54b)

carbanions formed by treatment of sulfoxides with methyl lithium[30] give rise to varying ratios of diastereomeric products depending to a great extent on the different lithium salts present in the medium, i.e. LiCl, LiBr, LiI, $LiClO_4$, or other salts such as tetra-*n*-butyl ammonium perchlorate. Durst and Molin attribute these differences to various forms of species (**50**), ranging from covalently bound species to free carbanions, each of which may have different reactivity and stereoselectivity toward various electrophiles. Earlier Biellmann and Vicens[31] attributed considerable importance to ion-pairing phenomena in the stereoselectivity of reactions of α-lithio sulfoxides. The stereochemistry of H–D exchange α to the sulfinyl group in 2H-naphtho[1,8-bc]thiophen-1-oxide derivatives (**51**), (**52**), (**53**) compared to similar exchange in compounds (**54**) and (**55**) has been examined by Folli *et al.*[32] It was found that in compounds (**51**)–(**53**) the α-proton eclipsed by a sulfur lone pair has greater kinetic acidity than that of the diastereotopic protons eclipsed by the sulfinyl oxygen. This is opposite to the case of the bicyclic sulfoxides (**54a**) and (**54b**). Nishihata and Nishio[33] established that the course of carbonation of α-lithio sulfoxides to give α-methylsufinyl phenyl acetic acid (**60**), follows a similar path to that of deuteration or reaction with acetone. In all three cases the reaction proceeds with retention of configuration contrary to the methylation reaction which proceeds with inversion. The configuration of the product threo-(**60**) was further confirmed by the stereospecific synthesis of *R*-(**62**) from *R*-(**64**) and *S*-(**63**) (Scheme 9).

Treatment of sulfoxides with alkyl lithium reagents can give rise to two reactions: (a) displacement of one of the substituents by the alkyl group of the reagent and (b) α-hydrogen abstraction. It has been found[34] that methyl lithium gave mainly carbanion formation whereas stronger bases *n*-butyl lithium and t-butyl lithium gave 30–50% displacement, with phenyl being displaced faster than alkyl. When the reaction is carried out with optically active sulfoxides the products are found with essentially complete inversion of configuration. The results are best explained by an S_n^2 mechanism as shown in Scheme 10.



SCHEME 9



SCHEME 10

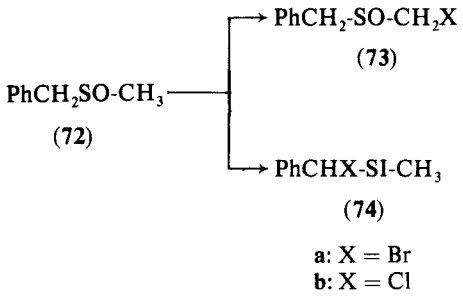
Kunieda and coworkers[35,36] prepared the optically active sulfoxide (+)-(*R*)-(**70**) from ethyl benzoate and (+)-(*R*)-methyl *p*-tolyl sulfoxide. Treatment of (**70**) with two equivalents of a Grignard reagent afforded mixtures of diastereomeric (**71**) with the $R_S S_C$ isomer in predominance. A model of 1,3-asymmetric induction is proposed analogous to that observed[37] in addition reactions of organometalics and ketons having a chiral center *β*- to the carbonyl group. When the reaction was carried out with one equivalent of the Grignard reagent and the hydrolysis with D_2O–D_2SO_4, the methylene hydrogens of recovered (+)-(*R*)-(**70**) were found to be about 50% deuterated.

(+)-(*R*)-(**70**) (**71**)

(Mixture of $R_S R_C$ and $R_S S_C$)

a: $R = CH_3$–, **b:** $R = C_2H_5$–, **c:** $R = n\text{-}C_3H_7$–, **d:** $R = C_6H_5CH_2$–

Montanari *et al.*,[38] have studied the stereochemical course of *α*-chlorination and *α*-bromination of optically active benzyl methyl sulfoxide (**72**) in pyridine with iodobenzenedichloride and bromine respectively. The halogenation at the methyl group takes place with retention at sulfur whereas halogenation at the benzylic methylene proceeds with inversion. In the case of the (*S*)-sulfoxide the reaction involves selective replacement of the pro-*S*-benzylic hydrogen and occurs with inversion of configuration at carbon. Further work on this field involves the highly stereoselective halogenation of optically active (*R*)-(+)-[*α*,*α*-$^2H_2$] dibenzyl sulfoxide (**76**).[39] One of the four possible diastereomers is obtained preferentially and further oxidation of the sulfoxide affords optically active *α*-halo sulfones. The sulfoxide (**76**) was prepared from the sulfinate (**75**). This stereo- and regio-selective reaction provides the first example of a non-enzymatic asymmetric induction due to isotopic dissymmetry.

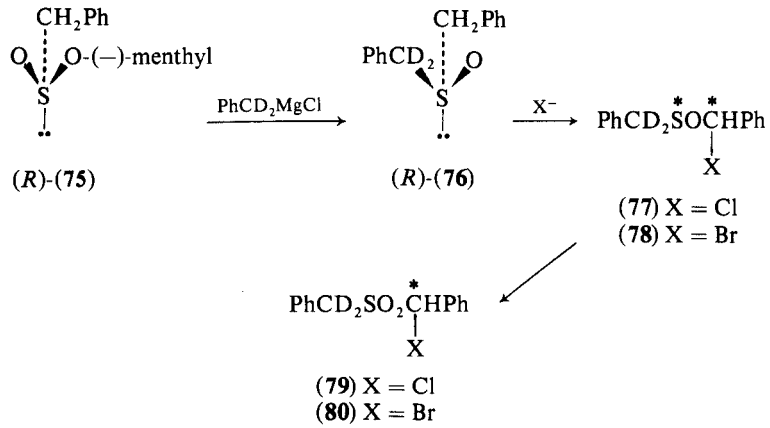


(**72**)

(**73**)

(**74**)

a: X = Br
b: X = Cl

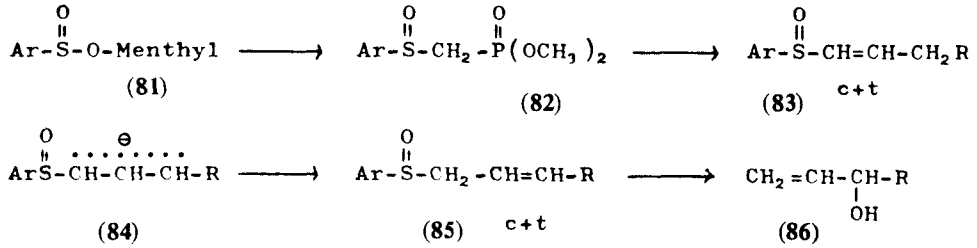


(*R*)-(**75**) (*R*)-(**76**)

(**77**) X = Cl
(**78**) X = Br

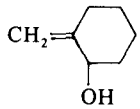
(**79**) X = Cl
(**80**) X = Br

It has been shown[40] that optically active alcohols may be obtained by a [2,3]-sigmatropic rearrangement of optically active β,γ-unsaturated sulfoxides. The desired sulfoxides were obtained from the corresponding menthyl sulfinates (**81**) as shown in Scheme 11 (Table I).

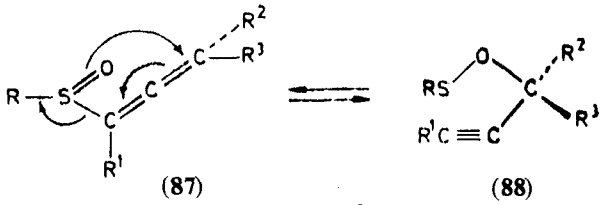


SCHEME 11

TABLE I

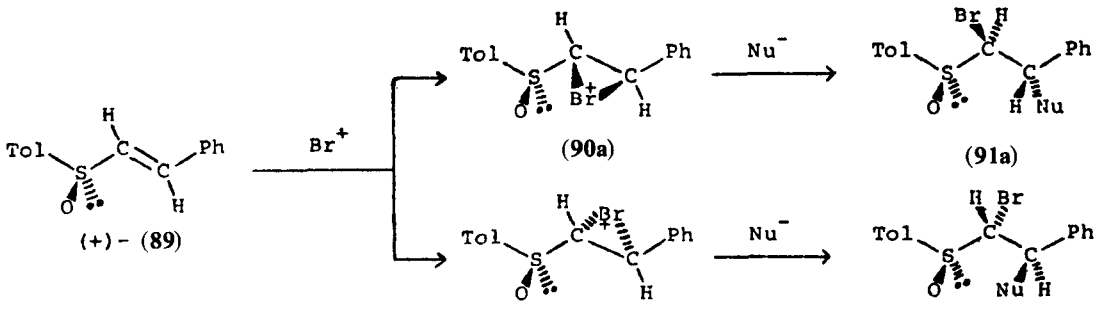
$\alpha\beta$-Unsaturated sulfoxide	Yield	Allyl alcohol	Yield	Optical purity%
p-CH_3–C_6H_4–S(=O)–CH=CH–CH_2–C_6H_5		CH_2=CH–CH(OH)–C_6H_5	58%	0
p-CH_3–C_6H_4–S(=O)–CH=CH–CH_2–$^nC_5H_{11}$	72%	CH_2=CH–CH(OH)–$^nC_5H_{11}$	72%	20
p-CH_3–C_6H_4–S(=O)–CH=	62%	CH_2= 	75%	60

Allenic sulfoxides (**87**) asymmetric at both sulfur and allene are obtained by treatment of menthyl sulfinates with propargyl Grignard reagents.[41,42] Epimerization at sulfur by the sulfoxide-sulfenate process takes place with the preservation of the asymmetry in the allene system (Scheme 12).



(**87**) (**88**)

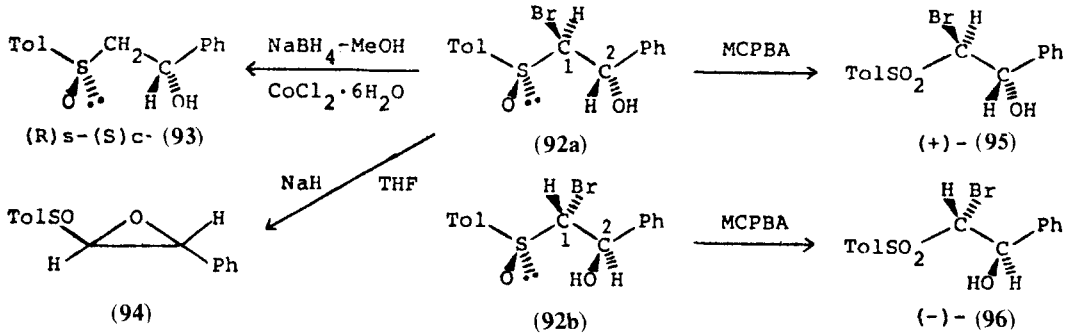
SCHEME 12



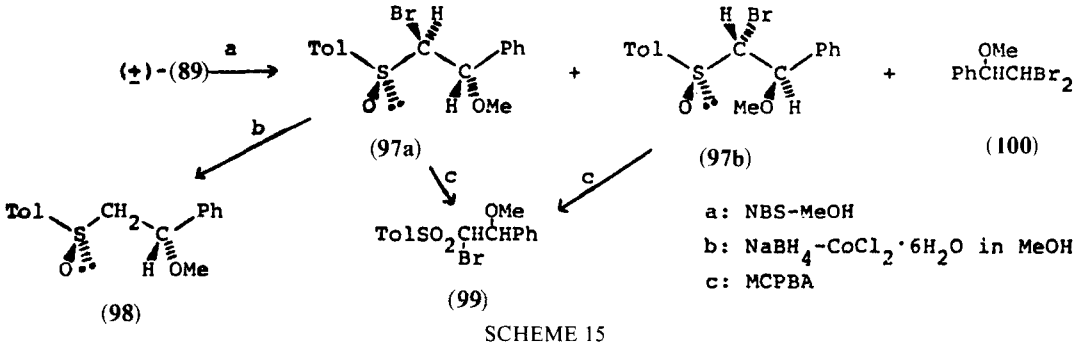
(+)-(**89**) (**90a**) (**91a**) (**90b**) (**91b**)

SCHEME 13

The stereochemical course of addition reactions to optically active vinylic sulfoxides has been further investigated by Tsuchihashi and coworkers. Highly selective electrophilic addition of BrOH and BrOMe has been observed[43] when (+)-(**89**) is treated with *N*-bromosuccinimide in aqueous dioxane or in methanol. The products obtained stem from nucleophilic attack on the bromonium intermediates (**90a**) and (**90b**) (Scheme 13). In both cases the preferred product had the structure (**91a**) ((**92a**) and (**97a**), Schemes 14 and 15).

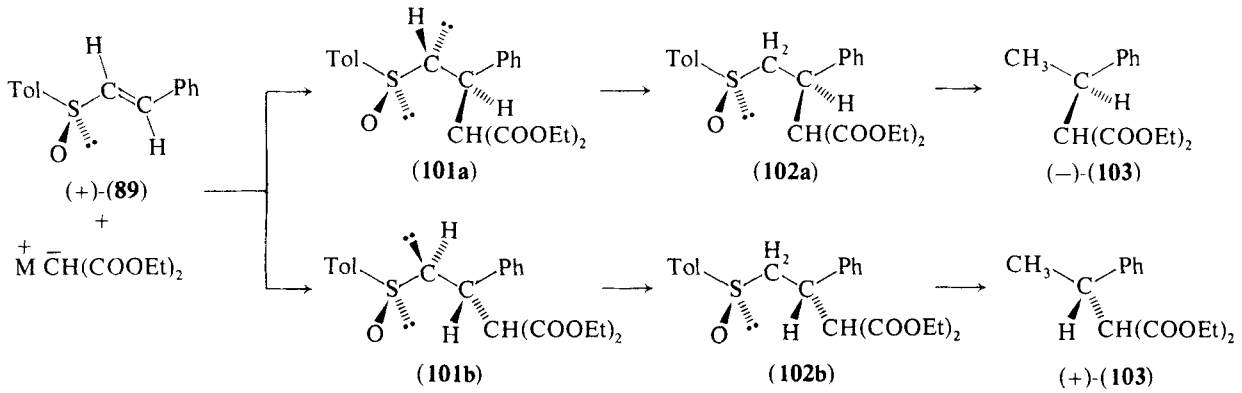


SCHEME 14

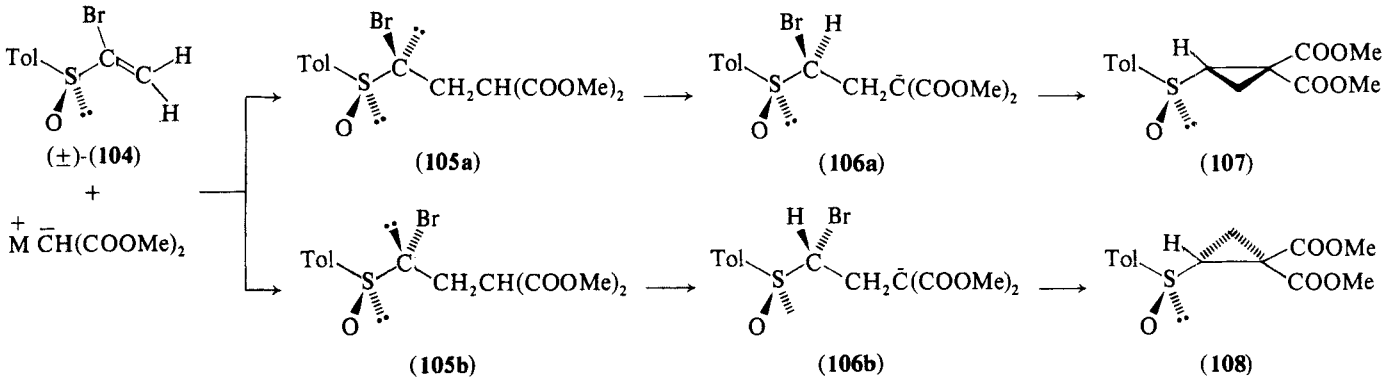


SCHEME 15

It was concluded that the optical purity of the major isomer (**92a**), was at least 97%, suggesting that the formation of (**90a**) is favored by the electronic demand of the adjacent chiral sulfinyl group, contrary to the previously shown[44] stereoselectivity of addition of diethyl malonate to (+)-(**89**) to give preferentially (**102a**) over (**102b**); it has now been found[45] that the stereoselectivity is highly solvent dependent and it is possible to obtain under the proper conditions, either diastereomer of (**102**) from (+)-(**89**). Subsequent reductive desulfurization of (**102a**) and (**102b**) results in the respective formation of (−)-(**103**) and (+)-(**103**) (Scheme 16).

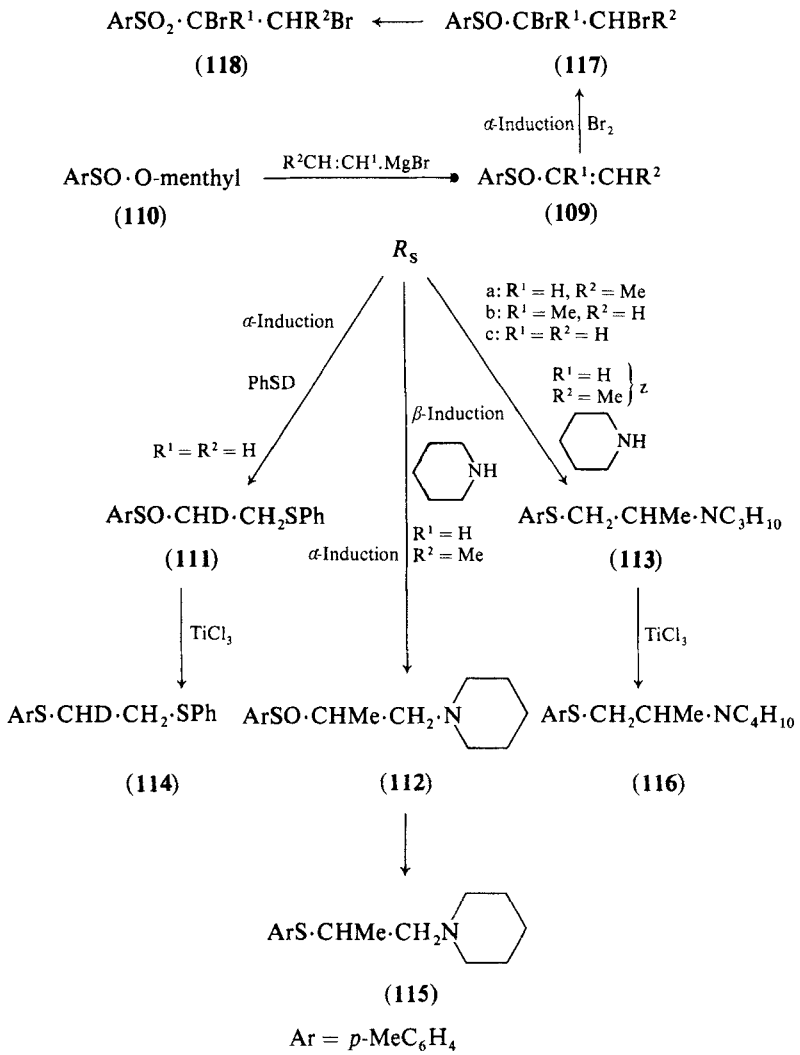


SCHEME 16



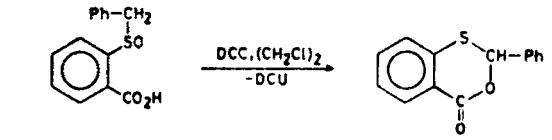
SCHEME 17

A second example of solvent induced stereoselectivity is shown in Scheme 17, where (**106a**) or (**106b**) are obtained preferentially depending on whether the reaction is carried out in methanol or tetrahydrofuran.

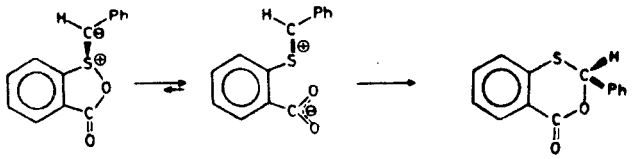


The nucleophilic addition to α,β-unsaturated chiral sulfoxides (**109**) proceeds[46] with high degree of asymmetric induction. The sulfoxides (**109**) obtained by the Andersen synthesis from menthyl sulfinate (**110**), were treated with various nucleophiles to give optically active sulfoxides (**111**), (**112**), (**113**), which were in turn reduced to the sulfides (**114**), (**115**), (**116**). Reaction of (**109**) with bromine gave (**117**), which upon oxidation gave the optically active sulfone (**118**).

Another reaction[47,48] where the stereochemical course is dependent on the reaction conditions involves the transfer of chirality of sulfur to carbon in compound (**119**) giving rise to optically active (**120**). When dicyclohexylcarbodiimide (DCC) was used it gave (**120**) of opposite sign of rotation (30% stereoselectivity), when the reaction was carried out in the presence of a small excess of acetic anhydride the sign of rotation of the product was also opposite to that of (**119**), whereas when acetic anhydride was used both as reagent and solvent, the opposite results were obtained. The mechanism suggested for the chirality transfer involves opening of (**121**) to the ion pair (**122**) with restriction of rotation around the partial double C—S bond, followed by recombination to (**120**). The stereoselectivity is attributed to the difference in reactivity of the benzylic diastereotopic protons.



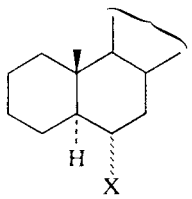
(**119**) (**120**)



(**121**) (**122**) (**120**)

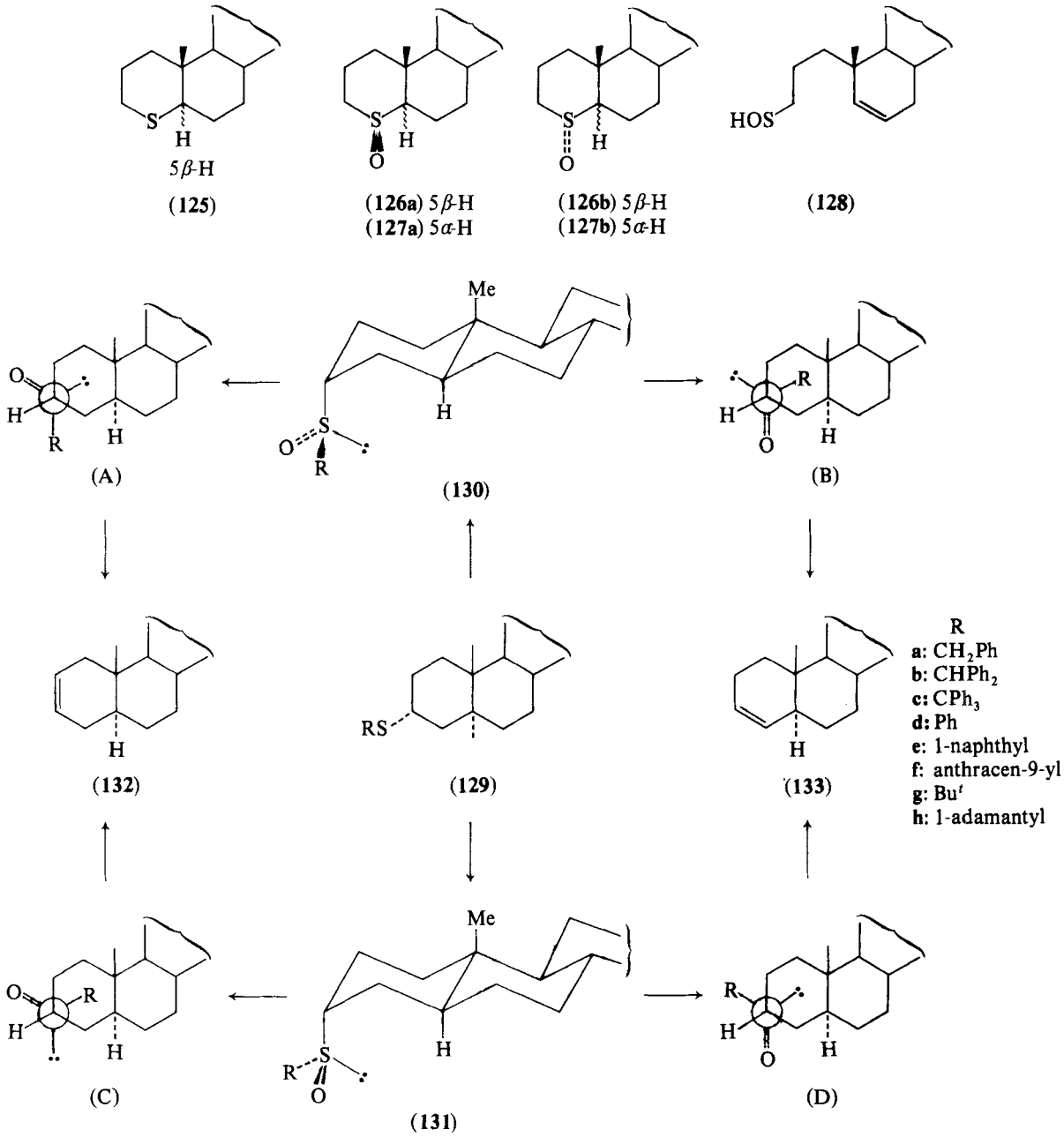
E Steroidal Sulfoxides

Novel steroidal sulfoxides have been described in three papers by Jones and coworkers. Diastereomeric steroidal allyl sulfoxides[49] (**123a**) and (**123b**) were separated chromatographically. Subsequently they were converted into the corresponding (*R*)- and (*S*)-6β-propylsulfinyl-5α-cholestanes (**124a**) and (**124b**). The chiroptical, uv, cd, and spectral, nmr, properties of these compounds are described in detail. It was shown that the influence of the solvent upon the chiroptical spectra of some of the sulfoxides depended on the chirality at sulfur. Other steroidal sulfoxides which incorporate the S=O as an integral part of the ring system have been described.[50] The elegant synthesis of all four diastereomeric sulfoxides (**126a**), (**126b**), (**127a**) and (**127b**) is presented. A nine-step sequence provided sulfide (**125**) which was oxidized with a variety of oxidants to give various ratios of the sulfoxides. The synthetic problems involved in the least conveniently available isomer (**126b**), were overcome when the sulfenic acid (**128**) was cyclized to (**126b**) via a six electron sigmatropic rearrangement.



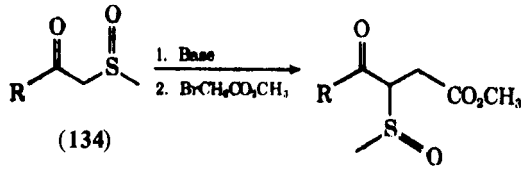
X

(**123a**)6β-(*R*)-S(O).$CH_2CH:CH_2$
(**123b**)6β-(*S*)-S(O).$CH_2CH:CH_2$
(**124a**)6β-(*R*)-S(O).$CH_2.CH_2.CH_3$
(**124b**)6β-(*S*)-S(O).$CH_2.CH_2.CH_3$

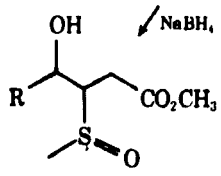


The thermolytic cleavage[51] of a series of diastereomeric sulfoxides (**130**) and (**131**) shows that regiospecific olefin formation occurs with the adamantyl sulfoxides (**130b** and **131b**) to give the olefins (**132**) and (**133**) respectively. Other sulfoxides (**b, e, f, g**) upon pyrolysis gave mixtures of (**132**) and (**133**). The fact that both (**130**) and (**131**) are obtained from a common sulfide (**129**) presents a method for the regiospecific generation of isomeric olefins from a common precursor. The thermolytic elimination[52] of CH_3SOH from sulfoxide (**136**) (R = 3β-acetoxy-androst-5-en-17β-yl) provides a method for the synthesis of the γ-lactone (**137**).

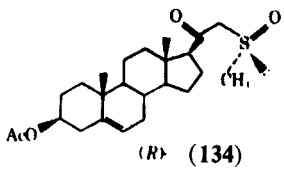
Novel chiral thiosulfinates (**139a**) and (**139b**) have been obtained[53] by treatment of the steroidal episulfoxide (**138**) with alcoholic sulfuric acid. Subsequent reaction of the thiosulfinates with Grignard reagents gave the corresponding sulfoxides (**140a**) and (**140b**).



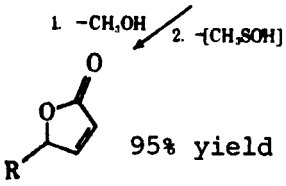
(134) (135)



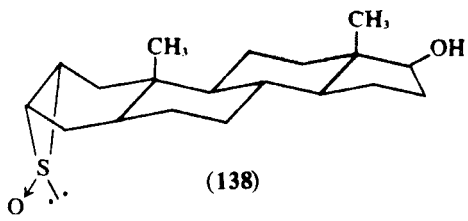
(136)



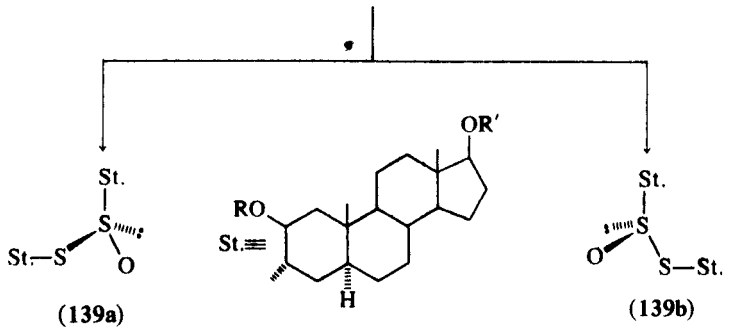
(R) (134)



(137)



(138)



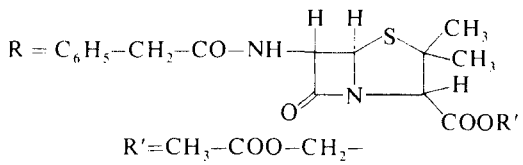
(139a) (139b)

a: R = Me, R' = H
b: R = Me, R' = Ac
c: R = Et, R' = Ac

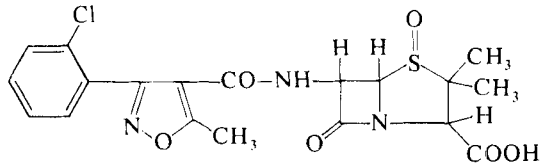
(S)-(140a) (R)-(140b)

F Penicillin and Cephalosporin Sulfoxides and Related Compounds

The continuously expanding research related to all aspects of β-lactam antibiotics is witnessed by the many recent review articles published, some of these are listed at the beginning of this paper. A large number of the reactions studied concern a variety of aspects of penicillin and cephalosporin sulfoxides. This group of compounds constitutes at present the single largest family of chiral sulfur compounds under active investigation. High yields of penicillin and cephalosporin sulfoxides are obtained[54] upon oxidation of the sulfides with polymer supported peroxy acids. A similar selectivity in the course of the oxidation to that of the monomeric oxidating agents is reported. Penicillin G at 40° upon elution through a column containing the resin gave 91% of sulfoxide when the residence time was 30 minutes. Other β-lactam antibiotics such as 6-aminopenicillanic acid and ampicillin have been efficiently oxidized[55] to the respective sulfoxides with peracetic acid. A novel[56] reduction of penicillin and cephalosporin sulfoxides has been reported to take place in the presence of phosphorus pentasulfide. Several unexplored mechanistic possibilities are suggested including oxygen–sulfur exchange followed by spontaneous extrusion of sulfur. X-ray crystallographic have been reported for sulfoxides (**141**) and (**142**).[57,58] The configuration of α- and β-penicillin sulfoxides has been established[59] on the basis of

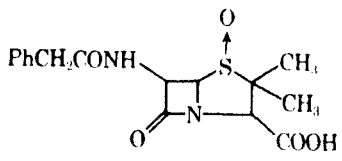


(**141**)

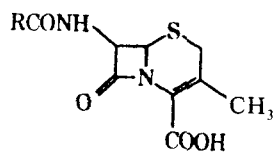


(**142**)

^{13}C magnetic resonance. A clear pattern of changes in the chemical shifts of C-2, -3, -5, -6 and the C-2 methyl groups is observed in a series of sulfide, α-sulfoxide, β-sulfoxide and sulfone. Subsequent to the initial discovery of Morin *et al.*[60] that penicillin sulfoxides can be rearranged into desacetoxycephalosporins, a large number of research groups have further investigated this type of reaction. The efficient rearrangement of the sulfoxides of free acids without concomitant decarboxylation has been reported by two groups. Verweij *et al.*[61] carried out the rearrangement in the presence of trimethylchlorosilane and a weak base such as α-picoline to give a 55% yield of Δ-3 cephalosporin (**144**) and some of (**145**). When the reaction was carried out in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) the isolated yield of Δ-3 cephalosporin rose to 78%. Mikolaczyk *et al.*[62] succeeded in rearranging the sulfoxide free acids in the presence of mildly acidic reagents such as diethyl nitromalonate, phenols, imides, picric acid. Other reagents such as hexafluorobenzene, 1-chloro-2,4-dinitrobenzene also catalyzed the reaction, giving rise to Δ-3 cephems without decarboxylation. Penicillin sulfoxide esters (**146**) and (**148**) have been rearranged[63] when treated with diethyl phosphorycyanidate (DEPC) to give mixtures of cephems (Schemes 18 and 19).

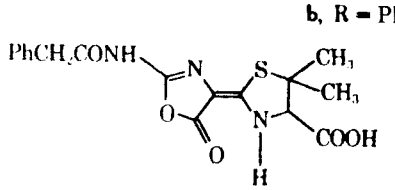


(**143**)

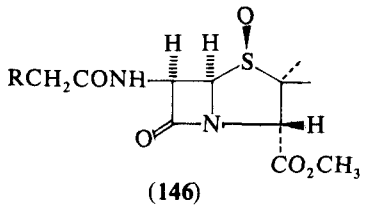


(**144**) a, R = PhCH(NH2)

b, R = $PhCH_2$

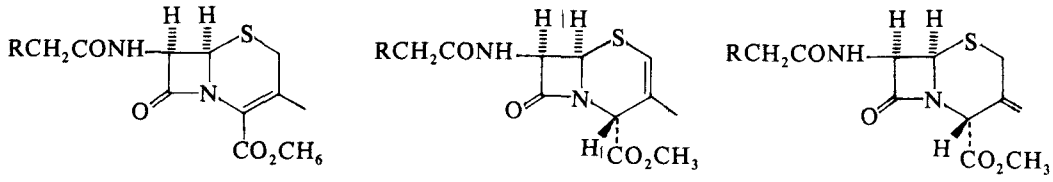


(**145**)



(146)

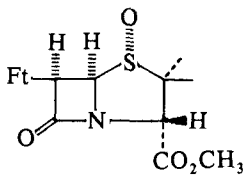
NC.PO $(OEt)_2$ | heat



(147a) (147b) (147c)

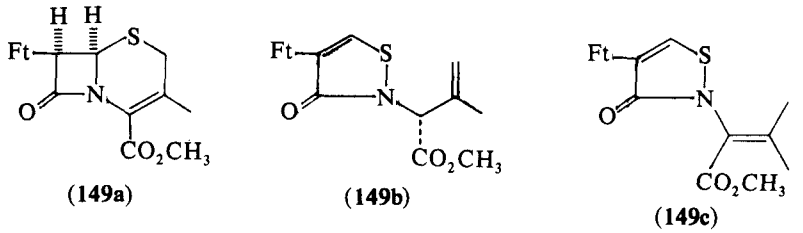
a: R = phenyl
b: R = phenoxy

SCHEME 18



(148)

NC.PO $(OEt)_2$ | heat

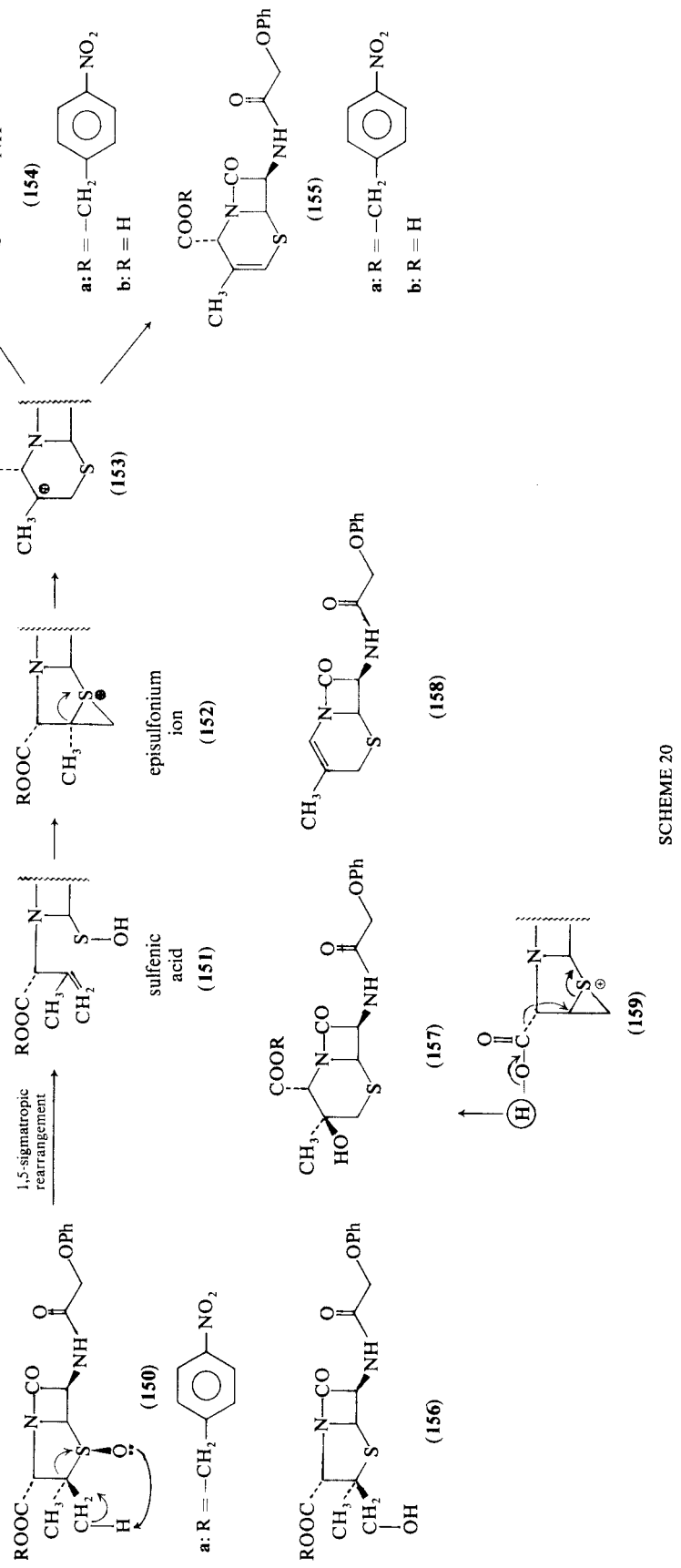


(149a) (149b) (149c)

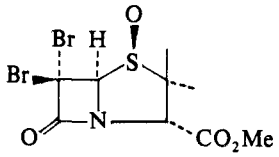
Ft = phthalimido

SCHEME 19

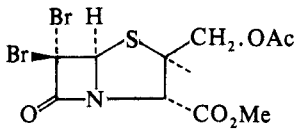
The mechanism of penicillin-(*S*)-sulfoxide rearrangement into Δ-2 and Δ-3 cephems have been explored by Valcavi and Salati.[64] Under a variety of conditions they isolated Δ-2 and Δ-3 cephems derived from a common carbonium ion (**153**); however, no evidence for the formation of hydroxy penam (**156**) and cephem (**157**) was detected. When the reaction was carried out on the free acid the decarboxylated (**158**) was obtained by a concerted rearrangement and decarboxylation of episulfonium ion (**159**) (Scheme 20). In a related study Nayler and coworkers[65] carried out the rearrangement on the sulfoxide (**160**) and isolated a mixture of four products: two epimeric penicillins (**161**), cepham (**162**) and cephem (**163**). Several articles have discussed the behavior of penicillin sulfoxides in the presence of halogenation reagents. Kukolja *et al.*[66] made a detailed study of the reaction of penicillin sulfoxides and thionyl chloride. The initial step involves S—C_2 cleavage with the formation



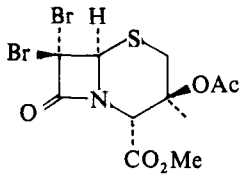
SCHEME 20



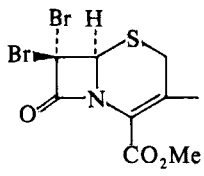
(160)



(161)

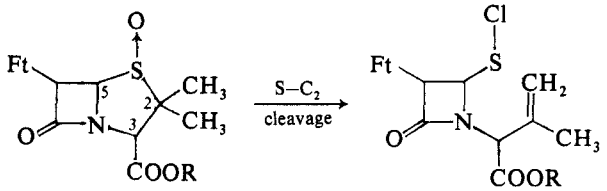


(162)

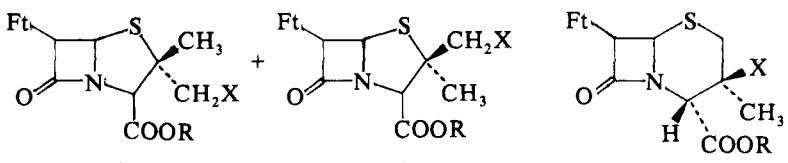


(163)

of the sulfenyl chloride (**165**) which cyclized to the isomeric halopenams (**166a**) and (**167a**). Isomer (**166a**) upon subsequent treatment with silver acetate or silver nitrate gave only penam derivatives (**166b**) and (**166c**) whereas (**167a**) gave penams (**167b**) and (**167c**) as well as cephams (**168a**), (**168b**), (**168c**). The different courses of these reactions are explained in terms of two isomeric thiiranium ions (**169**) and (**170**) where (**169**) is only loosely stabilized and short lived and is selectively attacked by the nucleophile (acetate or nitrate) to give only product (**166b**) or (**166c**), whereas (**170**) is much more stable allowing the formation of both penam and cepham products. The authors further suggest that the intermediate thiiranium ion might be a common intermediate in the biosynthesis of penicillin N and cephalosporin C.



(164) (165)

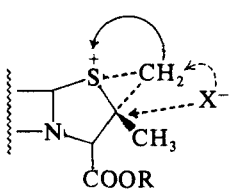


(166) (167) (168)

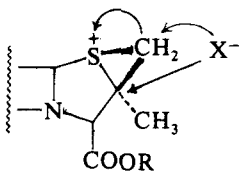
a: X = Cl
b: X = OAc
c: X = ONO_2

a: X = Cl
b: X = OAc
c: X = ONO_2

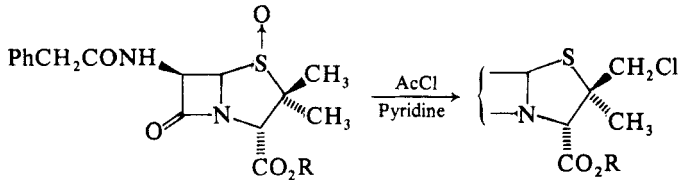
a: X = OAc
b: X = ONO_2
c: X = Cl



(169)



(170)



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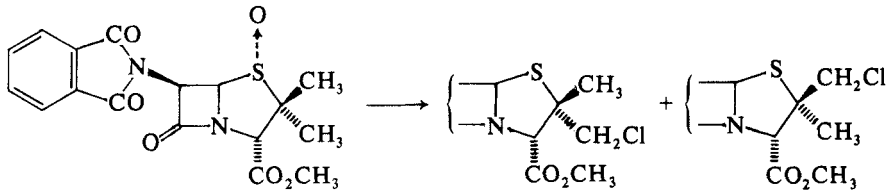
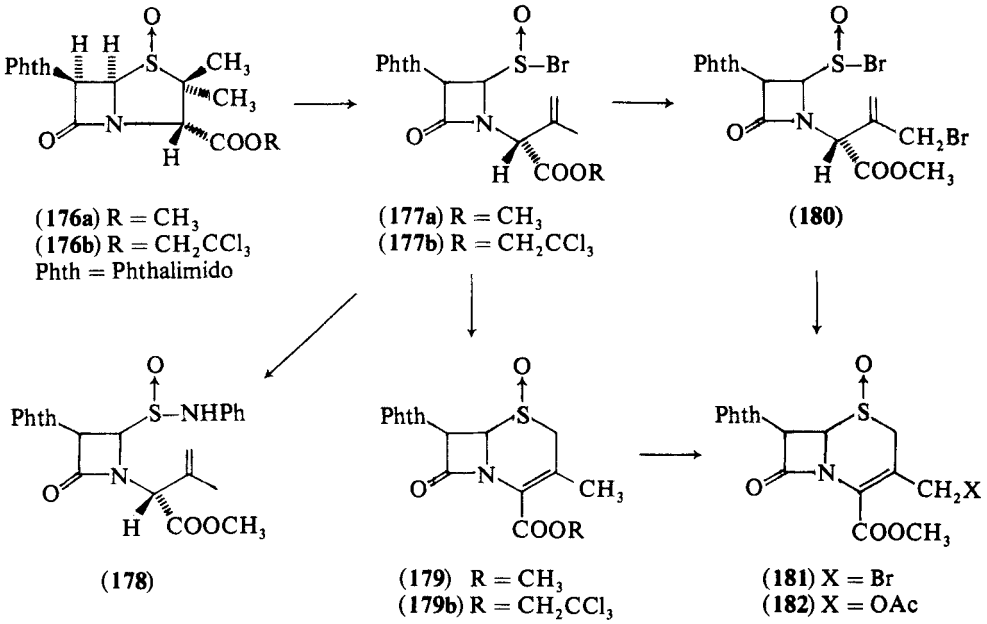


(173) (174) (175)

Similar halopenam products have been obtained[67] upon treatment of sulfoxides (**171**) and (**173**) with acetyl chloride in pyridine. Halogenation reagents such as *N*-bromosuccinimide (NBS) when reacted with penicillin sulfoxides (**176**) gave[68] the corresponding sulfinyl bromides (**177**). These could be converted to the amides (**178**) or cyclized to sulfoxi-cephems (**179**). Moreover (**177**) were converted to the bromomethyl derivatives (**180**) in the presence of NBS and benzoyl peroxide. Cyclization of (**180**) gave the corresponding 3-bromomethyl-cephem sulfoxides (**181**) which upon treatment with silver acetate gave the acetoxy derivative (**182**) in 45% yield. The sulfinyl halides (**183**) derived from penicillin sulfoxides have also been used[69] in the synthesis of novel tricyclic cephalosporins (**187**)–(**189**), in addition to sulfoxide (**186**). Reduction of (**187**) and (**189**) followed by removal of the phthalimido protecting group and reacylation with phenyl acetyl chloride gave antibacterial products (**190**) and (**191**). In a parallel study Kukolja *et al.*[70] have shown that the sulfinyl halide may be cyclized to the cephalosporin sulfoxide (**194**) which contains an exocyclic methylene. The reaction is carried out in the presence of $SnCl_4$ by an intramolecular ene reaction (**195**). It was also shown that the β-methyl group subsequently becomes the exocyclic methylene in the product (Scheme 21). Cephalosporins having an exocyclic methylene group have proven to be very important intermediates in the synthesis of microbiologically active compounds[71] (**200a**) and (**200b**).



(**176a**) R = CH_3
(**176b**) R = CH_2CCl_3
Phth = Phthalimido

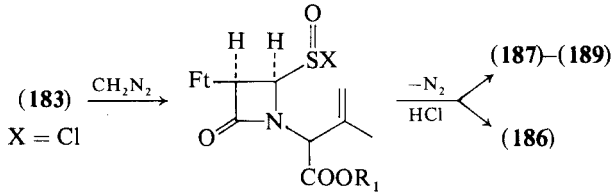
(**177a**) R = CH_3
(**177b**) R = CH_2CCl_3

(**180**)

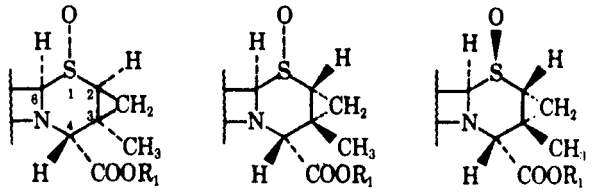
(**178**)

(**179**) R = CH_3
(**179b**) R = CH_2CCl_3

(**181**) X = Br
(**182**) X = OAc

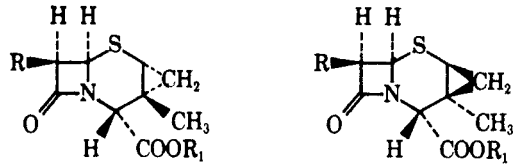


(**184**) X = CHN_2
(**185**) X = CH
(**186**) X = CH_2Cl

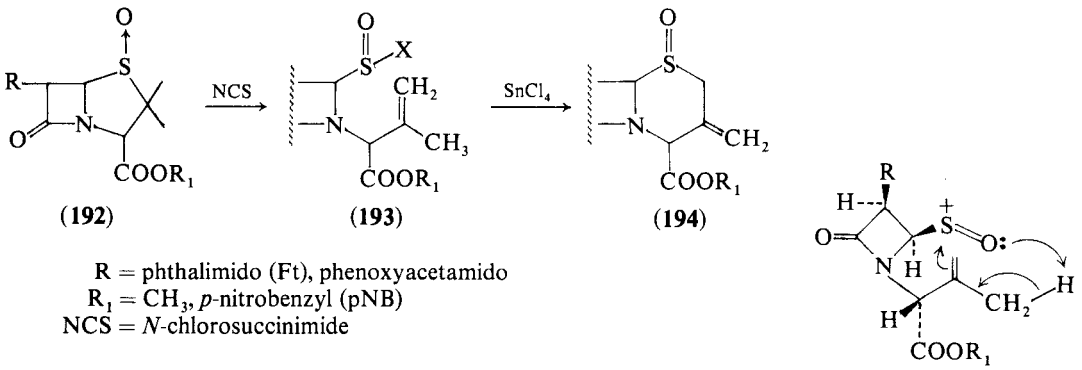


(**187**) (**188**) (**189**)

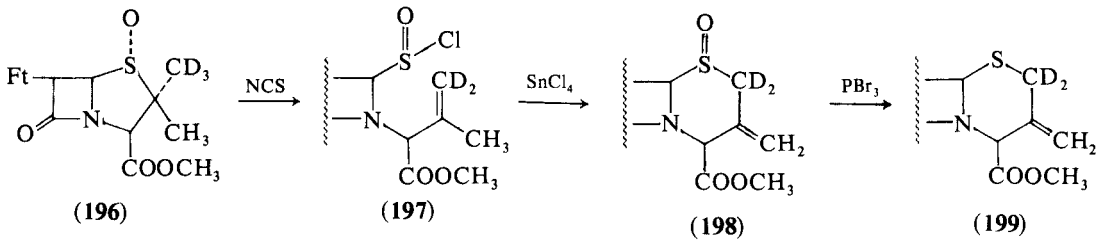
Ft = phthalimido, R_1 = *p*-nitrobenzyl (pNB)



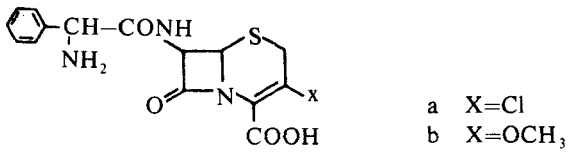
(**190**) R = $PhCH_2CONH$, R_1 = H (**191**) R = $PhCh_2CONH$, R_1 = H



R = phthalimido (Ft), phenoxyacetamido
R_1 = CH_3, *p*-nitrobenzyl (pNB)
NCS = *N*-chlorosuccinimide

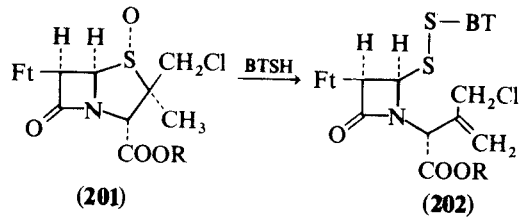


SCHEME 21

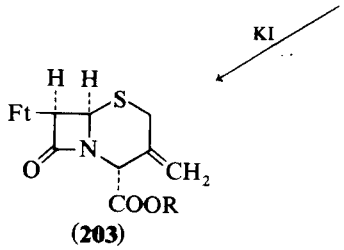


a X=Cl
b X=OCH$_3$

(200)

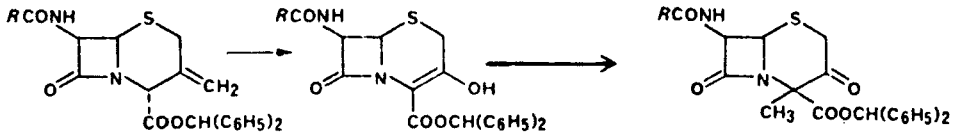


(201) (202)

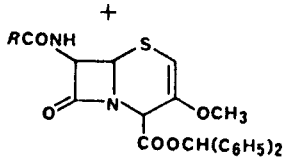


(203)

Other routes[72] for the synthesis of exocyclic methylene cephams also involve penicillin sulfoxides. The intermediate (**202**) was obtained from 2β-chloromethyl penam-1-(*R*)-sulfoxide (**201**) which was cyclized to (**203**) upon treatment with potassium iodide in acetone. Ozonolysis of the exomethylene cephams[73] provided the 3-hydroxy cephems (**205**) which upon subsequent methylation gave a mixture of (**206**) and (**207**). Compound (**207**) was isomerized to the Δ3-compound (**208**) via the sulfoxide (**209**).



(204) (205) (206)



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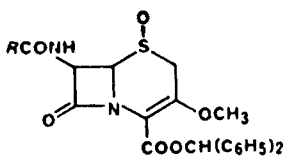

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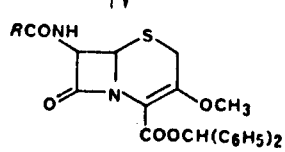
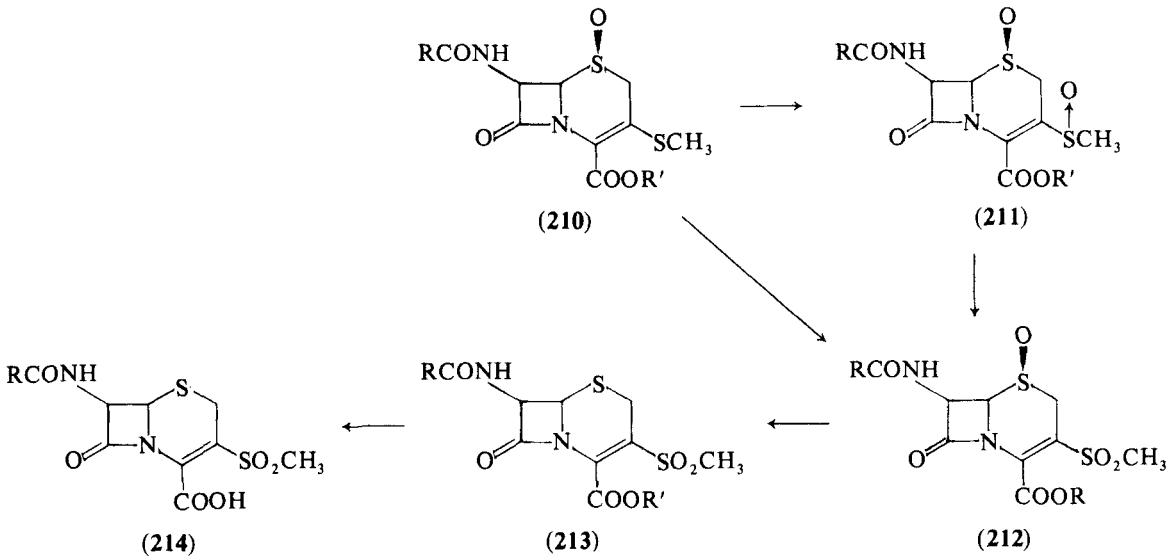
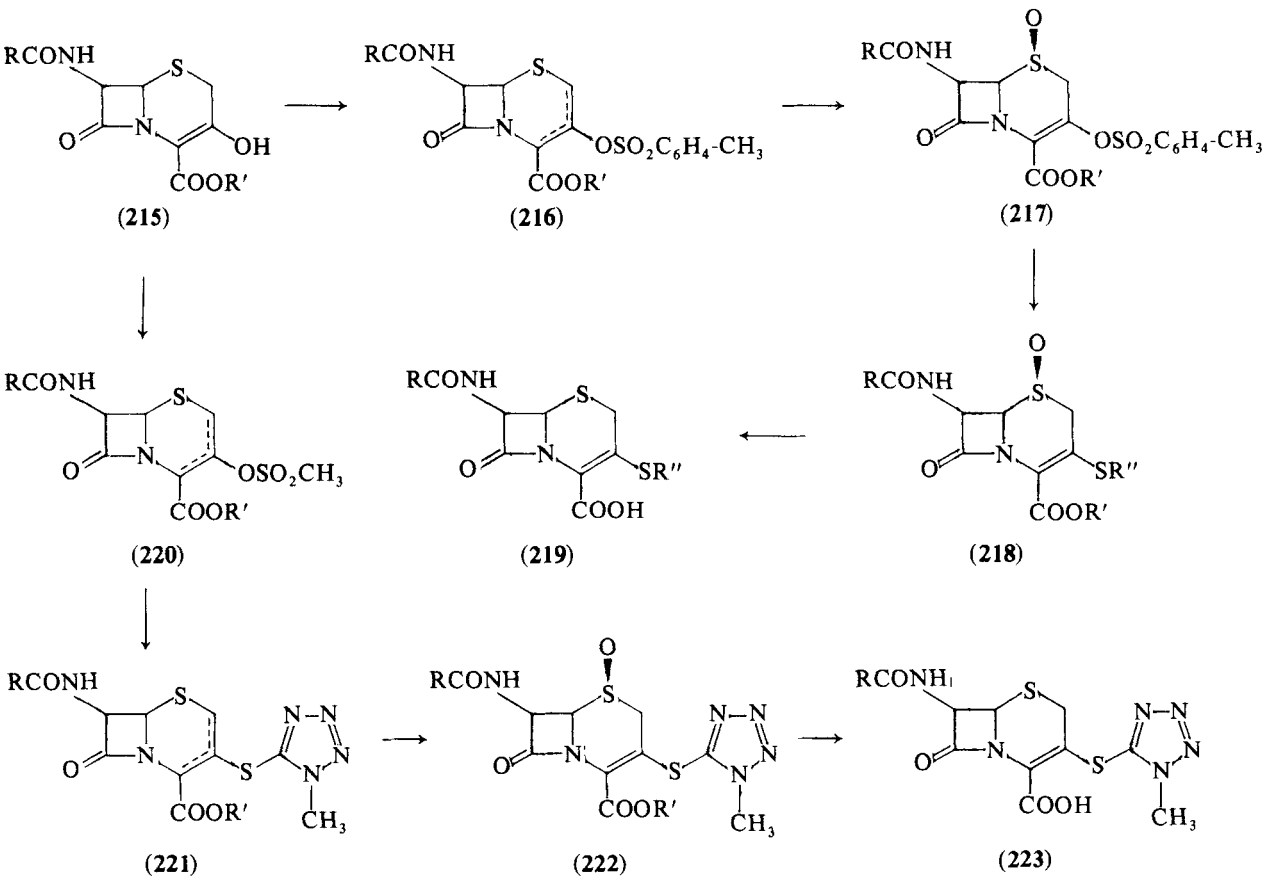


(208)



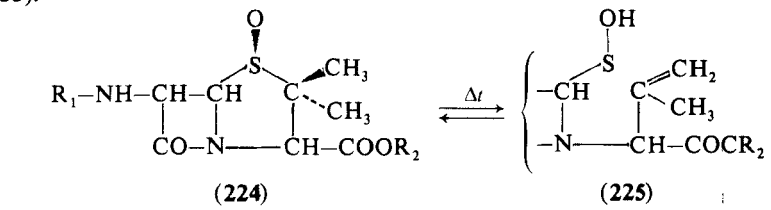
SCHEME 22

Other 3-heterosubstituted cephems (**213**), (**218**), (**222**) were prepared[74] via the corresponding sulfoxides (Schemes 22 and 23).

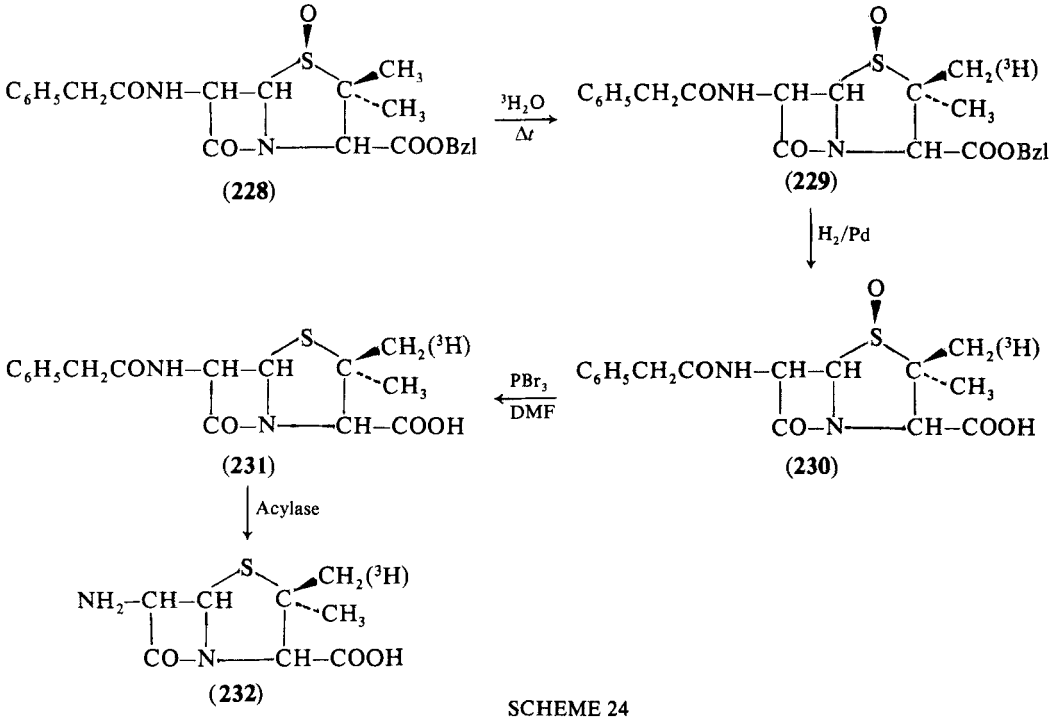


SCHEME 23

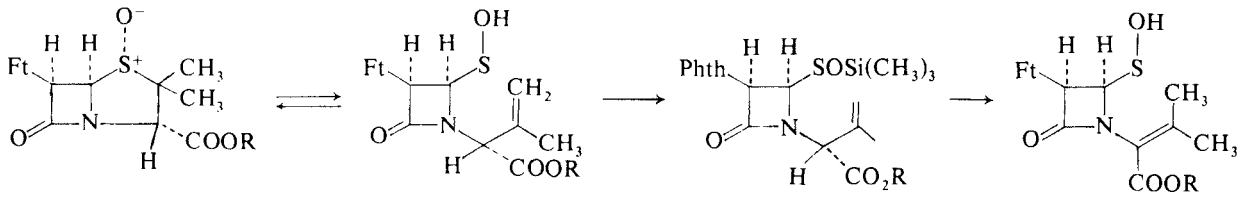
It has been well established that penicillin sulfoxides are in thermal equilibrium with sulfenic acids. This has been previously shown by incorporation of deuterium into the 2-β-methyl group (**227**). A similar method has been used[75] for the preparation of tritiated 6-aminopenicillanic acid, (**232**) (Scheme 24). The first example of the isolation of a sulfenic acid has been described by Chou *et al.*[76] Thermolysis of (**233**) in ethyl acetate gave after crystallization a 60% yield of starting sulfoxide and 10% of the crystalline sulfenic acid (**234**) mp 152–153°. It was also shown[77] that this sulfenic acid can be trapped and thus protected when generated in the presence of a silylating agent. Furthermore, the isomeric sulfenic acid (**236**) may be obtained upon mild hydrolysis of the silyl ester, (**235**).



$R_1 = C_6H_5CH_2CO-$ or $C_6H_5OCH_2CO-$
$R_2 = C_6H_5CH_2-$ or CH_3-

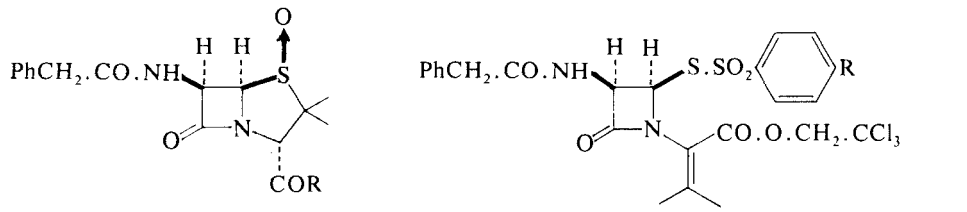


SCHEME 24

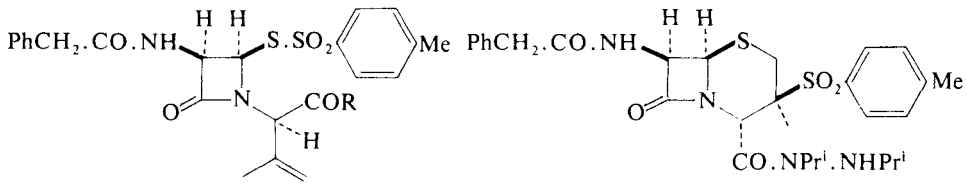


(233) (234) (235) (236)

The versatility of the reagents capable of trapping sulfenic acids obtained from penicillin sulfoxides has been discussed previously.[1c] Many of these trapped sulfenic acids have been used in subsequent reactions. Barton *et al.*[78] obtained thiosulfonates (**238**) (R = OCH_2CH_3) and (**239a**) (R = $NMeNMe_2$) or (**239b**) (R = NiPrNHiPr) upon thermolysis of (**237**) in the presence of toluene or *p*-methoxybenzenesulfinic acids. Compound (**239b**) was accompanied by (**240**). In an extension of earlier work Sammes and coworkers[79] have shown that thermolysis of (**241a**) (R = OCH_2CCl_3) with dimethyl butynedioate gave two inseparable compounds which upon further reduction of the sulfoxide function gave (**243**), but in the presence of triethylamine or alumina gave (**242**). When (**241b**) (R = OCH_3) was thermolyzed under similar conditions, sulfoxides (**244**) and (**245**) were obtained. The former isomer was unstable and cyclized to (**242**) whereas (**245**) isomerized to (**246**). When (**241**) was thermolyzed in the presence of ethyl propiolate it gave two isomers. The major component (**247**) isomerized to (**248**) when treated with triethylamine. Subsequent ozonolysis of (**248**) gave (**249**) which decomposed upon attempted hydrolysis, whereupon the *β*-lactam ring was destroyed. Ozonolysis of (**244**) and (**245**) followed by triethylamine or silica treatment gave sulfoxide (**250**) as a mixture of epimers at position 4. When the trapping reaction was carried out on (**241c**) (R = NiPrNHiPr) the respective (**244c**) and (**245c**) were isolated, which were unaffected by triethylamine. Ozonolysis of (**244c**) gave (**251**). The Michael-type addition of diethylsodiomalonate on (**245c**) and (**252**) similarly with ethylsodioacetate (**253**) was obtained. The latter compound reacted with diazomethane to form (**254**) (R = NiPrNHiPr). Subsequent oxidation of the hydrazide function with lead tetra-acetate gave the acids (**254**) (R = OH) which were esterified with diazomethane to (**255**). Further ozonolysis of (**255**) followed by hydrolysis of the oximide (**256**) gave (**257**). Reduction of (**257**) with phosphorus tribromide gave (**258**). In another series of reactions, sulfoxide (**259**) was treated as before with dimethyl butynedioate. The major product was not (**260**) but (**261**), whose formation is explained as indicated in formula (**260**). Four products (**262**), (**263**), (**264**) and (**265**) were isolated from the thermal rearrangement of (**259**) in the absence of trapping agent. The latter two are formed from (**266**). Selective ozonolysis of (**261**) gave (**267**) whereas osmylation followed by treatment with sodium disulfite gave (**268**).



(237) (238)



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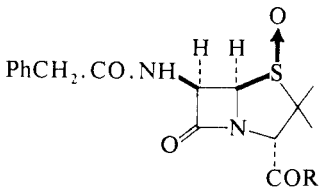

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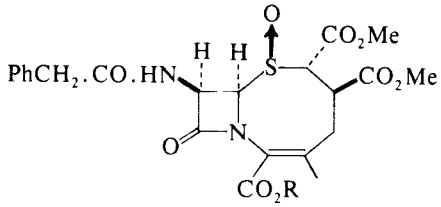

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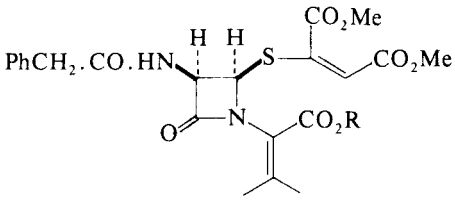

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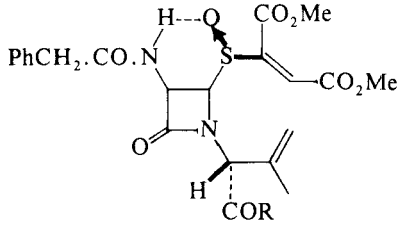

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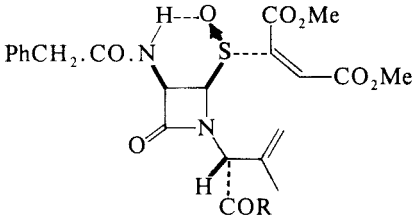

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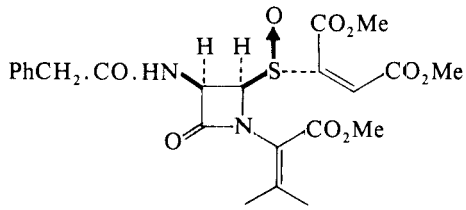

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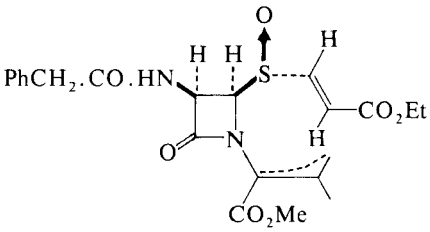
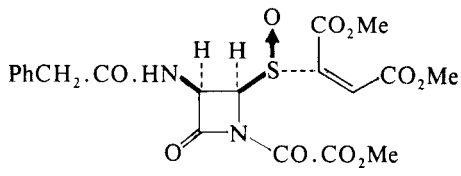


(247) $\beta\gamma$-isomer
(248) $\alpha\beta$-isomer



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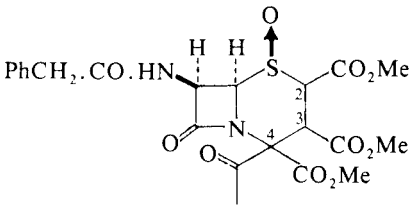

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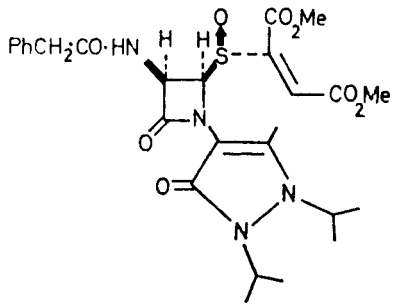

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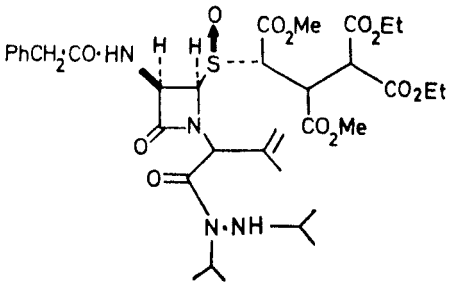

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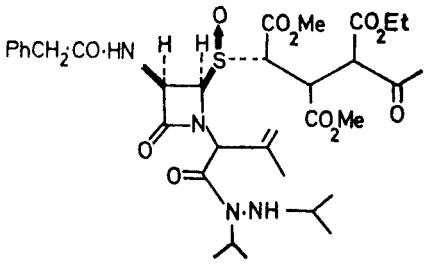

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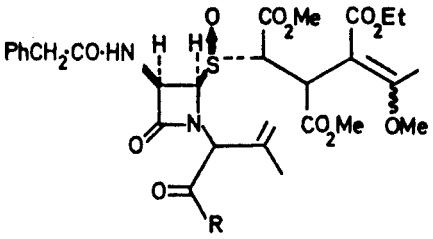

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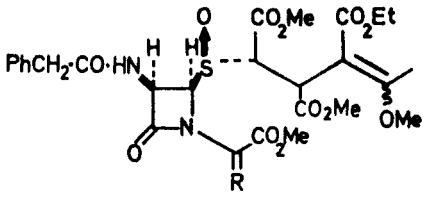
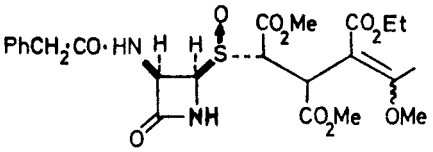


(255) R = Me_2C
(256) R = O



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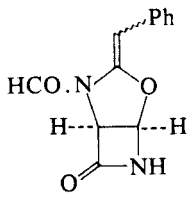

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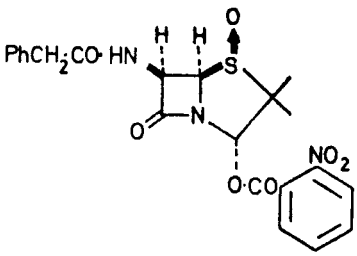

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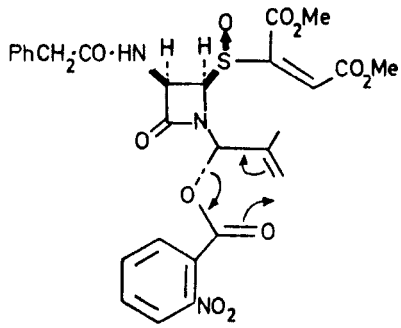

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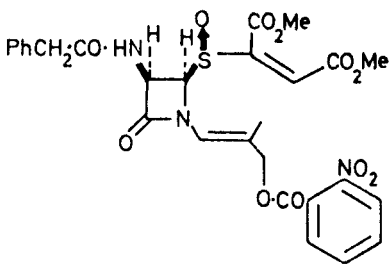

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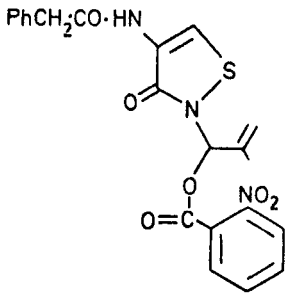

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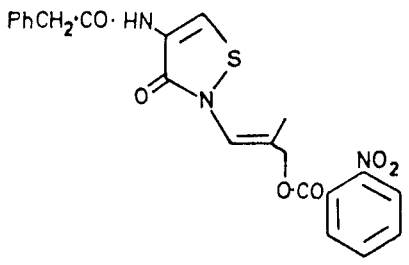

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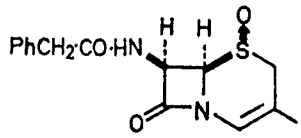

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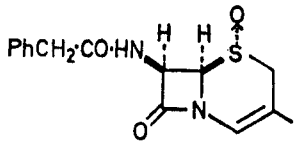

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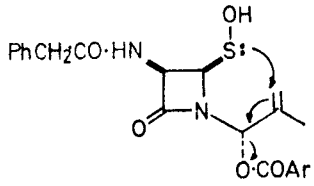

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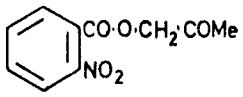

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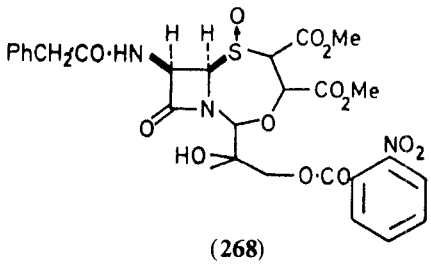
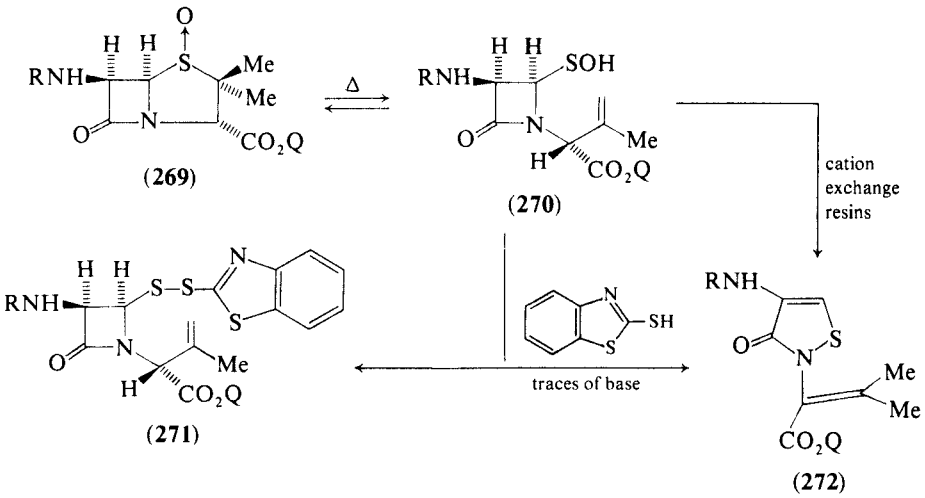
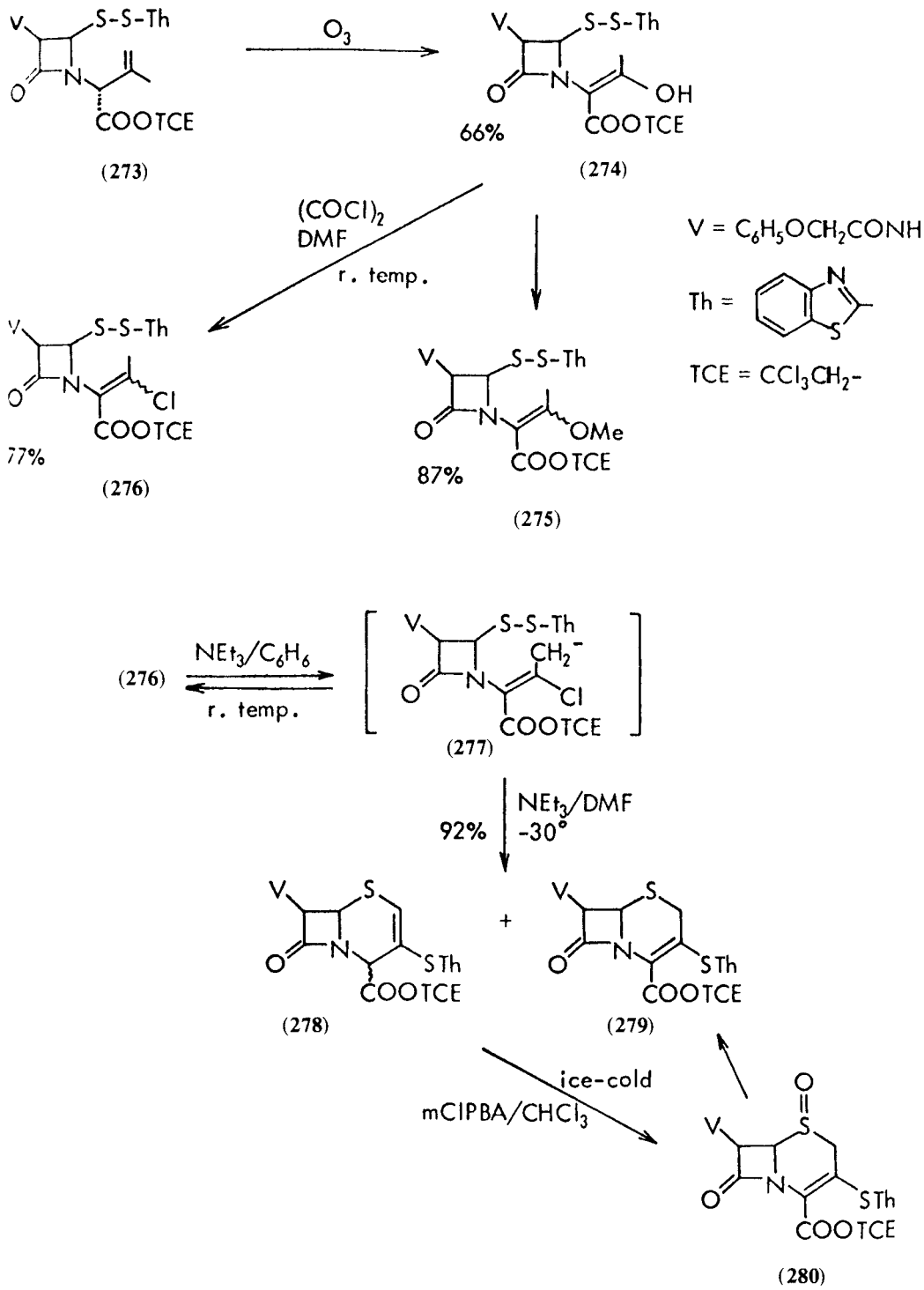


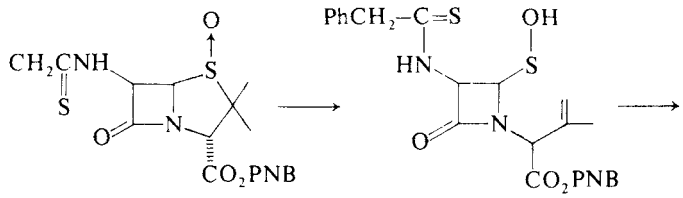
(268)

2-Mercaptobenzothiazole is one of the most frequently used trapping agents for sulfenic acids. In the absence of base, sulfoxides (**269**) reacted[80] with 2-mercaptobenzothiazole to form the disulfides (**271**), whereas in the presence of base, the isothiazolones (**272**) were obtained. Azetidinone disulfide (**273**) when ozonolyzed afforded ester (**274**) which was converted into (**275**) and (**276**) when treated with diazomethane or oxalyl chloride respectively. In the presence of triethylamine (**276**) gave mixtures of (**278**) and (**279**).[81] Oxidation of (**278**) gave sulfoxide (**280**) which was reduced to cephem (**279**).



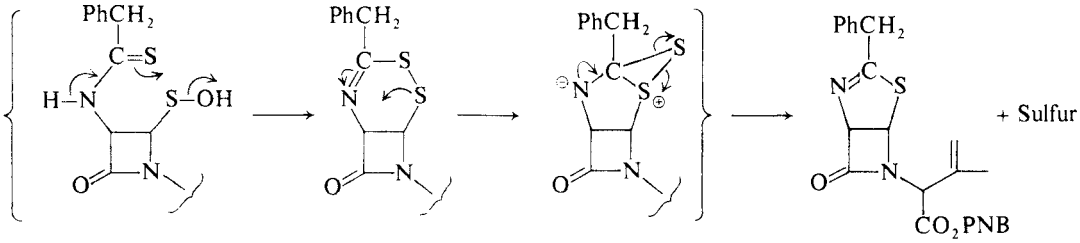
(269) (270) (271) (272)





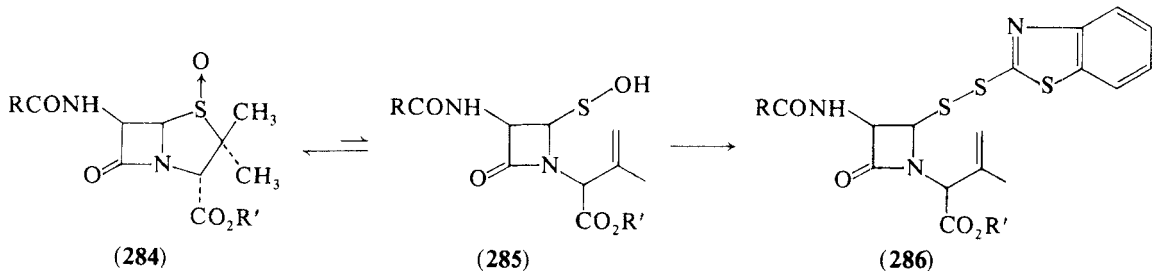
(281) (282)

PNB: pNO$_2$.C$_6$H$_5$.CH$_2$–

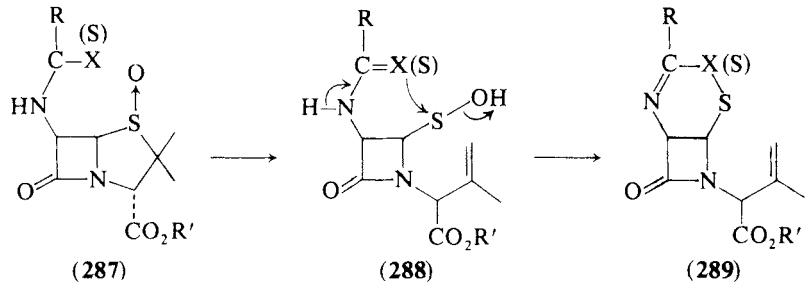


(283)

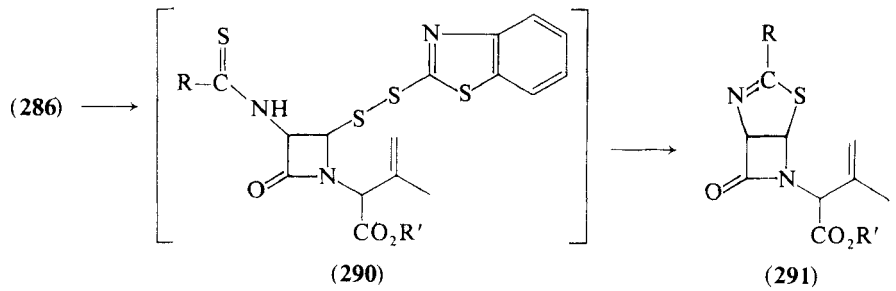
SCHEME 25



(284) (285) (286)

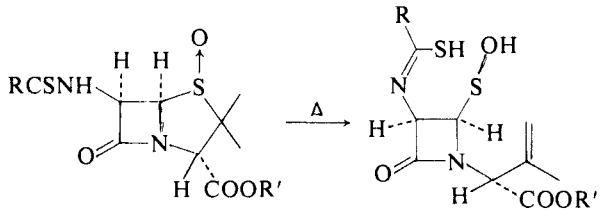


(287) (288) (289)

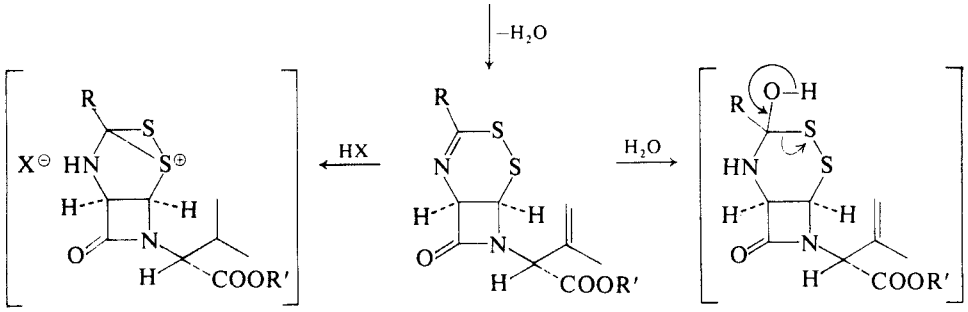


(290) (291)

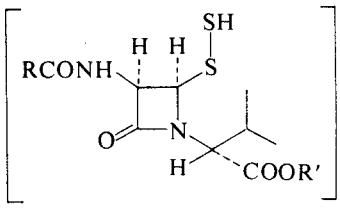
SCHEME 26



(292) (293)



(294a) (294) (295)



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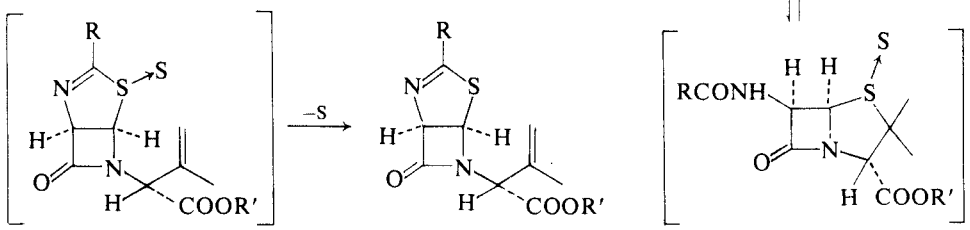
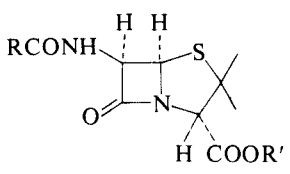
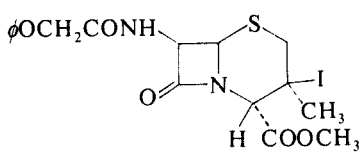


(300) (299) (297)

R	R′
a: ϕOCH_2	CH_3
b: ϕO	CH_3
c: ϕO	H
d: CH_3S	CH_3



(298)



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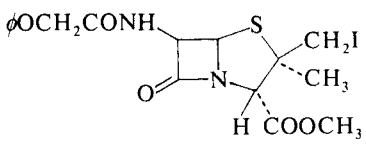
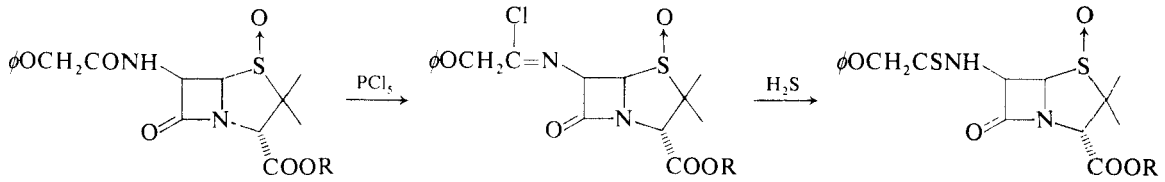


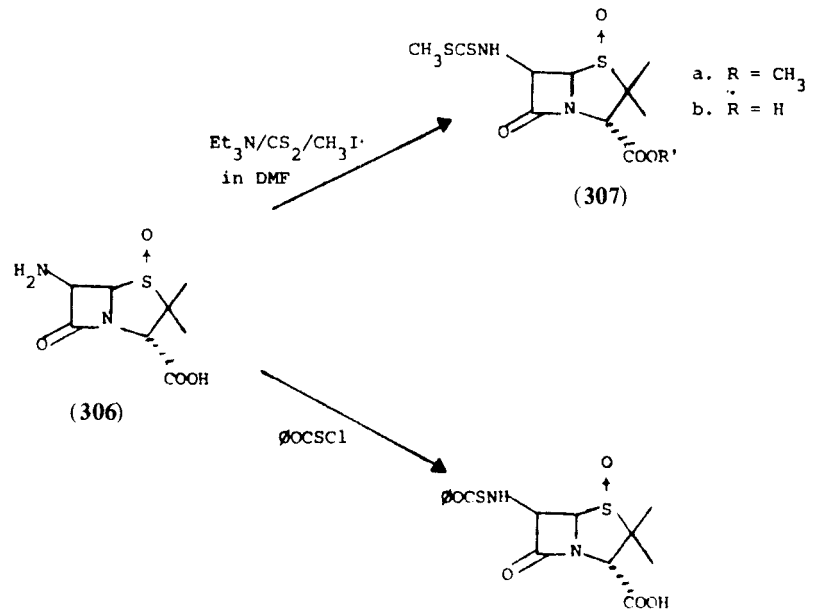
(302)

A new[82] intramolecular trapping of a sulfenic acid has been observed when sulfoxide (**281**) was thermolyzed to give (**283**). The reaction involved dehydration and sulfur extrusion steps (Scheme 25). An analogous sulfur extrusion reaction[83] was observed when the disulfide (**286**) was treated with P_2S_5 to give (**291**) (Scheme 26). Micetich *et al.*[84,85] reported the isolation of the disulfide intermediate (**294**) prior to the sulfur extrusion. The stability of (**293**) depended on the R group, thus (**294b**) (R = $C_6H_5OCH_2$) and (**294c**) (R = C_5H_5O) were recrystallized without decomposition. But (**294a**) rearranged to (**298**) and (**299**) via the indicated sulfur extrusion of the thiosulfoxide intermediates (**297**) and (**300**). The disulfide (**294**) was further used in the synthesis of 3-iodo cephams (**301**) and iodo penams (**302**).[86]



(**303**) (**304**) (**305**)

a: R = CH_3, *b*: R = $Si(CH_3)_3$, c: R = H

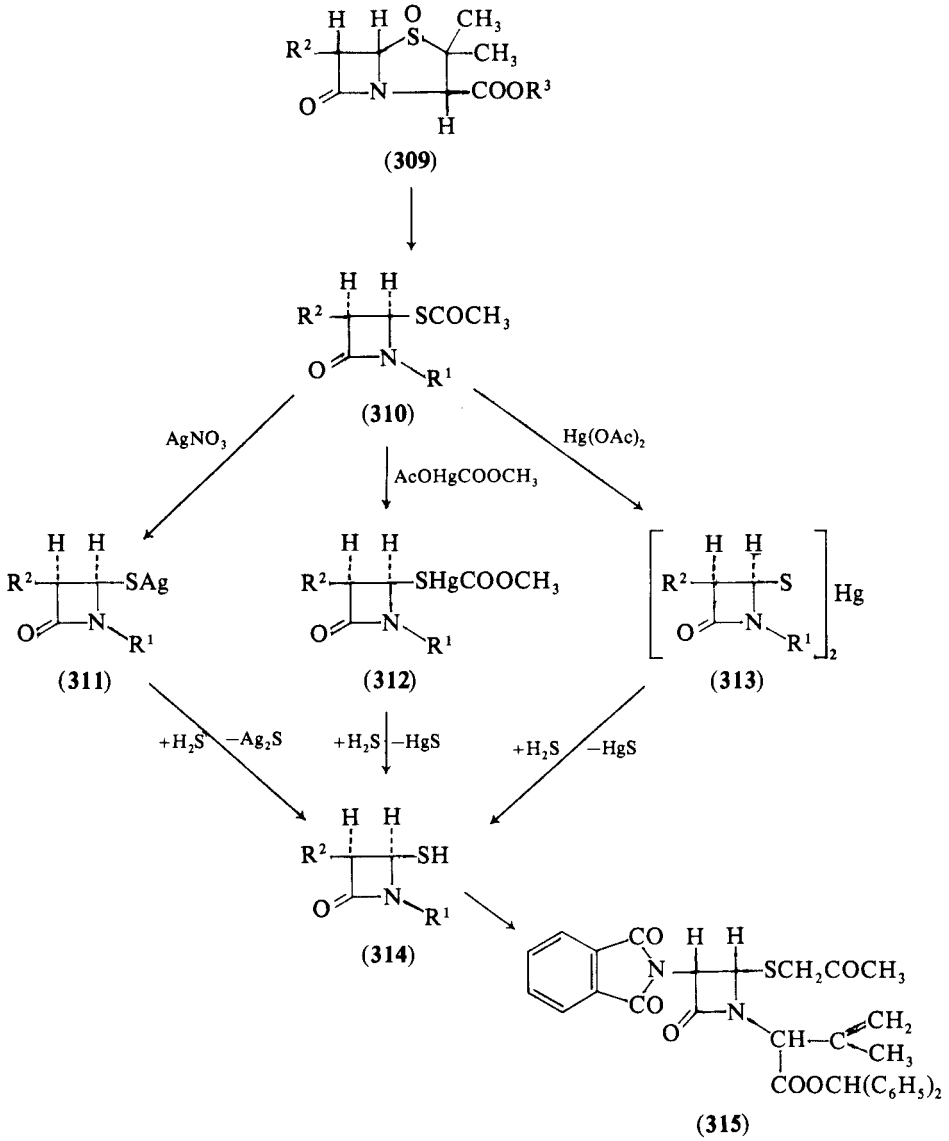


(**307**)

(**306**)

(**308**)

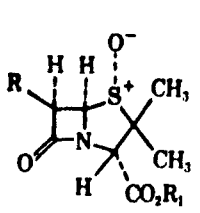
Other 6-thioamides (**305**) and 6-thiocarbamates (**307**) and (**308**) of penicillin sulfoxides have been reported.[86] Other trapping experiments have led[87] to the formation of (**310**) upon thermal rearrangement of sulfoxide (**309**) in the presence of triethylphosphite and acetic anhydride. Compound (**310**) has been subsequently used in the synthesis of (**314**) and (**315**). A unique intermolecular trapping reaction[88] between two molecules of sulfenic acid (**318**) gave thiosulfinate (**319**). The sulfenic acid (**318**) (R_2 = H) was obtained upon aqueous hydrolysis of its trimethylsilyl ester (**318**) (R_2 = Me_3Si). The thiosulfinate (**319**) on brief heating or prolonged standing, produced the novel thioxo-β-lactam (**320**). The isomeric (**321**) was also prepared via trapping of sulfenic acid with *n*-pentyl mercaptan to give (**322**) which was oxidized to (**328**) and then thermally decomposed to (**321**).



Sulfenic acids have also been postulated by Baldwin and coworkers[89] in their total synthesis of penicillin G. The procedure used involved first the stereospecific preparation of sulfoxide (**324**), its rearrangement to (**325**), Epoxidation of (**325**) to (**326**) followed rearrangement to (**327**) which was oxidized to a mixture of diastereomeric sulfoxides which upon thermal syn-elimination gave only one stereoisomeric sulfenic acid which cyclized to (**328**).

In an analogous synthesis, the intermediacy of a sulfenic acid has also been proposed[90] in the course of the free radical catalyzed rearrangement of sulfoxide (**330**) to penicillin sulfoxide (**332**). The sulfoxide (**330**) was prepared by oxidation of the corresponding thiazoline (**329**).

The process for Δ-2→Δ-3 isomerization of cephems which involves (a) oxidation of the 2-cephem to the sulfoxide, (b) isomerization of the double bond Δ-2 to Δ-3 and (c) reduction of the Δ-3-cephem sulfoxide to the sulfide was used by Bickel and coworkers[91] in their preparation of 3-carboxycephems, (**342**), (**348**), (**353**) (Schemes 27 and 28). The sequence was also used[92] in the synthesis of 3-fluoromethyl-Δ-3-cephem (**358**) (Scheme 29).



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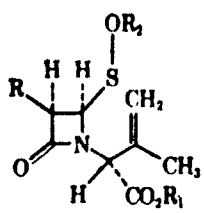

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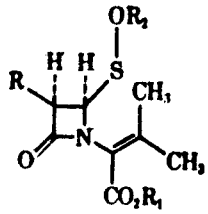

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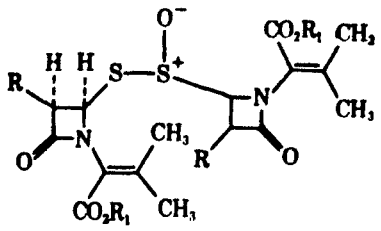

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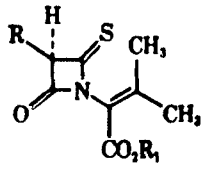

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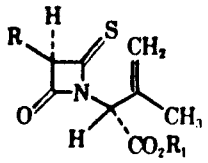

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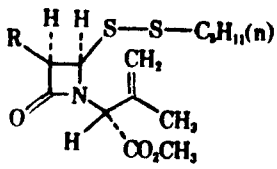

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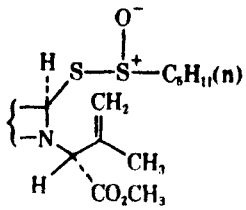
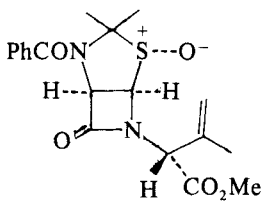


(323)

R = phthalimido
R_1 = CH_3, *p*-nitrobenzyl (*p*-$NO_2C_6H_4CH_2$), H, trimethylsilyl (Me_3Si)
R_2 = H, Me_3Si



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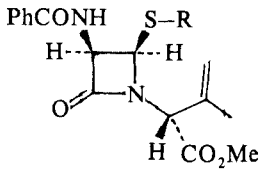
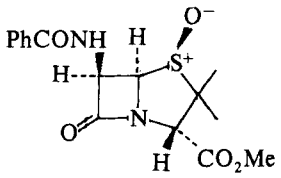


(325) R = $-CH_2\overset{O}{\overset{\|}{C}}CH_3$

(326) R = $-CH_2\overset{O-CH_2}{\overset{\diagdown\diagup}{C}}CH_3$

(327) R = $-CH_2\overset{CHO}{\overset{|}{C}}CH_3$ (H)



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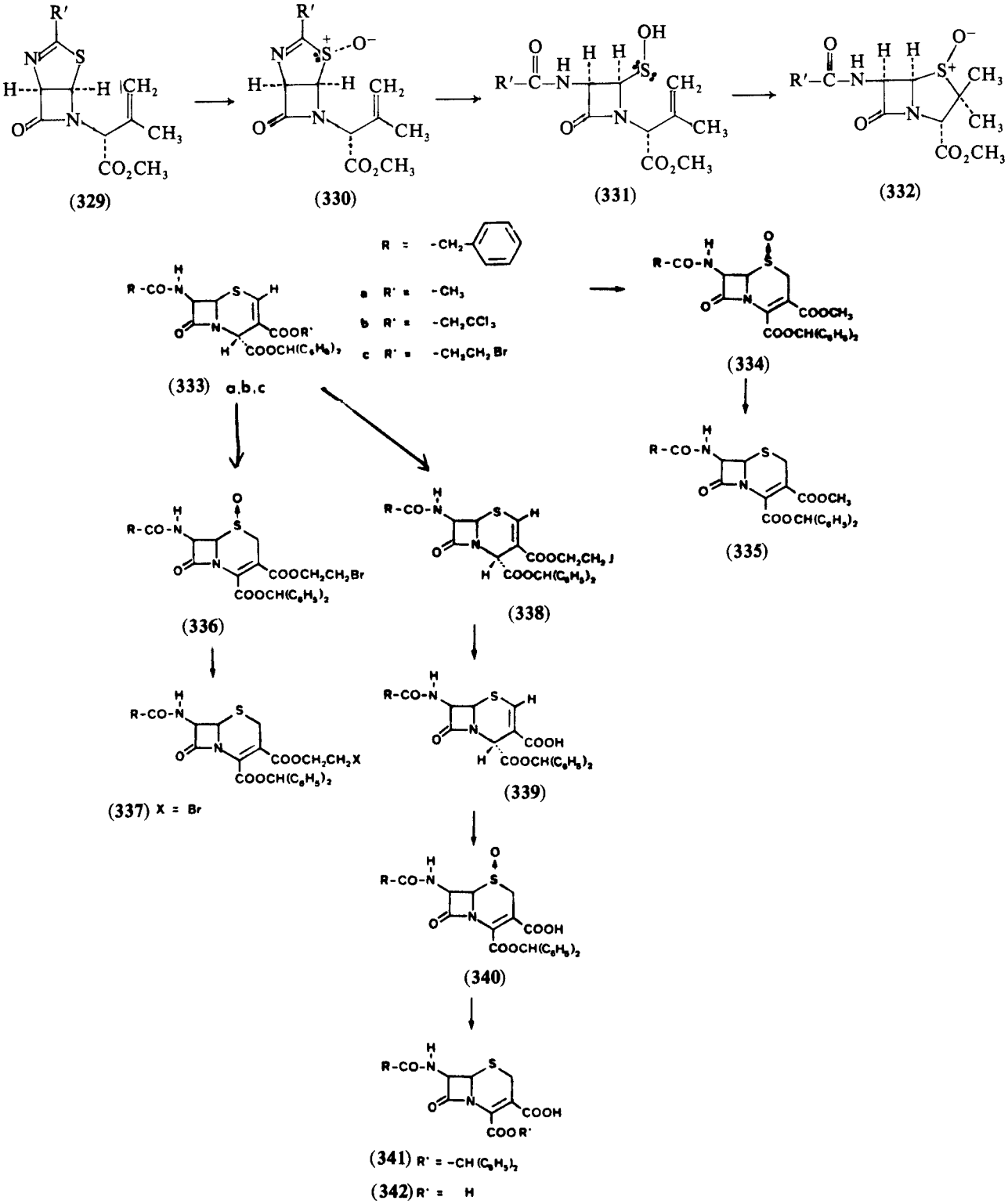
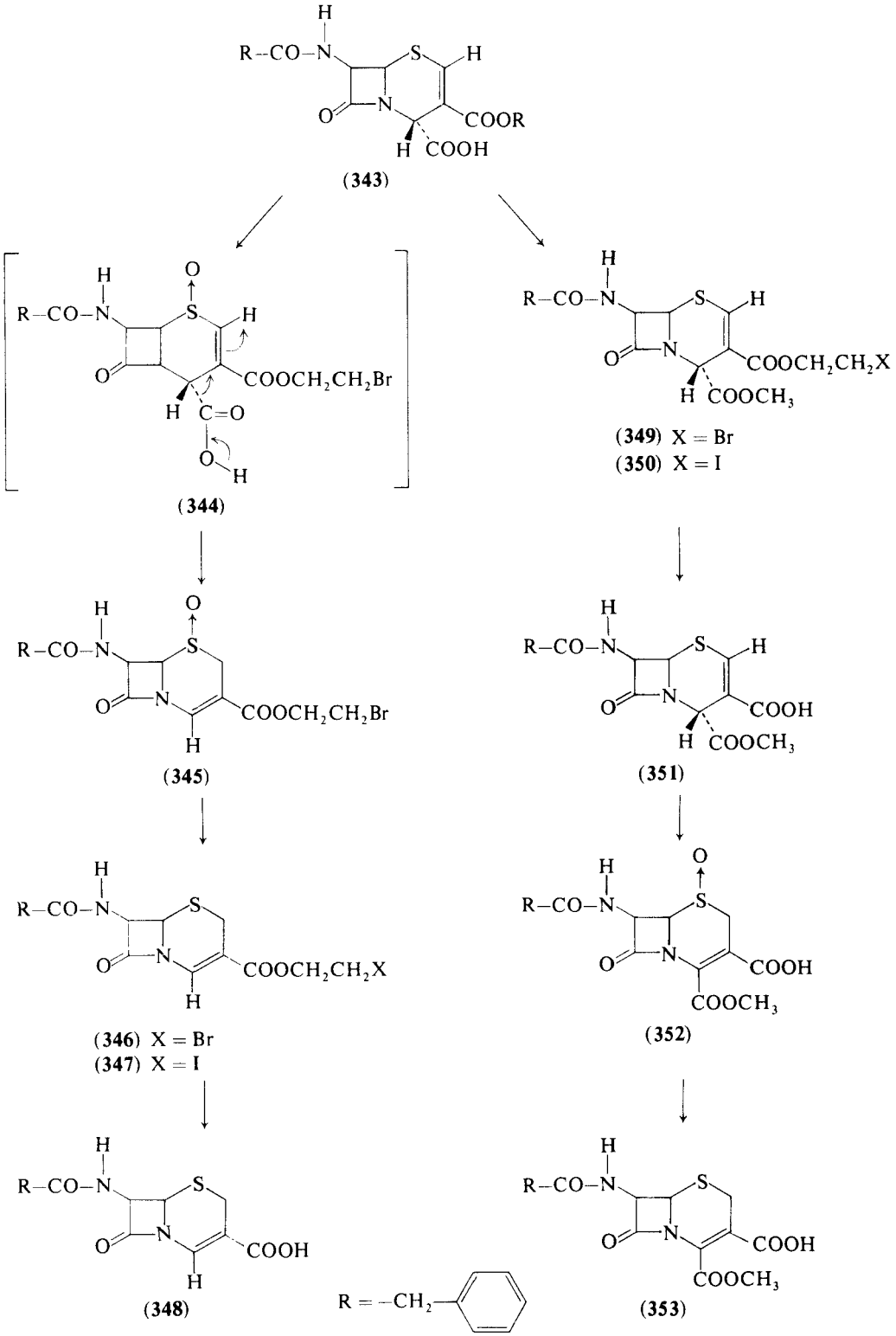
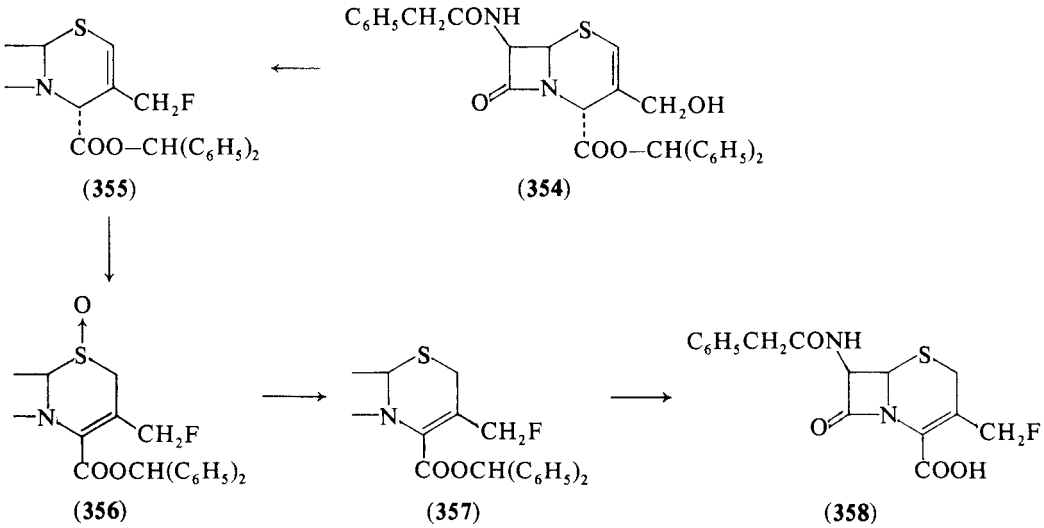


SCHEME 27

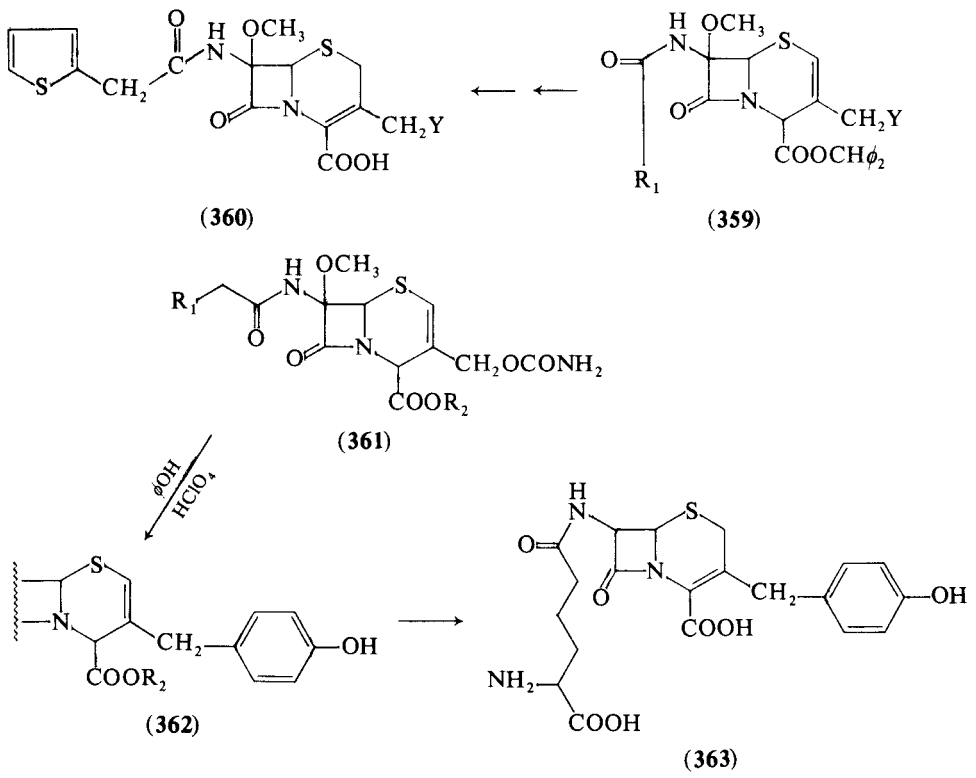


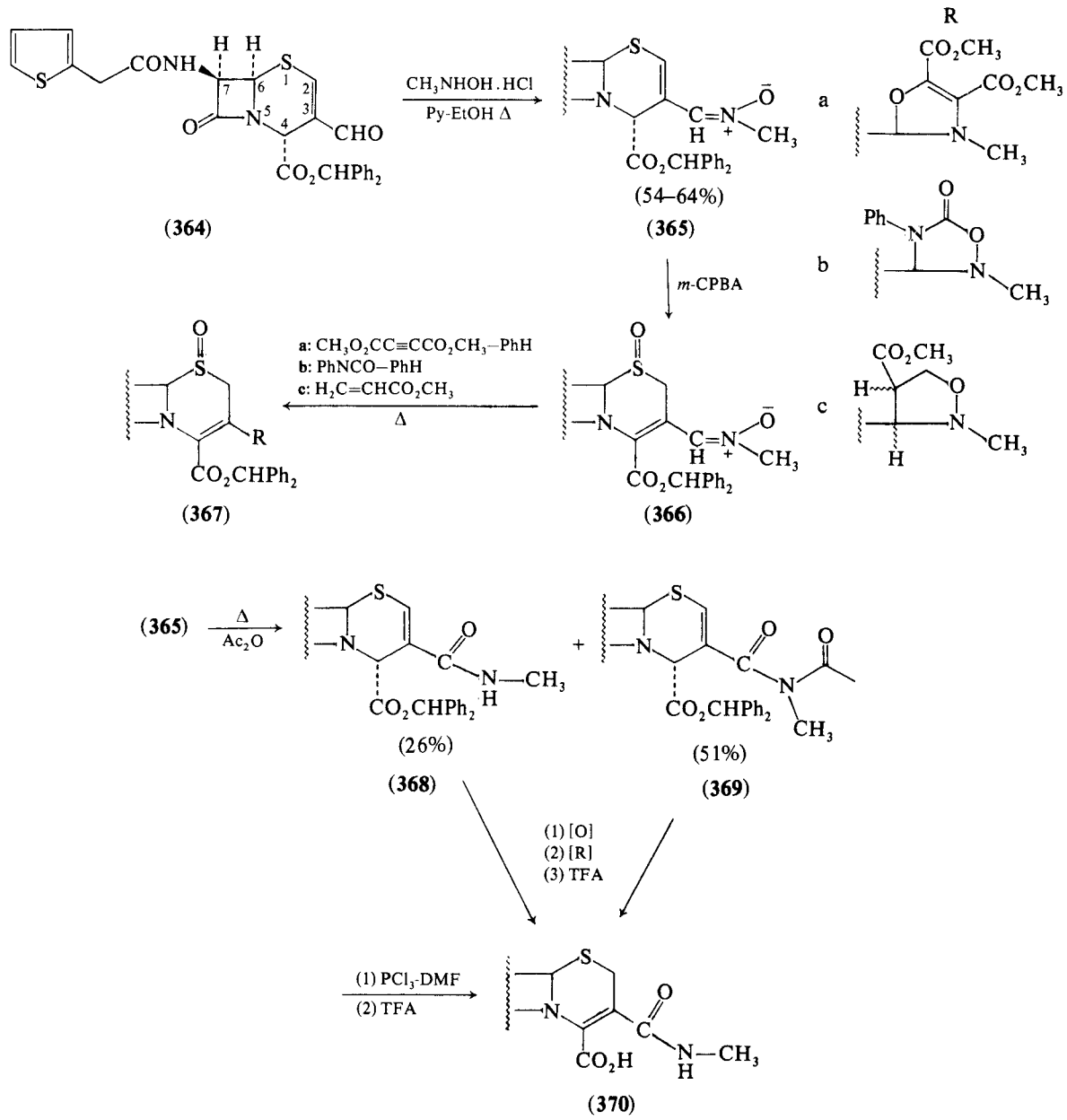
SCHEME 28



SCHEME 29

The active antibiotics (**360**) were obtained[93] from the corresponding cephems (**359**) by this process. Other cephamycin derivatives were treated analogously.[94] The phenolic cephem (**362**) prepared from (**368**) upon treatment with phenol and perchloric acid was isomerized via the sulfoxide to compound (**363**). Novel cephem-*N*-methylnitrones (**365**) have been reported[95] to undergo concomitant sulfur oxidation and Δ-2→Δ-3

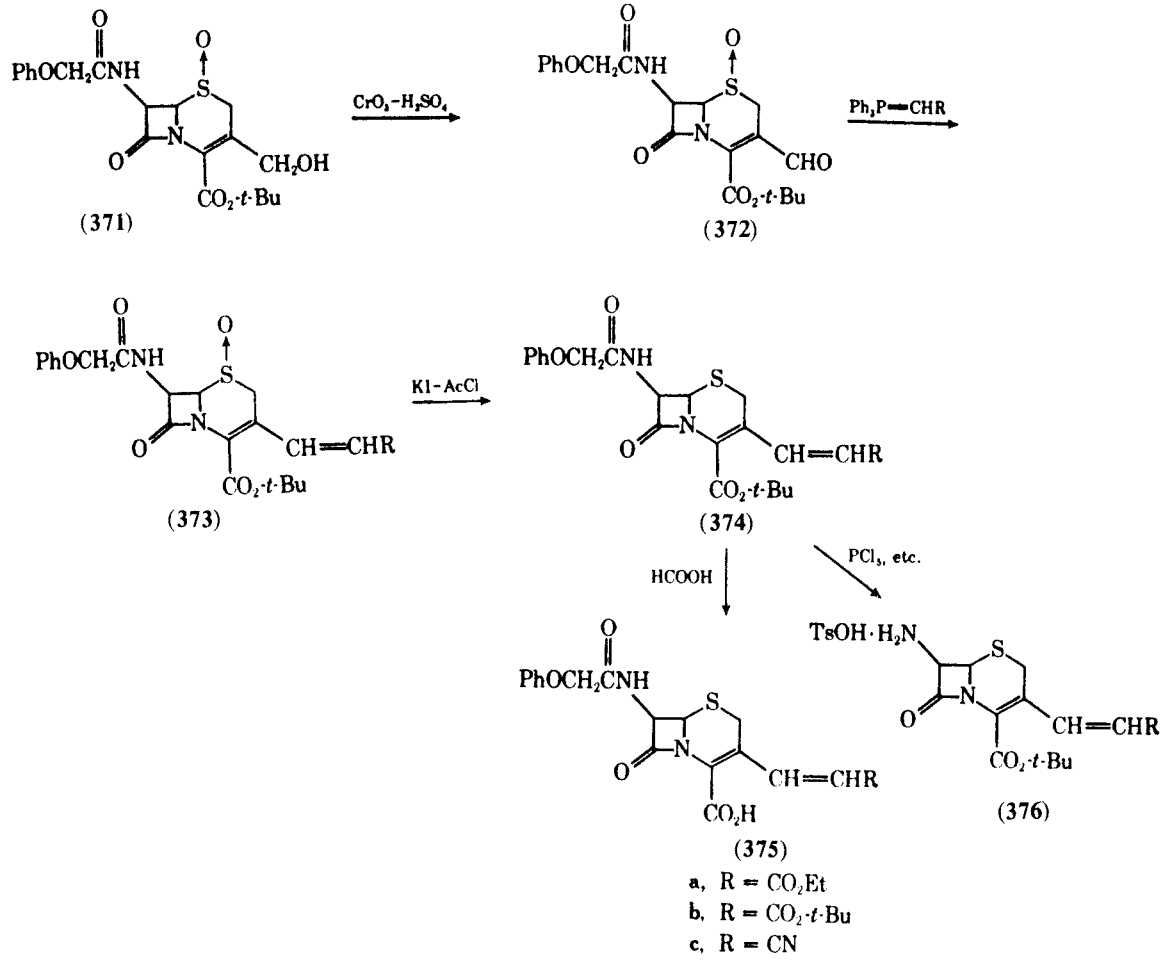




SCHEME 30

isomerization to (**366**). Sulfoxide (**366**) underwent a series of condensations with dimethyl acetylenedicarboxylate to (**367a**), with phenyl isocyanate to (**367b**), and with methyl acrylate to (**367c**). Reduction of the sulfoxide followed by ester cleavage gave the corresponding carboxylic acids which had lost some of their Gram negative activity relative to cephalothin. The 3-*C*-*N*-methyl carboxamides (**368**) were obtained upon reaction of (**365**) with PCl_3-DMF or alternatively by the reaction of (**365**) with acetic anhydride to give amide (**368**) and imide (**372**), both of which were converted to (**370**) (Scheme 30).

A number of cephalosporin sulfoxides have been reported in articles dealing with various synthetic aspects of β-lactam antibiotics. Webber *et al.*[96] prepared a series of 3-substituted-vinyl cephalosporins (**375**) active against a number of Gram negative organisms, making use of sulfoxide intermediates (**371**), (**372**) and (**373**).

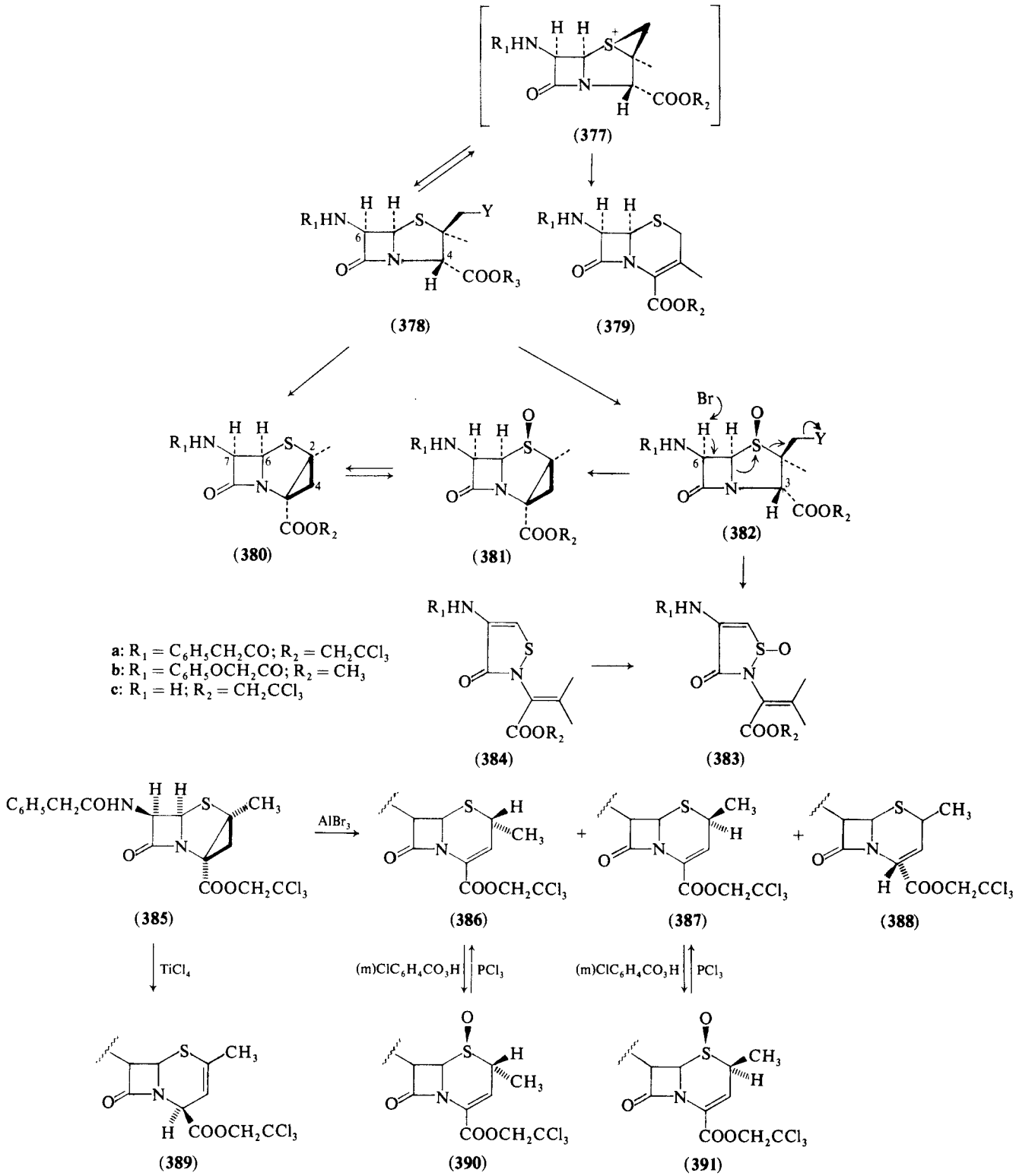


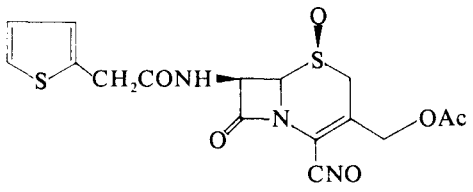
A novel tricyclic β-lactam derivative (**380**) has been prepared by intramolecular nucleophilic displacement.[97] The synthesis of (**380**) is accompanied by concomitant formation of cephem (**379**). The formation of (**379**) can be prevented by carrying out the cyclization on sulfoxide (**382**). In addition of the tricyclic sulfoxide (**381**) some (**383**) was also obtained. Compound (**381**) was further reduced to sulfide (**380**).

Subsequently[98] it was shown that the tricyclic compound (**385**) could undergo cyclopropane ring opening in the presence of Lewis acids, to give all possible stereoisomers (**386**), (**387**), (**388**) and (**389**). The configurational assignment of (**389**) and (**390**) was based on the nmr analysis of the corresponding β-sulfoxides (**390**) and (**391**).

Another tricyclic β-lactam sulfoxide (**393**) has been prepared[99] from the corresponding sulfoxide (**392**).

The methylthiolation of sulfoxide (**394**) has been studied.[100] Treatment of (**394**) at −78° with a base followed by $MsSCH_3$ gave (**395**) without a shift of the double bond. At higher temperature the 2,2-dimethylthio compound (**396**) was obtained. In the presence of excess base, compounds (**397**) and (**398**) were obtained. Further methylthiolation gave the trimethylthiolated product (**399**). The formation of (**397**) is suggested to take place by methylthiolation of the tri-anion (**400**). The configuration of (**395**) was assigned on the basis of NOE studies, with values obtained as indicated in (**401**). Compounds (**402**), (**403**) and (**404**) were obtained analogously from the corresponding phenyl thiobenzenesulfonate and trimethylene dithiotosylate. Methylation of (**395**) gave a mixture of (**405**), (**406**) and (**407**), and benzylation gave (**408**). Subsequent reduction of (**395**) gave back sulfoxide (**394**) and sulfide (**409**). Compound (**396**) under these conditions gave (**395**) together with (**410**). Reduction of (**406**) or (**407**) gave a mixture of (**411**), (**412**) and (**413**).





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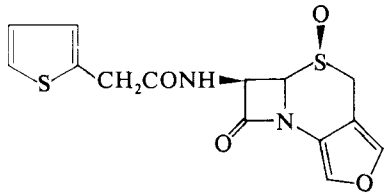
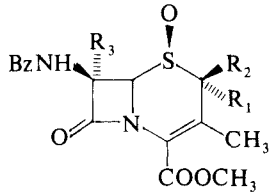
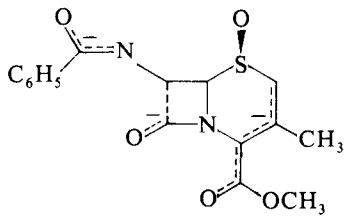


(393)



(394) $R_1 = R_2 = R_3 = H$
(395) $R_1 = SCH_3$, $R_2 = R_3 = H$
(396) $R_1 = R_2 = SCH_3$, $R_3 = H$
(397) $R_1 = R_2 = H$, $R_3 = SCH_3$
(398) $R_1 = R_3 = SCH_3$, $R_2 = H$
(399) $R_1 = R_2 = R_3 = SCH_3$
(402) $R_1 = SC_6H_5$, $R_2 = R_3 = H$
(406) $R_1 = CH_3$, $R_2 = SCH_3$, $R_3 = H$
(407) $R_1 = SCH_3$, $R_2 = CH_3$, $R_3 = H$
(408) $R_1 = CH_2C_6H_5$, $R_2 = SCH_3$, $R_3 = H$
(412) $R_1 = CH_2C_6H_5$, $R_2 = SCH_3$, $R_3 = H$
(413) $R_1 = R_3 = H$, $R_2 = CH_3$



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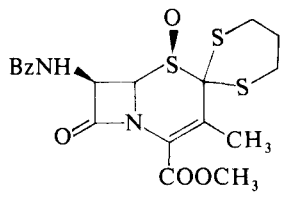
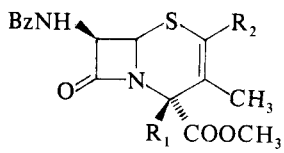
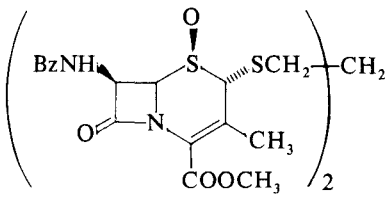


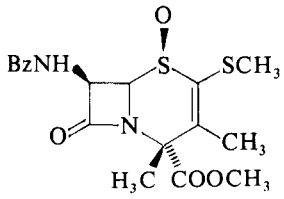
(403)



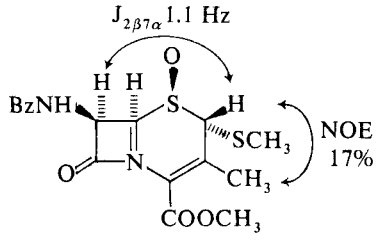
(409) $R_1 = R_2 = H$
(410) $R_1 = H$, $R_2 = SCH_3$
(411) $R_1 = H$, $R_2 = CH_3$



(404)



(405)

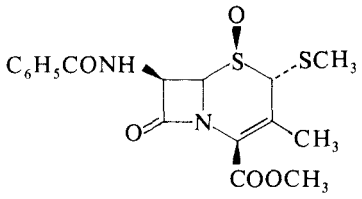


(401)

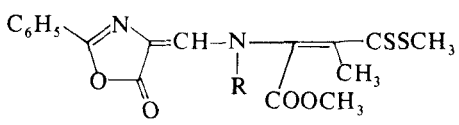
Subsequently[101] the sulfoxide (**414**) when treated with acetic acid in the presence of potassium acetate gave compound (**415**) as a mixture of isomers. Reduction of sulfoxides (**416**) and (**417**), and further treatment of the sulfides with lithium diisopropylamide afforded the same azlactone (**415**). Furthermore, reduction of (**418**) gave (**419**) and (**420**) which produced only trace amounts of (**415**) and mainly (**421**). Finally sulfoxides (**422**) and (**423**) were also rearranged to azlactones (**424**) and (**425**) respectively, upon treatment with acetic anhydride in pyridine. These constitute the first examples of cephalosporin-azlactone interconversions.

In the course of the synthesis of C_7-alkylated 7-aminocephalosporin derivatives Wiering and Wynberg reported[102] the synthesis of sulfoxide (**426**) by an unusual sulfur oxidation in the presence of trialkylborane-water (Scheme 31).

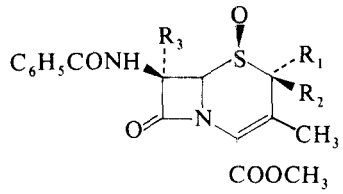
Fukumara *et al.*[103] in an attempt to isolate penicillin iminoethers treated sulfoxide (**427**) with PCl_5 followed by alcohols and isolated phosphoramide-penicillin sulfoxides (**428**) and (**429**). Rearrangement of sulfoxides (**428**) and (**429**) gave the cephems (**430**) and (**431**) and isothiazolone (**432**).



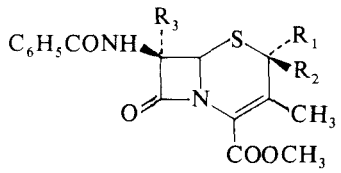
(414)



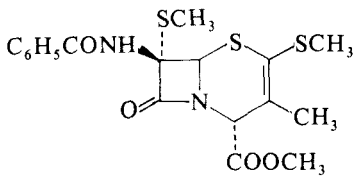
(415) R = H



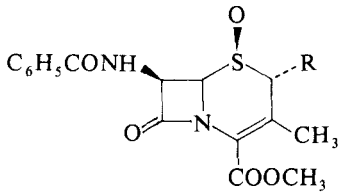
(416) $R_1 = R_2 = R_3 = SCH_3$
(417) $R_1 = R_2 = SCH_3$, $R_3 = H$
(418) $R_1 = R_3 = SCH_3$, $R_2 = H$



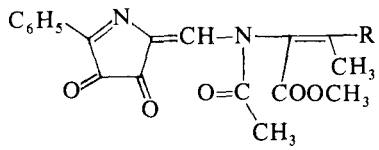
(419) $R_1 = R_3 = SCH_3$, $R_2 = H$
(420) $R_1 = H$, $R_2 = R_3 = SCH_3$



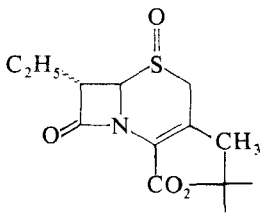
(421)



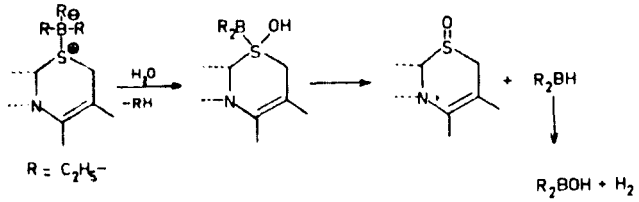
(422) $R = SC_6H_5$
(423) $R = OCH_3$



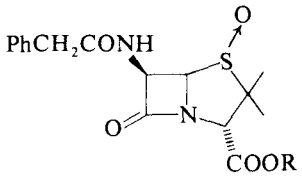
(424) $R = CSSC_6H_5$
(425) $R = CSOCH_3$



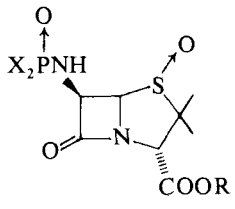
(426)



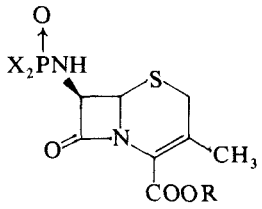
SCHEME 31



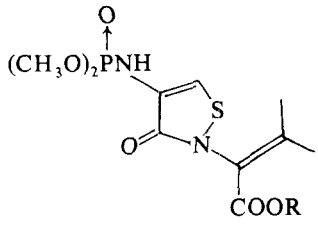
(427)



(428) $X = OCH_3$
(429) $X = OC_2H_5$

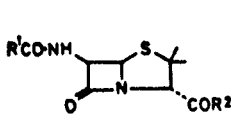


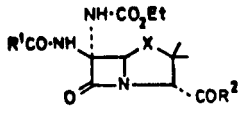
(430) $X = OCH_3$
(431) $X = OC_2H_5$

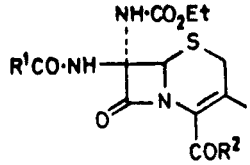


(432)

A series of articles have been published by Campbell and coworkers dealing with several aspects of the reactions of penicillins and cephalosporins with *N*-chloro-*N*-sodioamides. Three main types of reactions have been reported. Those reactions whereby functionalization takes place at the C-6 of penams or C-7 of cephams, those where functionalization takes place at the position C-2 and C-4 of penicillins and rearrangements with thiazolidine ring opening of the penicillins. Upon treatment[104,105] of penicillins (**435**)–(**438**) with *N*-chloro-*N*-sodiourethane (**433**) a urethane function was introduced at position 6 with the formation of (**439**)–(**442**). Oxidation of (**439**) and (**441**) with meta-chloro-perbenzoic acid gave the corresponding sulfoxides (**443**) and (**445**) as a mixture of R and S diastereomers, indicating that both amido groups may direct the course of the oxidation. Penicillamide (**438**), however, gave only the *R*-sulfoxide (**444**). This is attributed to the bonding of the oxidant with the 3-α-t-butylcarbamoyl group assisting in the direction of the oxidation. Excess oxidant brought about the formation of sulfone (**446**). Furthermore, sulfoxide (**441**) rearranged in DMF-acetic anhydride to cephem (**447**).



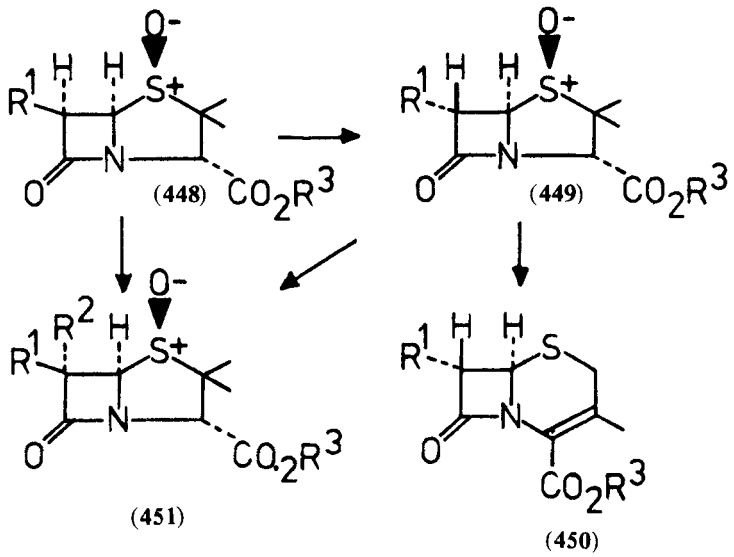




$RO.CO\bar{N}Cl\ Na^+$	R^1	R^2	R^1	R^2	X
(**433**) R = Et	(**435**) $PhO.CH_2$	OMe	(**439**) $PhO.CH_2$	OMe	S
(**434**) R = $Cl_3C.CH_2$	(**436**) $Cl_3C.CH_2$	$O.CH_2Ph$	(**440**) $CCl_3.CH_2$	$O.CH_2Ph$	S
	(**437**) $PhO.CH_2$	$O.CH_2.CCl_3$	(**441**) $PhCH_2$	$O.CH_2.CCl_3$	S
	(**438**) $PhCH_2$	$NHBu^t$	(**442**) $PhCH_2$	$NHBu^t$	S
			(**443**) $PhO.CH_2$	OMe	SO(*R*,*S*)
			(**444**) $PhCH_2$	$NHBu^t$	SO(*R*)
			(**445**) $PhO.CH_2$	$O.CH_2.CCl_3$	SO(*R*,*S*)
			(**446**) $PhO.CH_2$	$O.CH_2.CCl_3$	SO_2

(**447**) R^1 = $PhO.CH_2$; R^2 = $Cl_3O.CH_2.O$

Subsequent investigation[106,107] into the behavior of penicillin sulfoxides with *N*-chloro-*N*-sodio-*p*-toluenesulfonamide revealed that epimerization as well as incorporation of a second amido group takes place at position 6 to give sulfoxides (**449**) and (**451**). The epi-penicillanate sulfoxide (**449**) was rearranged to the corresponding epi-cephalosporanate (**450**). The *R*-sulfoxide (**452**) under the same conditions gave (**453**), where

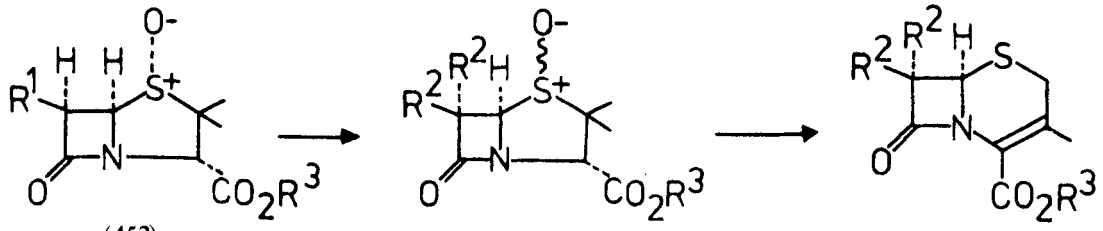


(**448**) (**449**) (**451**) (**450**)

R′ = $PhOCH_2CONH$– R^2 = EtOCONH– R^3 = CH_3

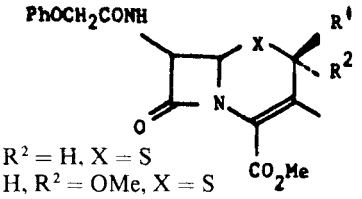
both the hydrogen and the 6-acylamino group of the starting sulfoxide were replaced. Compound (**453**) was also rearranged to the cephem (**454**). The difference in reactivity of (**448**) and (**452**) stems from different stereochemistry of the sulfoxides. The *R*-(**452**) forms an *N*-chloramide in the first step which can lead to the formation of the 6-imine product (**453**). This is precluded in the case of (**448**) due to the proximity effects between the NH-group and the sulfoxide.

In addition to the functionalization at position 6 of the penicillanate sulfoxides, functionalization at the positions 2 and 4 of the cephalosporins has been observed.

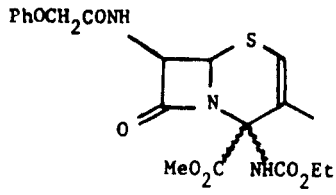


(452) (453) (454)

Sulfide (**455**) when treated[108] with *N*-chloro-*N*-sodiourethane gave (**456**) and (**457**), whereas under these conditions sulfoxide (**458**) gave the dichloro derivative (**459**). It was also observed that in the presence of an excess of *N*-chlorourethane in wet tetrahydrofuran, a mixture of *R*- and *S*-sulfoxides **458** is obtained.

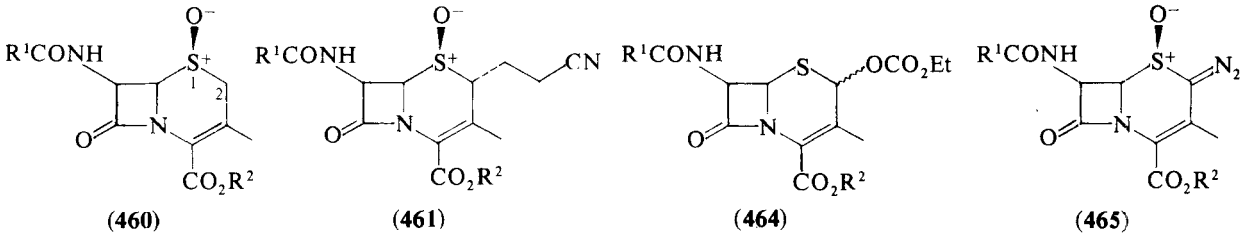


(**455**) $R^1 = R^2 = H$, X = S
(**457**) $R^1 = H$, R^2 = OMe, X = S
(**458**) $R^1 = R^2 = H$, X = S–O
(**459**) $R^1 = R^2$ = Cl, X = S–O

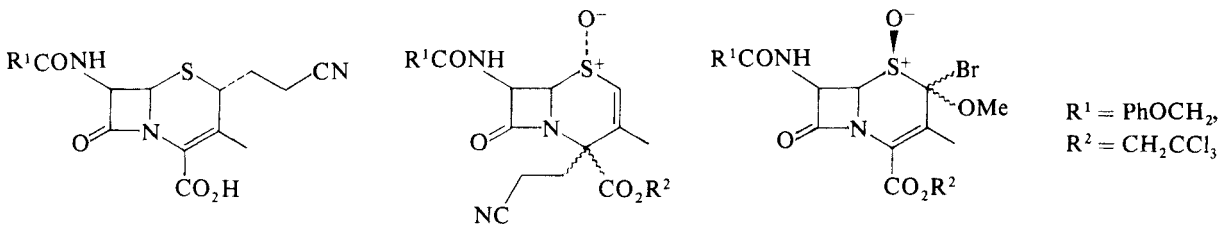


(**456**)

Other functionalizations at C-2 and C-4 of cephalosporins, involve[109,110] alkylation of sulfoxide (**460**) when treated with acrylo-nitrile-triethylamine to give (**461**), which was reduced and deesterified to (**462**). In contrast to the reaction of (**460**), the (*R*)-1 oxide gave the C-4 Michael-adduct (**463**). Sulfoxide **460** with ethyl chloroformate gave the 2α- and 2β-carbonates (**464**), presumably via Pummerer rearrangement. Furthermore when sulfoxide (**460**) reacted with tosyl chloride the diazosulfoxide (**465**) was formed. This compound reacted further with NBS-methanol to give sulfoxide (**466**).



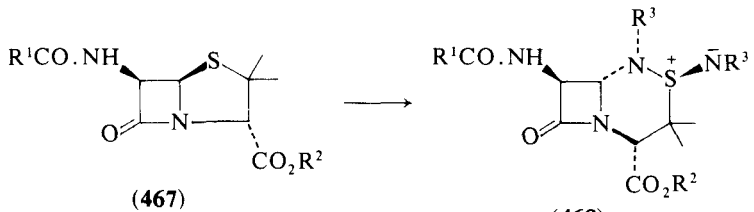
(**460**) (**461**) (**464**) (**465**)



(**462**) (**463**) (**466**)

R^1 = $PhOCH_2$,
R^2 = CH_2CCl_3

A novel synthesis of β-lactam sulfinimidamides[111,112] involves the treatment of penams (**467**) with chloramine T to give compounds (**468**). The structure of (**468**) was unambiguously established by x-ray crystallography of (**468a**). This unusual reaction takes place only when penams possessing a 6β-secondary amide group, and not with 6β-phthalimidopenicillanates or methyl 6,6-dibromopenicillanate.



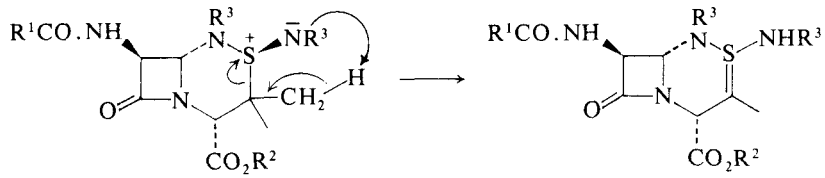
(**467**)

(**468**)

a $R^1 = PhCH_2$, $R^2 = Me$
b $R^1 = PhO.CH_2$, $R^2 = Me$
c $R^1 = Me$, $R^2 = PhCH_2$
d $R^1 = PhO.CH_2$, $R^2 = PhCH_2$
e $R^1 = PhCH_2$, $R^2 = CCl_3.CH_2$

a–d: $R^3 = Ts$

Several mechanistic paths for the formation of (**468**) are discussed. Subsequent thermal rearrangement[113,114] of (**469**) gave (**470**) via a β-elimination reaction analogous to the Morin rearrangement.



(**469**) (**470**)

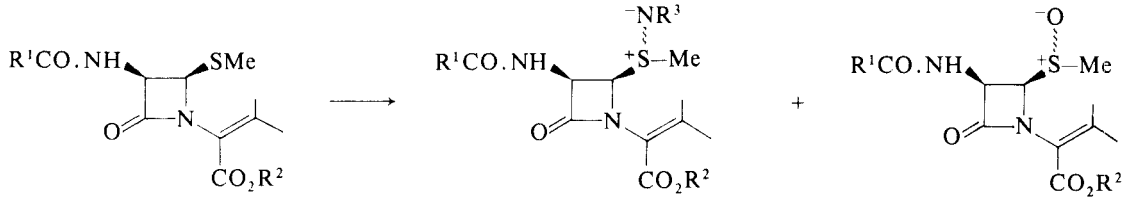
Other reactions of penicillin related compounds with chloroamine T were carried out[115] on the 4-(methylthio)azetidin-2-one (**471**) giving a mixture of sulfimide (**473**) as a single enantiomer of unknown configuration and sulfoxide enantiomers (**475a,b**). These sulfoxides could be obtained directly by oxidation of (**471**) with *m*-chloroperbenzoic acid. Thermal rearrangement of (**473**) gave oxazoline (**478**). The same compound was obtained upon attempted oxidation of (**473**) to the corresponding sulfoximide or attempted reduction over 10% palladium on charcoal. Similar reactions were carried out on (**472**) to form (**474**) and (**476**), and (**479**). Oxidation of (**476**) gave also (**480**).

Under similar conditions, the absence of a secondary amide group such as in (**483**) did not prevent the formation of sulfimide (**484**) and sulfoxides (**485**). However, (**481**) appeared to be essentially unreactive.

Other azetidin-2-one sulfoxides[116] such as **486** and **487** reacted with *N*-chloro-*N*-sodio urethane to give the 3,3-disubstituted azetidin-2-one (**489**). However, (**488**) did not react indicating involvement of the secondary amide side chain in the reaction of (**486**) and (**487**). When the sulfide (**490**) was treated under these conditions, in addition to the expected (**492**), the 3-acetamido-3-urethane sulfimide (**491**) was also isolated. Compounds (**491**) and (**492**) were converted by oxidative elimination into oxazoline azetidinones (**493**) and (**494**) respectively.

In the course of studies[117] on the epimerization of penicillin sulfoxides (**495**) in the presence of DBN it was found that in addition to the epimers (**496**), the isothiazolones (**497**) are also formed. The reaction takes place with both *S* and *R* sulfoxides. It is suggested that the reaction proceeds by a mechanism whereby the C-6 proton is abstracted without prior removal of the secondary amido hydrogen. In the case of (**495cz**) no epimer (**496cz**) was detected, however, some of the air-oxidized product (**498**) was also formed.

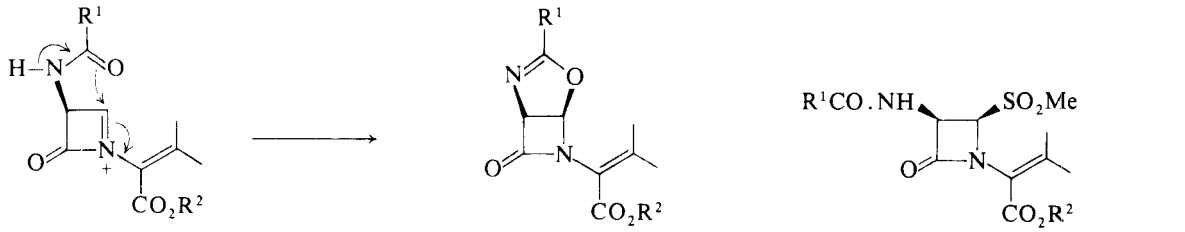
A novel 5,6-bond cleavage of penicillin sulfoxides has been described by Nakana *et al.*[118] in an attempted methoxylation at position 6 of sulfoxides (**500**). Treatment of (**499**) with a three-fold excess of *tert*-butylhypochlorite and sodium borate in methanol gave a mixture of products (**501**)–(**504**). Compound (**502**) was converted into (**505**).



(471) $R^1 = Me$, $R^2 = PhCH_2$
(472) $R^1 = PhO.CH_2$, $R^2 = PhCH_2$

(473) $R^1 = Me$, $R^2 = PhCH_2$, $R^3 = Ts$
(474) $R^1 = PhO.CH_2$, $R^2 = PhCH_2$, $R^3 = Ts$

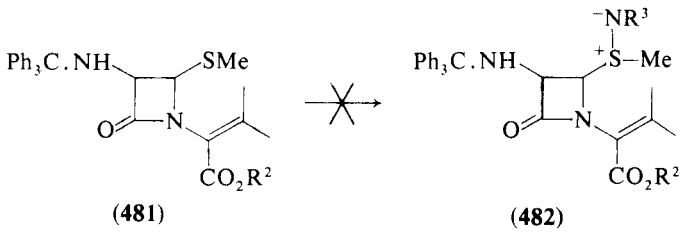
(475) a, b: $R^1 = Me$, $R^2 = PhCH_2$
(476) a, b: $R^1 = PhO.CH_2$, $R^2 = PhCH_2$



(477)

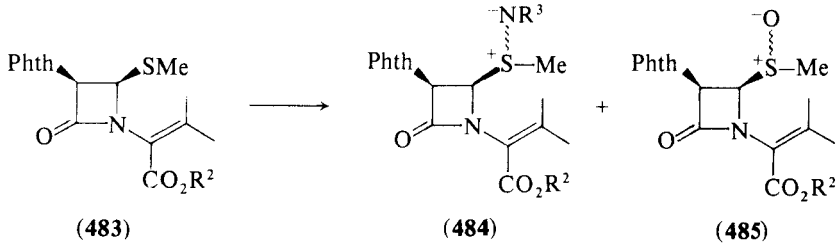
(478) $R^1 = Me$, $R^2 = PhCH_2$
(479) $R^1 = PhO.CH_2$, $R^2 = PhCH_2$

(480) $R^1 = PhO.CH_2$, $R^2 = PhCH_2$



(481)

(482)



(483)

(484)

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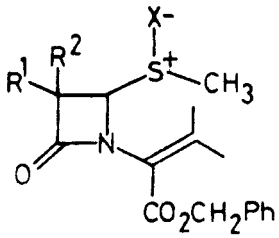
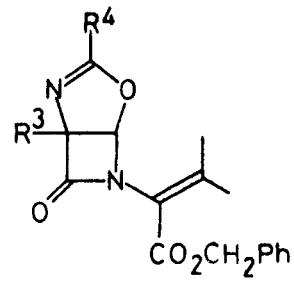
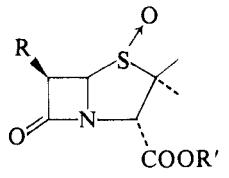


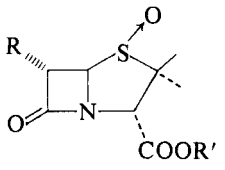
(486) $R^1 = MeCONH$, $R^2 = H$, $X = O$
(487) $R^1 = PhOCH_2CONH$, $R^2 = H$, $X = O$
(488) $R^1 = Phthalimido$, $R^2 = H$, $X = O$
(489) $R^1 = R^2 = EtO_2CNH$, $X = O$
(490) $R^1 = MeCONH$, $R^2 = H$, $X = NTs$
(491) $R^1 = MeCONH$, $R^2 = EtO_2CNH$, $X = NTs$
(492) $R^1 = R^2 = EtO_2CNH$, $X = NTs$



(493) $R^3 = EtO_2CNH$, $R^4 = OEt$
(494) $R^3 = EtO_2CNH$, $R^4 = Me$



(495)



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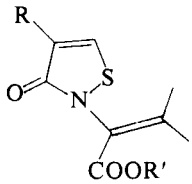

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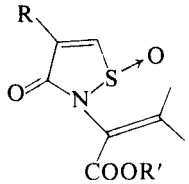

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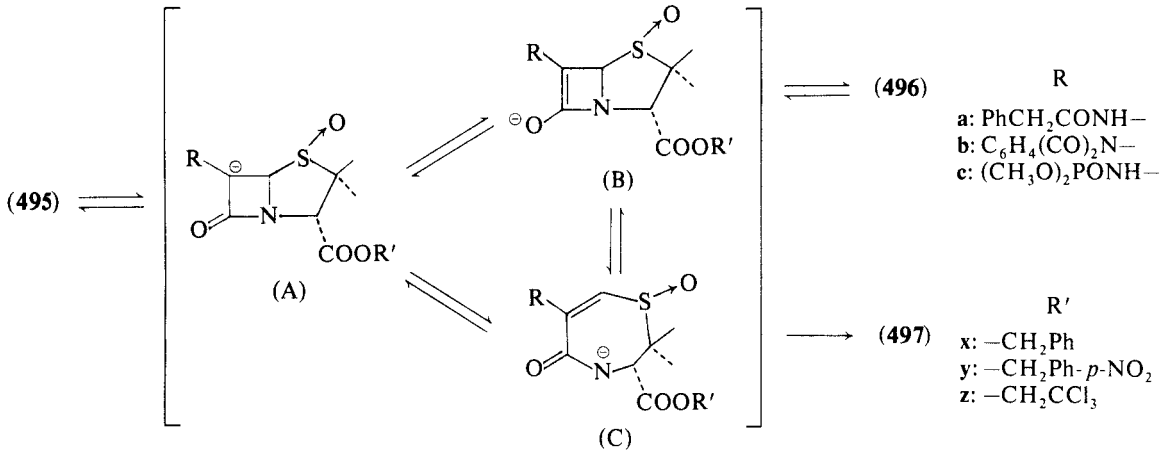

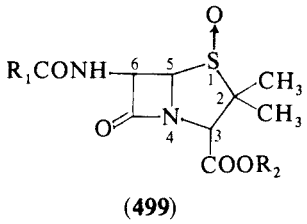

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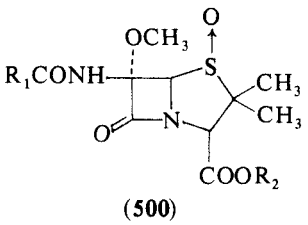

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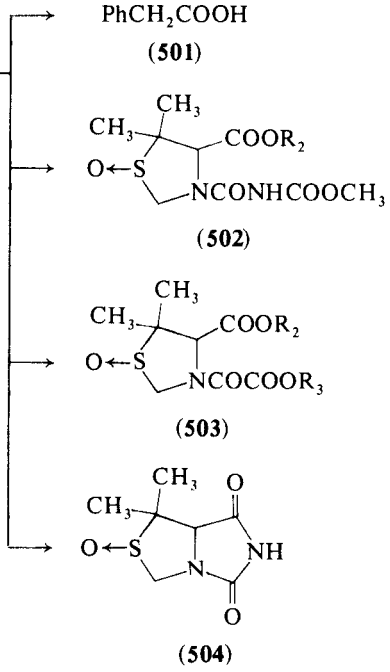
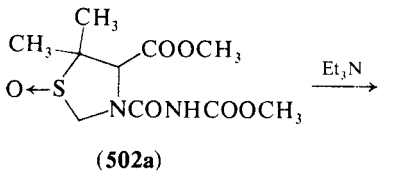
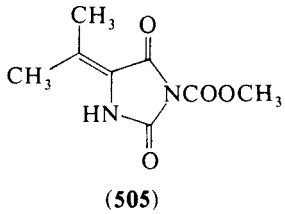


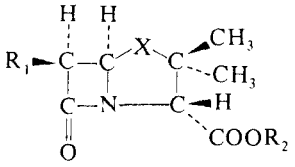


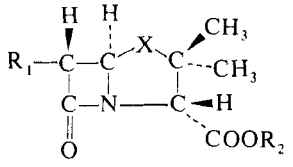
(502a)



(505)

Configurational assignments of the oxidation products of penicillin (**510**) and 6-epipenicillin (**509**) have been carried out[119] with the help of nuclear Overhauser effects, aromatic solvent induced shifts and by sulfoxide band chemical shift perturbation. Deuterium incorporation was studied in the course of isomerization of (**512**) and (**508**) to the corresponding *S*-oxides (**506**) and (**507**).

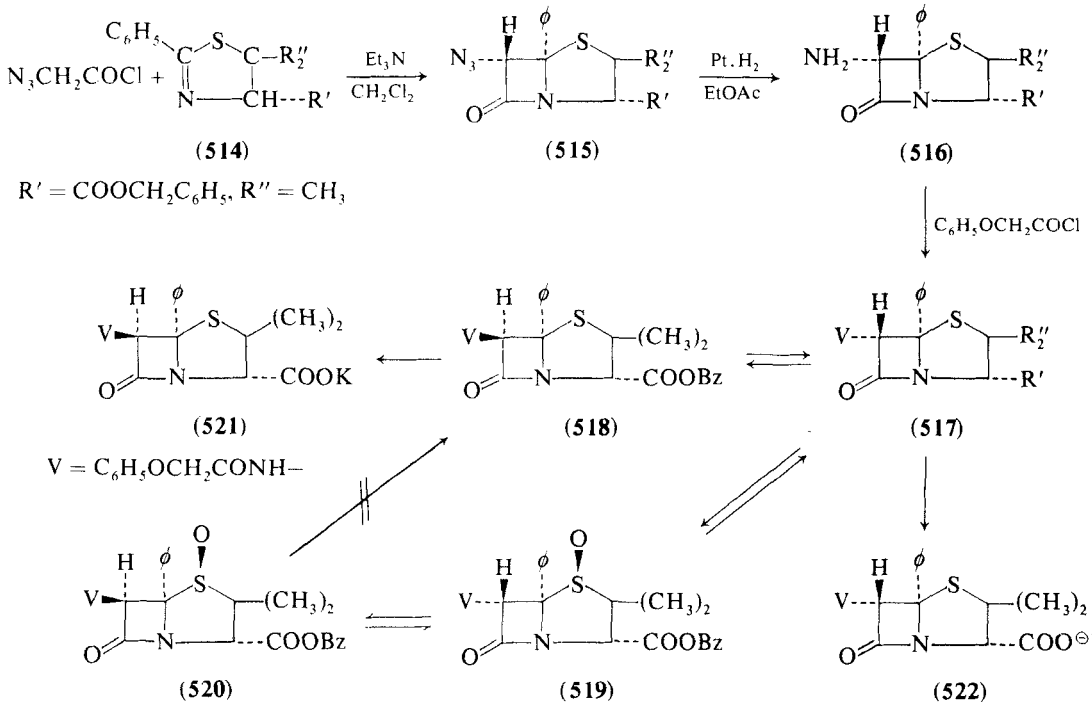




	R_1	R_2	X
(**506**)	$C_6H_5OCH_2CONH-$	$C_6H_5CH_2-$	S—O
(**510**)	$C_6H_5OCH_2CONH-$	$C_6H_5CH_2-$	S
(**511**)	$C_6H_5OCH_2CONH-$	$C_6H_5CH_2-$	S---O
(**512**)	$C_6H_5OCH_2CONH-$	H	S---O
(**513**)	$C_6H_5OCH_2CONH-$	CH_3	S---O

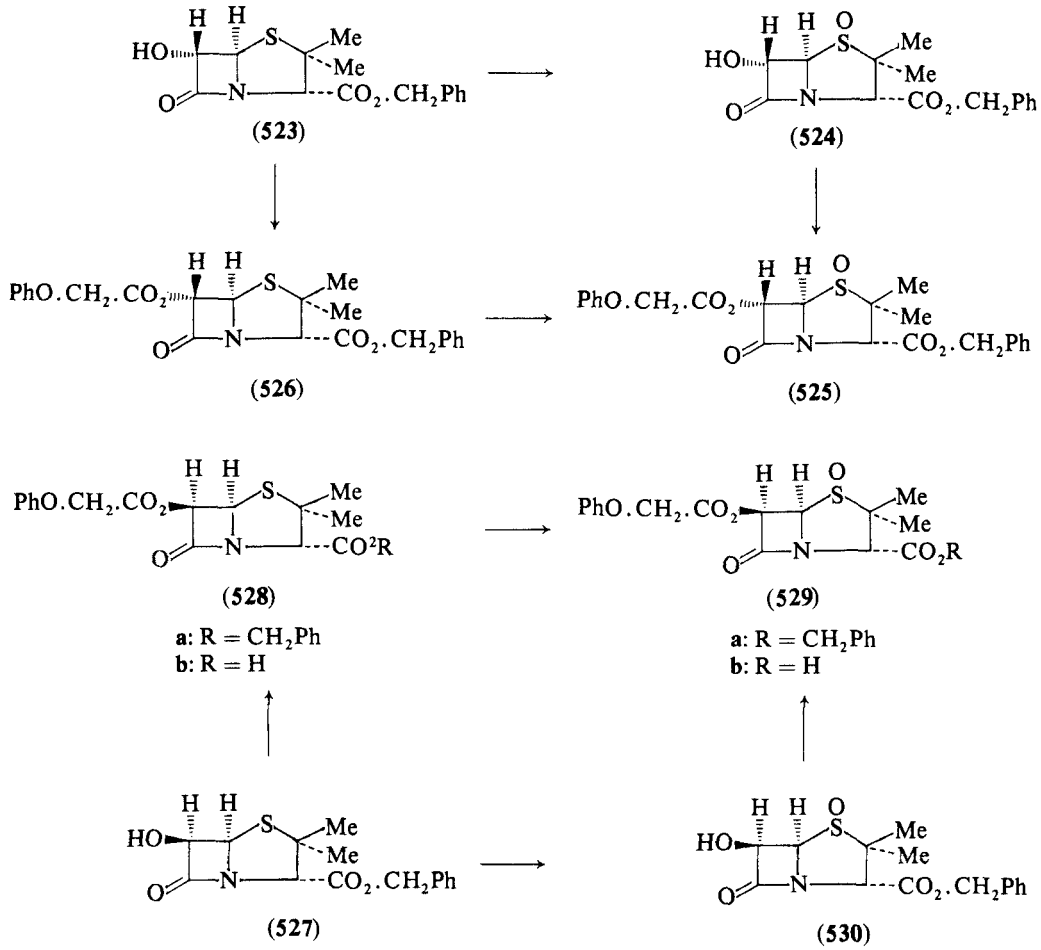
	R_1	R_2	X
(**507**)	$C_6H_5OCH_2CONH-$	$C_6H_5CH_2-$	S—O
(**508**)	$C_6H_5OCH_2CONH-$	$C_6H_5CH_2-$	S---O
(**509**)	$C_6H_5OCH_2CONH-$	$C_6H_5CH_2-$	S

Vanderhaeghe and Thomis[120] prepared epipenicillin (**517**) (Scheme 32) and attempted epimerization at position 6 to give the natural penicillin configuration, via the sulfoxide (**518**). Under the basic conditions used some of the expected isomer (**520**) was indeed formed; however, this product could not be deoxygenated to (**518**) presumably due to strong hydrogen bonding between the sulfoxide oxygen and the 6-amido side chain. The desired (**521**) was obtained by direct epimerization of (**517**) to (**518**), followed by hydrogenolysis of the ester group. Of the two epimeric products (**521**) and (**522**) only the former showed a low degree of antimicrobial activity.



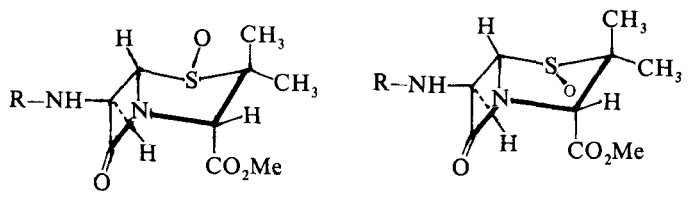
SCHEME 32

The synthesis of 6α- and 6β-phenoxyacetoxypenicillanates (**526**) and (**528**) and their (*S*)- and (*R*)-sulfoxides (**525**) and (**529**) has been described.[121] (*S*)-(**525**) was obtained by oxidation of (**526**) or by phenoxyacetylation of (*S*)-(**524**) which in turn was prepared via oxidation of (**523**). The sulfoxide (*S*)-(**529a**) when isomerized in



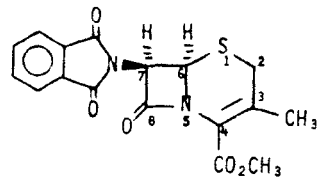
the presence of DBN gave a mixture of (*S*)-(**529a**) and (*S*)-(**525**). However, when a solution of (*S*)-(**529a**) and (*S*)-(**525**) was kept overnight only the hydrolysis product (*S*)-(**524**) was obtained. (*S*)-(**525**) could not be epimerized under these conditions. Sulfide (**529b**) was obtained from (**529a**) by hydrogenolysis of the benzyl group followed by reduction with phosphorus tribromide.

In the course of oxidation of 5-epi-benzylpenicillin methyl ester[122] a mixture of (*R*)- and (*S*)-sulfoxides in the ratio of 1 : 2 is obtained which indicated that neither sulfoxide configuration is likely to be stabilized by internal hydrogen bonding with the side chain amide proton. The conformations assigned are those of (*S*)-(**531**) and (*R*)-(**532**), obtained from the proton and carbon magnetic resonance spectra of these isomers.

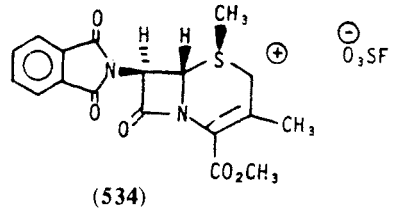


R = $C_6H_5CH_2CO$–

A novel type of chiral sulfonium cephalosporin derivative has been described by Herron.[123] Treatment of (**533**) with methyl fluorosulfonate gave a 30% yield of crystalline optically active (**534**), epimeric at position 6. In order to elucidate the mechanism of the formation of (**534**), conversions (**535**)–(**538**) were carried out. The sulfonium salt (**538**) was enantiomeric with (**534**). It was suggested that the mechanistic path for the formation of (**534**) from (**533**) proceeded via (**541**) as indicated. Compound (**534**) is quite reactive and in the presence of $NaOCH_3/CH_3OH$-DMSO at −78° it gave (**539**).



(533)



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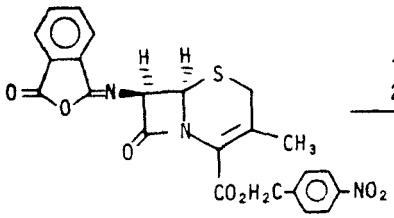

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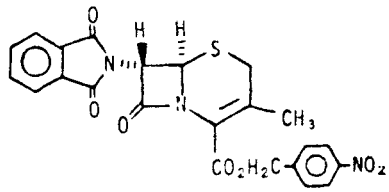

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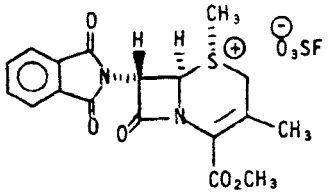

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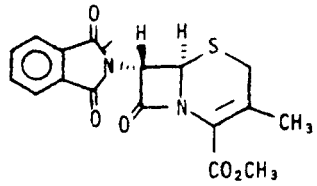

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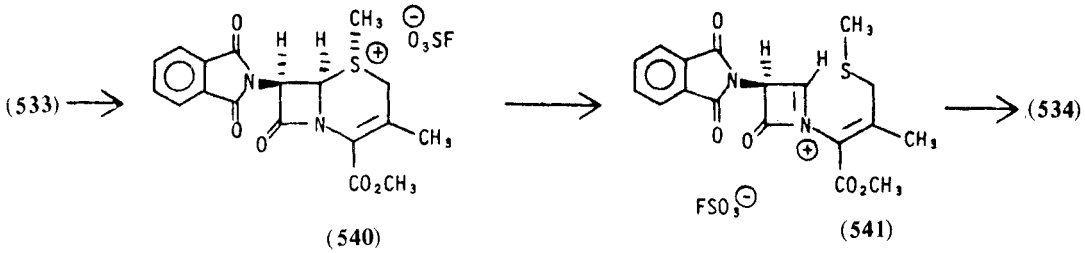

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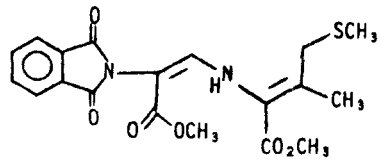
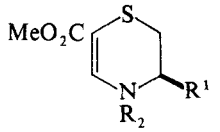
(541)

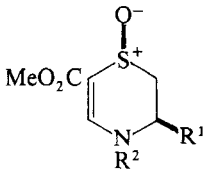


(539)

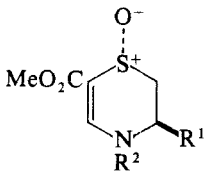
A number of recent publications by Stoodley and coworkers have dealt with reactions of compounds related to β-lactam antibiotics, and some of these involve optically active sulfoxides. It has been established[124] by chemical evidence that sulfoxide (**544**) derived from acid (**542**) has an *R* configuration. Oxidation of lactone (**548**) gave a single racemic sulfoxide. This implied either racemization of the lactone or of the sulfoxide product during work up. It was subsequently shown that the lactone was optically stable and that it was possible to obtain the corresponding optically active sulfoxide when the isolation was carried out at low temperature, which indicated that the racemization was thermally induced. The ester sulfoxide (**545**) obtained from (**543**), as well as the sulfoxide obtained from (**552**) also underwent thermal racemization. The lactone sulfoxide (**555**) obtained from (**554**) when isolated at low temperature was shown to be optically pure, upon conversion to the corresponding sulfone. The sulfoxide (**555**) also racemized thermally. Similar reactions took place on ester (**553**). All these sulfoxide isomerizations took place by enantiomeric and not diastereomeric interconversions. The authors propose that a sulfenic acid intermediate (**551**) participated in the racemization. It was further shown that lactone (**549**) underwent thermal racemization readily, whereas (**550**) was thermally stable,



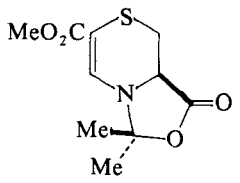
(**542**) $R^1 = CO_2H$, $R^2 = H$
(**543**) $R^1 = CO_2Me$, $R^2 = H$



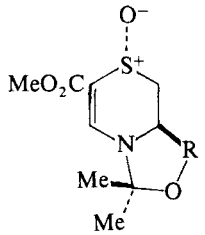
(**547**) $R^1 = CO_2Me$, $R^2 = CH_2.OEt$



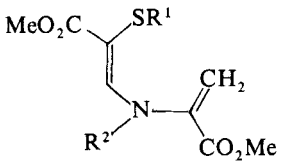
(**544**) $R^1 = CO_2H$, $R^2 = H$
(**545**) $R^1 = CO_2Me$, $R^2 = H$
(**546**) $R^1 = CO_2Me$, $R^2 = CH_2.OEt$



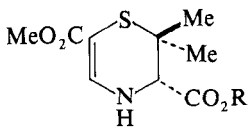
(**548**)



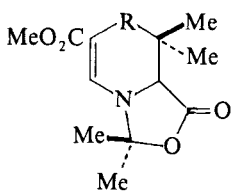
(**549**) R = CO
(**550**) $R = CH_2$



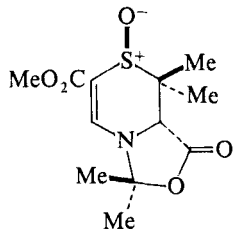
(**551**) $R^1 = OH$, $R^2 = H$



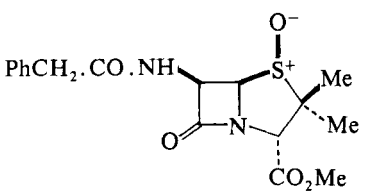
(**552**) R = H
(**553**) R = Me



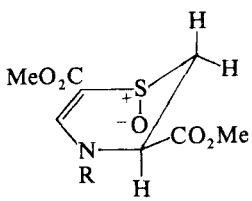
(**554**) R = S



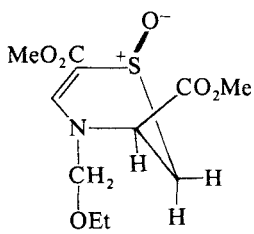
(**555**)



(**556**)



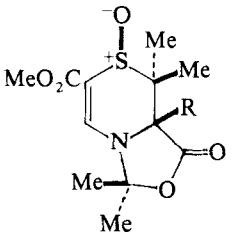
(**557**) R = H
(**558**) $R = CH_2.OEt$



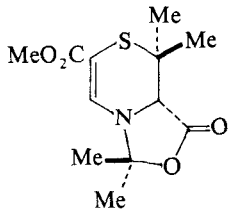
(**559**)

suggesting that the sigmatropic hydrogen shifts responsible for the racemization are markedly influenced by the acidity of the migrating hydrogen atom. A difference between (**555**) and (**556**) lies on the fact that the penicillin sulfoxide undergoes the sigmatropic rearrangement, whereby the hydrogen of the 2β-methyl group shifts even though the 3-hydrogen atom is more acidic. From the nmr spectra it was concluded that sulfoxides (**545**), (**546**), and (**547**) adapt configurations (**557**), (**558**) and (**559**) respectively.

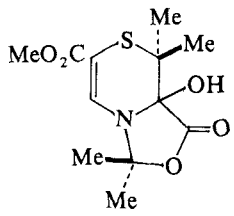
It was further shown[125,126] that the attempted reduction of sulfoxide (**560**) with acetyl chloride to thiazine (**562**) gave hydroxythiazine (**563**) via the acetoxysulfonium (**565**) and sulfenic anhydride (**564**). When the reaction was carried out in the presence of two equivalents of acetyl chloride two new products were obtained. One of them was the racemic (**561**) and the other was (**566**).



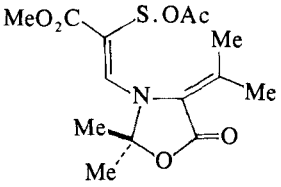
(**560**) R = H
(**561**) R = OH



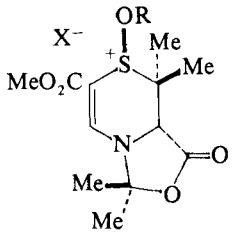
(**562**)



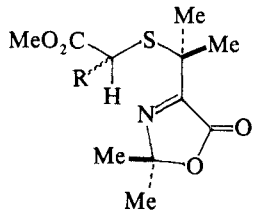
(**563**)



(**564**)

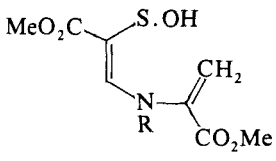


(**565**) R = Ac, X = Cl

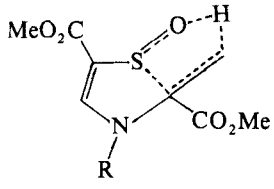


(**566**) R = Cl

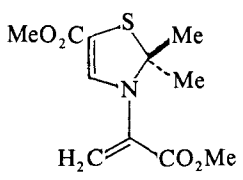
The thermal equilibration of thiazoline-*S*-oxides required[127,128] higher temperatures than the corresponding thiazine sulfoxides. Oxidation of thiazoline (**569**) to sulfoxide (**570**) followed by equilibration in refluxing toluene gave racemic (**571**) which underwent reequilibration with (**570**) in boiling toluene. The reaction is consistent with the intermediacy of sulfenic acid (**567**) by way of a coplanar transition state (**568**).



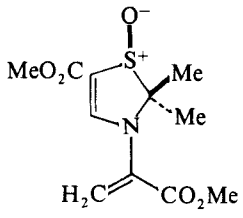
(**567**)



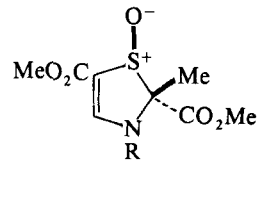
(**568**)



(**569**)



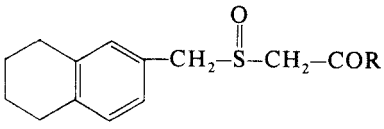
(**570**)



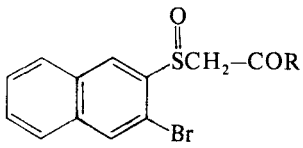
(**571**)

G *Sulfoxides with Handles for Resolution*

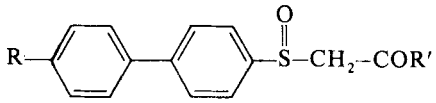
A number of new optically active substituted-sulfinylacetic acids and their derivatives (**572**)–(**576**) have been reported by Janczewski's group.[129–133]



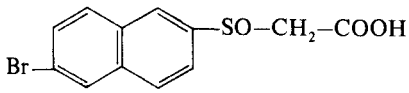
(**572**)



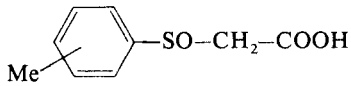
(**573**)



(**574**)



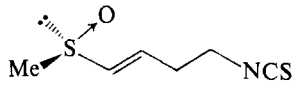
(**575**)



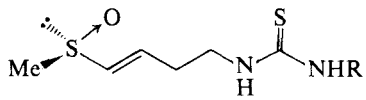
(**576**)

H *Naturally Occurring Optically Active Sulfoxides*

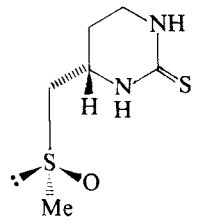
Sulphoraphene (**577**) when treated[134] under mild conditions with ammonia gives the thiourea (**578**). Under more severe conditions cyclization to the tetrahydropyrimidine-2-thiones (**579a**) and (**579b**) takes place. The absolute configurations of the latter were established by stereospecific synthesis.



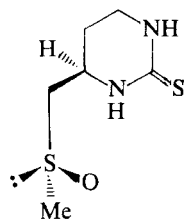
(**577**)



(**578**) R = H



(**579a**)



(**579b**)

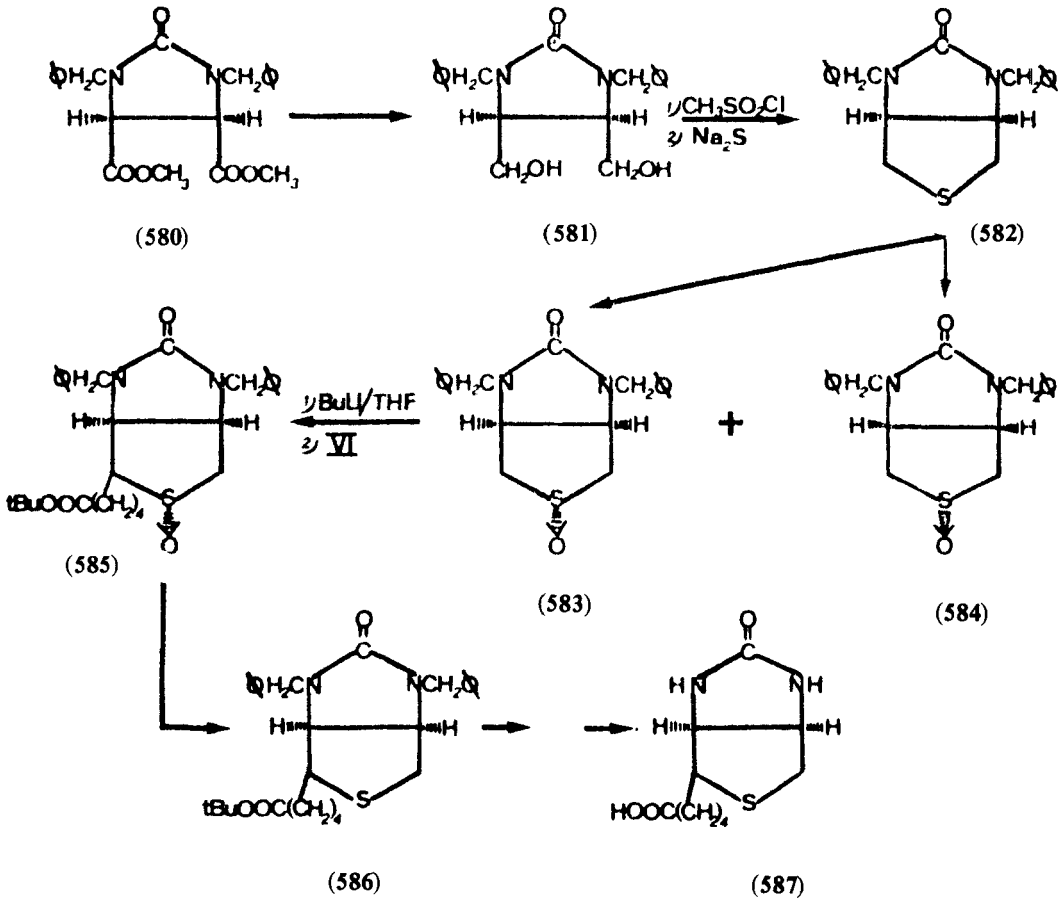
A novel total synthesis of biotine (**587**) has been described[135] which exploits the great stereoselectivity of alkylation at the α-position of the sulfoxide group of compound (**583**) (Scheme 33).

Extensive configurational analysis on biotin and its corresponding sulfoxides and sulfone have been carried out by Lett and Marquet.[136]

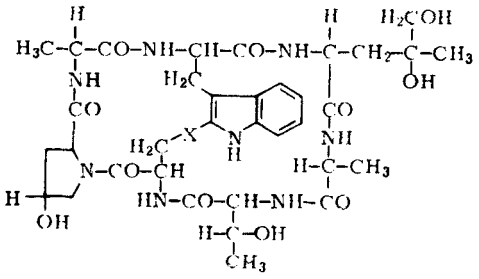
Oxidation of 2-ethylthio-L-tryptophan (**589a**) with hydrogen peroxide gave[137] two diastereomeric sulfoxides (**589b**) and (**589c**). X-ray analysis of (**589b**) revealed an *R*-configuration for the sulfoxide group. By analogy with the ord curve of (**589b**), the toxic phalloidin sulfoxide (**588**) can be assigned the same configuration.

Sulfoxide reduction[138] of the toxic *O*-methyl-α-amanitin (**590b**) gave the corresponding *S*-deoxo compound (**590a**) which is likewise toxic. Reoxidation of (**590a**) with hydrogen peroxide gave two diastereomeric sulfoxides (**590b**) and (**590c**), where (**590c**) showed one tenth of the toxic characteristics of (**590b**). Both diastereomeric sulfoxides upon oxidation gave to toxic sulfone (**590d**). Other minor components of the amanitin family identified[139] are (**591**).

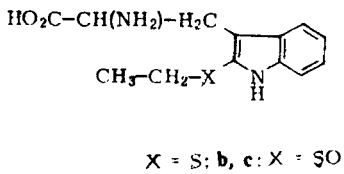
Two diastereomeric sulfoxides (**597a**) and (**597b**) have been obtained upon oxidation of *S*(2-methylpropylenyl)-L-cysteine (**595**).[140] Base catalyzed cyclization gave compounds (**598**) and (**599**) respectively.



SCHEME 33

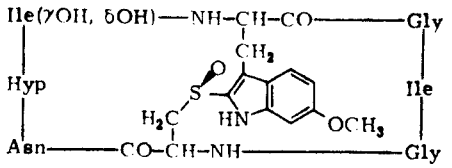


(588)

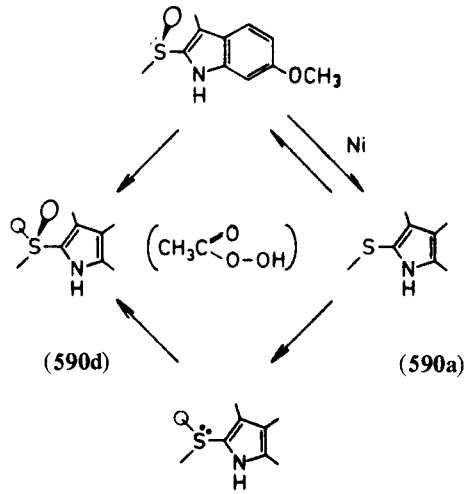


X = S; b, c: X = SO

(589a)

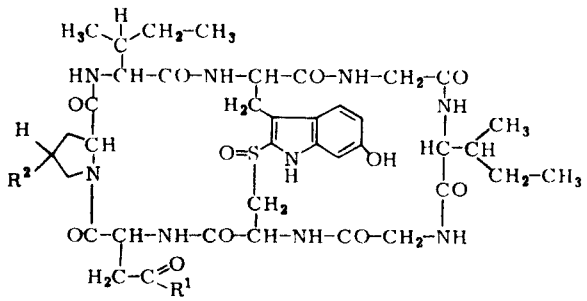


(R)-(**590b**)



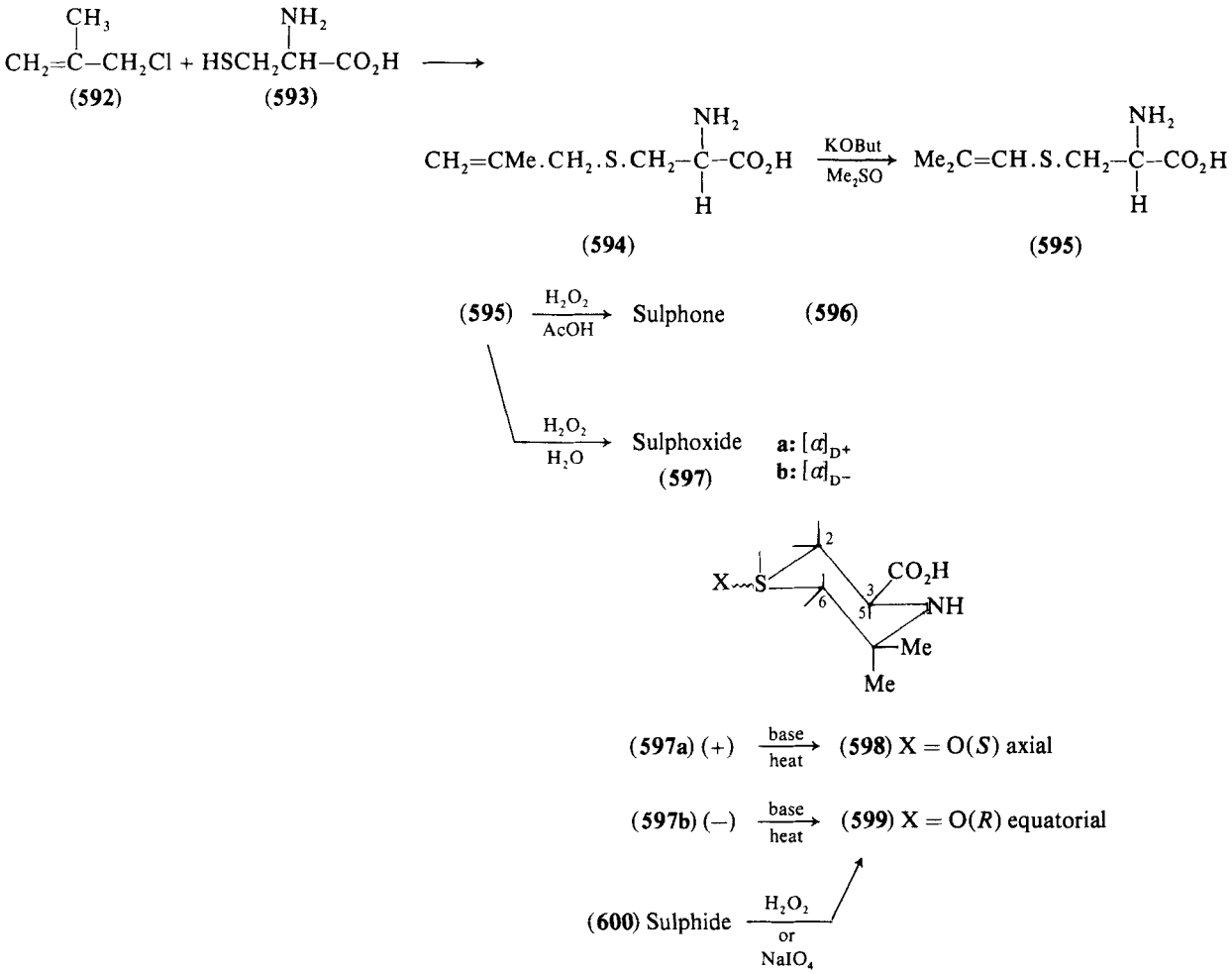
(**590d**) (**590a**)

(S)-(**590c**)



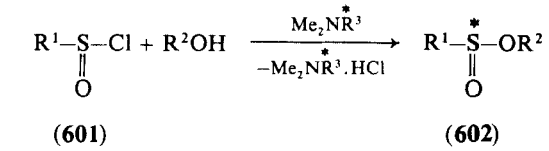
(**591**)	R^1	R^2
a	NH_2	OH
b	NH_2	H
c	OH	OH

Reduction of the cyclic sulfoxides and reoxidation of the obtained sulfide (**600**) gave exclusively the equatorial sulfoxide.

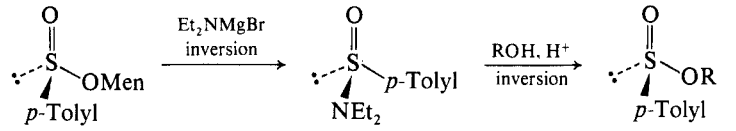


III SULFINATES

A novel asymmetric synthesis of optically active sulfinate esters (**602**) having sulfur as sole center of chirality has been shown[141] to take place when sulfinyl chlorides are condensed with achiral alcohols in the presence of optically active amines. Optical purities of up to 45% have been observed.



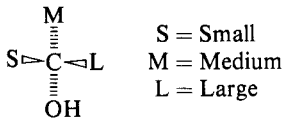
A second novel synthesis[142] of optically active sulfinates (**605**) involves the acid catalyzed alcoholysis of chiral sulfinamides (**604**). With primary alcohols, high degree of stereospecificity is obtained following an inversion mechanism. The stereospecificity decreases with secondary and tertiary alcohols.



(−)-(*S*)-(**603**) (+)-(*S*)-(**604**) (−)-(*S*)-(**605**)

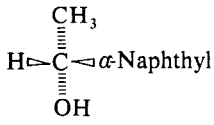
Men = menthyl

Pirkle and coworkers[143] have found that when the *p*-tolyl sulfinate ester of (**607**) is treated with methyl magnesium bromide the methyl *p*-tolyl sulfoxide obtained has the (*R*)-(+)-configuration. This is contrary to the general rule proposed by Mislow[144] in which sulfinates of alcohols whose structure can be defined in terms of structure (**606**) give upon treatment with methyl Grignard the (*S*)-(−)-methyl *p*-tolyl sulfoxide. Moreover the degree of asymmetric induction of the reaction follows the Hammet linear correlation dependent on the *p*-substituent on the phenyl ring. Several speculative transition states are proposed to explain the stereochemical course of the reaction.



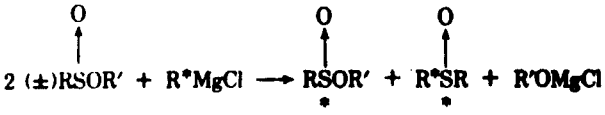
S = Small
M = Medium
L = Large

(**606**)

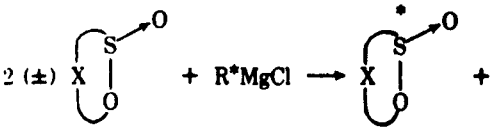


(**607**)

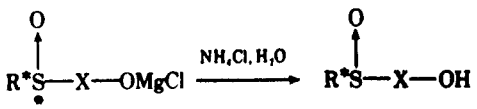
The direct determination of enantiomeric purity and absolute configuration of chiral sulfinates may be obtained[145] from the hydrogen nmr spectra in the presence of chiral fluoro alcohols (**608a–d**). This technique required optically active sulfinates which were prepared by kinetic resolution, involving reaction of racemic sulfinates (**612**), (**613**) with limited amounts of optically active Grignard reagents (**610**), (**611**). By this method the first examples of optically active cyclic sulfinates, sultines, (**612**) and (**613**) were obtained.



(**609**) (**610**) (**611**) (**614**)



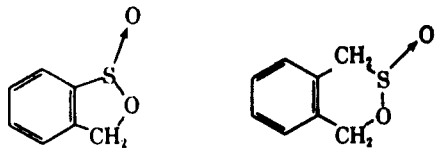
(**612**) (**613**) (**610**) (**611**)



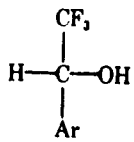
(**615**)

(**610**) R* = $CH_2CH(CH_3)CH_2CH_3$

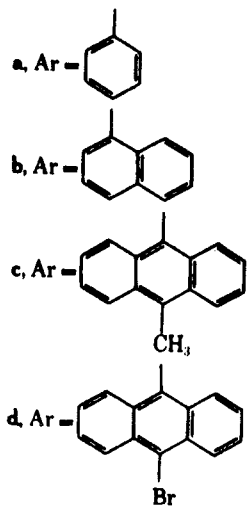
(**611**) R* = $CH_2CH(C_6H_5)CH_2CH_3$



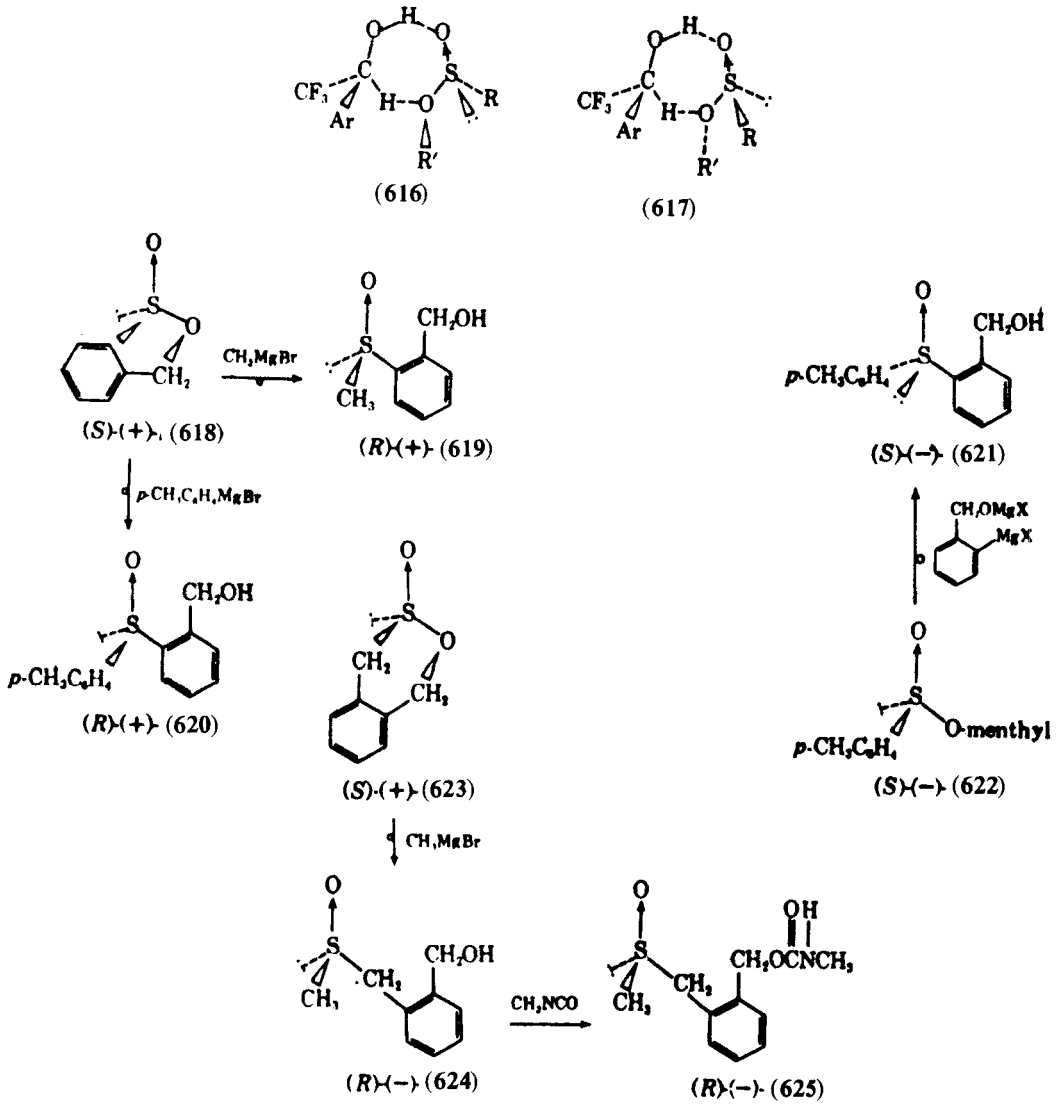
(**612**) (**613**)



(**608**)

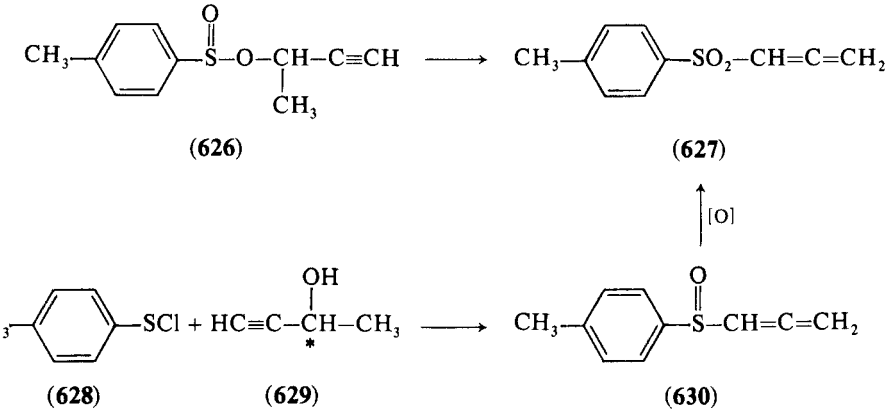


At 100 Hz in the presence of alcohols (**608c**) and (**608d**) sultine (**613**) showed clearly separated enantiomeric resonances of all four methylene protons. For all the S-enriched acyclic sulfinates (**609**) the (*S*)-(+)-fluoro alcohols cause the protons in the sulfinyl R group to have a low field sense of non-equivalence, whereas all alkoxyl R′ groups exhibit a high field sense of non-equivalence. Therefore it may be concluded that the dominant site of the secondary interaction in acyclic sulfinates is the alkoxyl oxygen as shown in structures (**616**) and (**617**). The absolute configurations assigned to sultines (**612**) and (**613**) were confirmed as shown in Scheme 34.



SCHEME 34

A highly stereospecific set of rearrangements of acetylenic esters of sulfinic and sulfenic acids has been observed[146] when the (+)-(*R*)-(**626**) ester upon thermal rearrangement gave levorotatory allenic sulfone (**627**) and when (+)-(*R*)-but-3-yn-2-ol (**629**) was treated with *p*-toluenesulfenyl chloride (**628**) to give levorotatory sulfoxide (**630**).

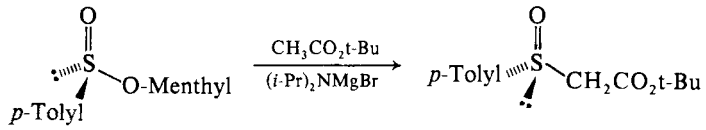


(626) (627) (628) (629) (630)

The optical rotation of (**627**) obtained from (**630**) showed a higher negative rotation than the sulfoxide suggesting a dextrorotatory contribution of the sulfoxide group to the optical rotation of (**630**). The proposed mechanism for the rearrangement involves a five member cyclic transition state schematically described in Scheme 35.

SCHEME 35

A new stereospecific synthesis of α-sulfinyl esters (**632**) involves[147] the reaction of an optically pure menthyl sulfinate (**631**) with the magnesium enolate of t-butylacetate. The reaction proceeds as expected with complete inversion of configuration.



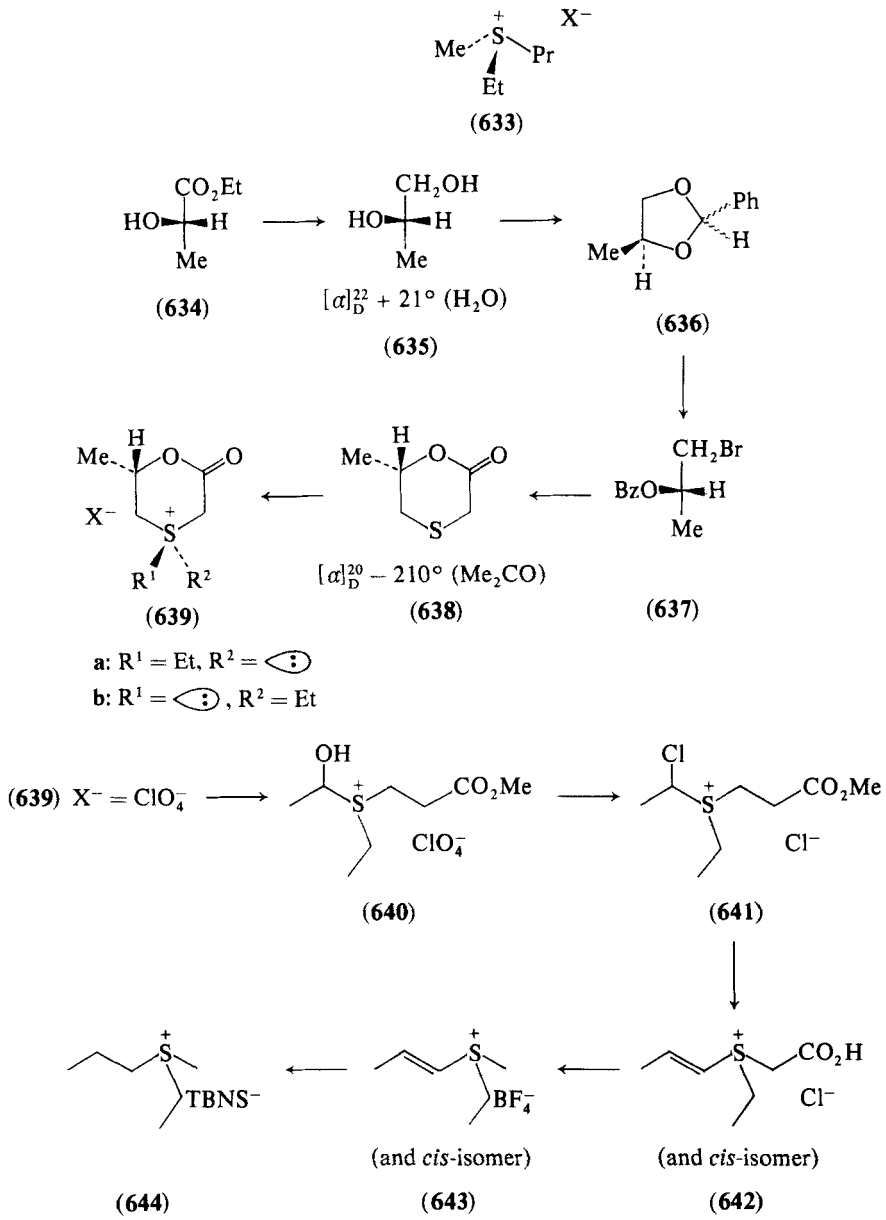
(−)*S*-(**631**) (+)*R*-(**632**)

IV SULFONIUM COMPOUNDS

Sulfonium Salts, Oxosulfonium Salts and Sulfonium Ylides

The absolute configuration of the simplest dextrorotatory trialkyl sulfonium salt (**633**) has been established by chemical correlations and confirmed by x-ray crystallography to have the *S*-configuration.[148] The cyclic sulfide (**638**) was alkylated to a mixture of diastereomeric sulfonium salts (**639**). One of the diastereomers was then further converted to (**644**). The same enantiomer was obtained via resolution of racemic (**644**) with α-bromo-π-camphorsulfonic acid.

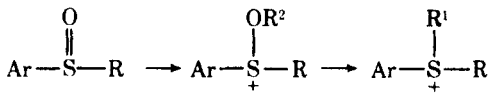
The steric course of the reaction whereby optically active dialkyl aryl sulfonium salts are prepared from optically active alkyl aryl sulfoxides by *O*-alkylation followed by treatment with dialkyl cadmium or alkyl Grignard reagents has been explored by Andersen *et al.*[149] (Scheme 36).



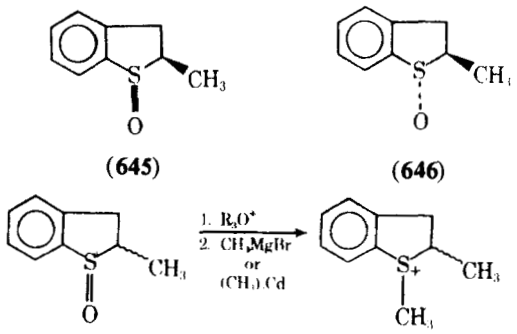
The reactions were carried out on the racemic isomeric sulfoxides (**645**) and (**646**) (Scheme 37).

As a model, the reactions were also carried out on optically active (*R*)-methyl *p*-tolyl sulfoxide. It was found that the reaction proceeds with inversion as is the case with most other nucleophilic substitutions as tri-coordinated sulfur; however, less stereospecificity is observed due to isomerization of the starting material.

The chiroptical properties including the first ord and cd spectral data on a series of dialkyl aryl sulfonium salts has been reported.[150] The sulfonium salts were obtained from the corresponding sulfoxides (Scheme 38).

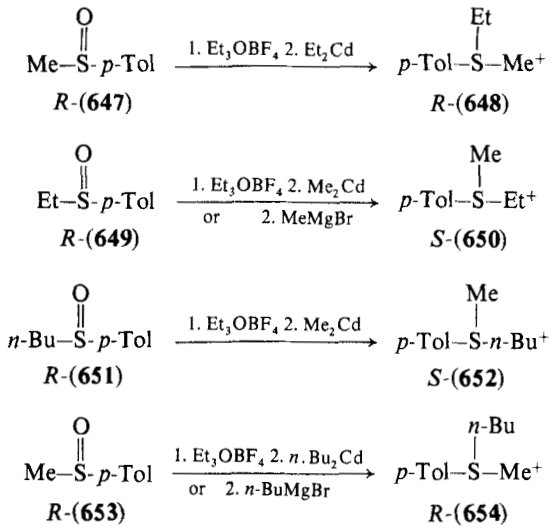


SCHEME 36



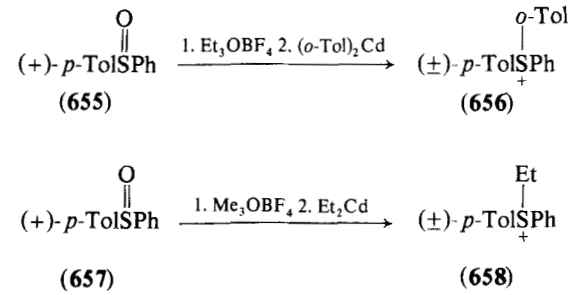
(645) (646)

SCHEME 37



SCHEME 38

The analogous reactions whereby the synthesis of optically active triaryl- or alkyldiaryl sulfonium salts were attempted (Scheme 39), produced only racemic sulfonium salts (**656**) and (**658**). In the case where dialkyl-sulfoxides were used as starting materials, the *O*-alkylated dialkyl sulfoxides did not react further with alkyl magnesium, alkyl cadmium or dialkyl magnesium reagents to form the desired trialkyl sulfonium salts.



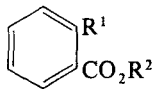
SCHEME 39

An acyloxysulfonium group has been postulated[151] as an intermediate in the reaction of sulfoxides with iodobenzene dichloride in the presence of carboxy groups. Depending on the reaction conditions, sulfones and α-chlorosulfoxides may be obtained. In the presence of silver ions (+)-(**660**) gave (–)-(**661**) whereas in their absence racemic (**661**) was obtained. The formation of the α-halo sulfoxides is stereospecific and proceeds with inversion at sulfur. Bromination of (**662**) in the presence of silver nitrate gives only one diastereomer (–)-(**664**).

A similar behavior is seen in the chlorination of (**662**) to (**663**). Oxidation of (**664**) gives (**665**), which upon subsequent reduction gives (−)-(**663**) 88% optically pure. Since the last reaction does not affect the sulfinyl group, it may be concluded that the bromination of (**662**) to (**664**) occurs with inversion at sulfur. The pathway postulated for the concomitant formation of α-chlorosulfoxides and sulfones is shown in Scheme 40.

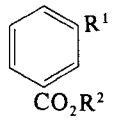
$R^1[CH_2]_2.CO_2R^2$

(**659**) $R^1 = Ph.SO$, $R^2 = Me$



(**660**) $R^1 = SO.Me$, $R^2 = Me$

(**661**) $R^1 = SO.CH_2Cl$, $R^2 = Me$

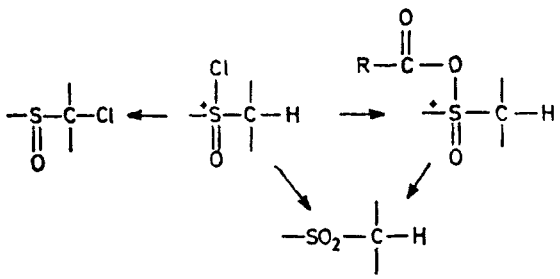


(**662**) $R^1 = SO.Et$, $R^2 = Me$

(**663**) $R^1 = SO.CHCl.Me$, $R^2 = Me$

(**664**) $R^1 = SO.CHBr.Me$, $R^2 = Me$

(**665**) $R^1 = SO_2CHBr.Me$, $R^2 = Me$



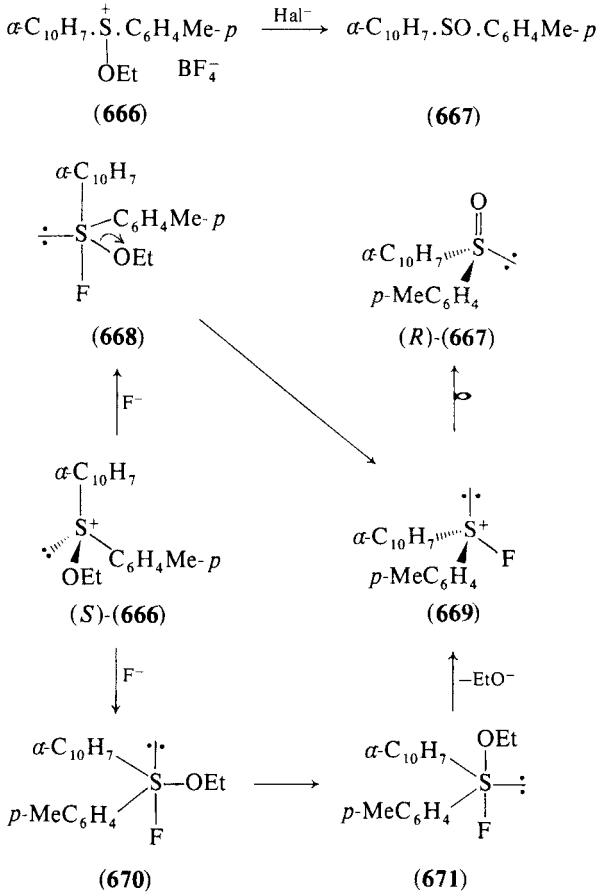
SCHEME 40

The stereochemical course of the reaction of optically active sulfonium salt (**666**) with halide ions[152] to give sulfoxide (**667**) depends on the nature of the halide. For chloride, bromide and iodide ions the reactions proceeds with retention at sulfur, whereas with fluoride net inversion is observed. In Scheme 41 are postulated two alternative pathways for the course of the reaction in the presence of fluoride ions, one involving apical attack by fluoride and equatorial departure of the leaving group ((**666**)→(**668**)→(**669**)→(**667**)) and Berry pseudorotation ((**666**)→(**670**)→(**671**)→(**669**)→(**667**)).

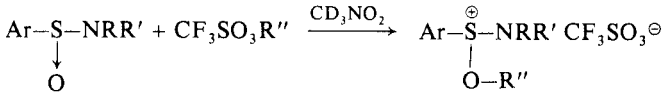
Minato *et al.*[153] reported that optically active salts (**672**) prepared either by resolution of diastereomers with optically active anions or by alkylation of optically active sulfinamides derived from optically active sulfinates, may be used as asymmetric alkylating agents, and the optically active sulfinamides can be recovered.

The asymmetric induction in the Sommelet rearrangement of chiral benzyl sulfonium salts has shown[154] that sulfonium salts (**673**) and (**674**), resolved via their (2*R*,3*R*)-hydrogen 2,3-dibenzoyltartrate salts, gave respectively (+)-(**676**) and (+)-(**677**) with about 20–25% asymmetric induction. Elution of (+)-(**673**) through a hydroxide exchange resin gave the ylide (+)-(**675**), which when treated with aldehydes produced racemic oxiranes.

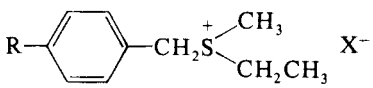
Chiral sulfonium ylides (−)-(**679**), (−)-(**680**) and (−)-(**682**) have been prepared[155] by acylation of (−)-ethylmethylsulfonium phenacylide (−)-(**678**), with benzoic anhydride, acetic anhydride and phenyl isocyanate respectively. Alkylation of (−)-(**678**) with dimethylsulfate gave the sulfonium salt (+)-(**681**). Compound (**681**) was also resolved via its dibenzoyltartrate salt. Under the resolution conditions the sulfonium salt (−)-(**681**) ($X = ClO_4^-$) was also isolated. The sulfonium ylides tended to racemize readily by pyramidal inversion.



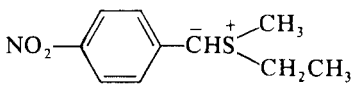
SCHEME 41



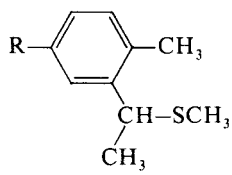
(672) { **a**: Ar = *p*-Tol, R = Ph, R′ = Me, R″ = Me
b: Ar = *p*-Tol, R, R′ = $(CH_2)_4$–, R″ = Et
c: Ar = Ph, R, R′ = $-CH_2CH_2OCH_2CH_2-$, R″ = Et
d: Ar = Ph, R, R′ = $-CH_2CH_2OCH_2CH_2-$, R″ = Me



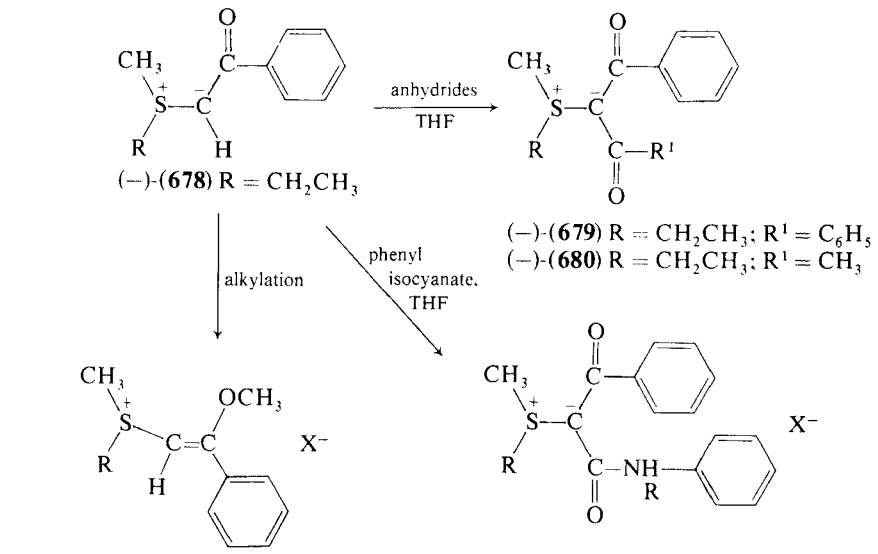
(+)-(**673**) R = NO_2, X = ClO_4
(+)-(**674**) R = Cl, X = ClO_4



(+)-(**675**)



(+)-(**676**) R = NO_2
(+)-(**677**) R = Cl



(−)-(**678**) R = CH_2CH_3

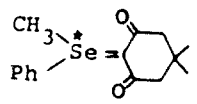
(−)-(**679**) R = CH_2CH_3; $R^1 = C_6H_5$

(−)-(**680**) R = CH_2CH_3; $R^1 = CH_3$

(+)-(**681**) R = CH_2CH_3; X = $CH_3SO_4^-$, ClO_4^-

(−)-(**682**) R = CH_2CH_3

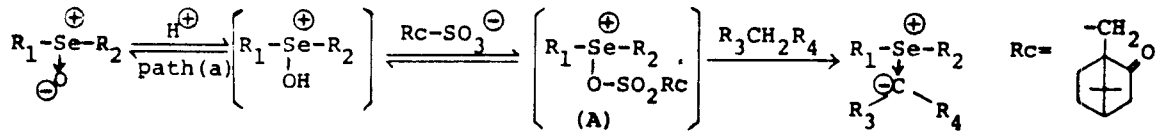
A related article reports[156] the first example of optically active selenonium ylides (**683**) obtained by asymmetric induction, when a solution of methyl phenyl selenoxide and *d*-10-camphorsulfonic acid in chloroform is treated with an equimolar amount of dimedone. Other selenonium ylides likewise obtained upon treatment with active methylene compounds are shown on Table II. The proposed mechanism of the reaction involves the formation of diastereomeric oxoselenonium salts A as shown in Scheme 42.



(**683**)

TABLE II

$R_1Se(O)-R_2$		Chem. yield (%)	$[\alpha]_D^{20}$	c	mp °C
Ph	CH_3	54.1	−0.96	1.9	123.5–124
o-$CH_3O-C_6H_4$	CH_3	96.8	−2.8	2.8	147–148
α-Np	CH_3	88.7	+0.91	2.9	162–164
Mesityl	CH_3	25.9	+4.9	1.7	oil
Ph	CH_2Ph	0.0	—	—	—



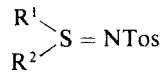
SCHEME 42

V SULFIMIDES, SULFOXIMIDES AND SULFODIIMIDES

A variety of novel methods for the synthesis of sulfimides, sulfoximides and sulfodiimides have been described. Partial reduction[157] of racemic sulfimides with L-(−)-cysteine gives unreacted sulfimides (**684**) in low optical yield (Table III).

TABLE III

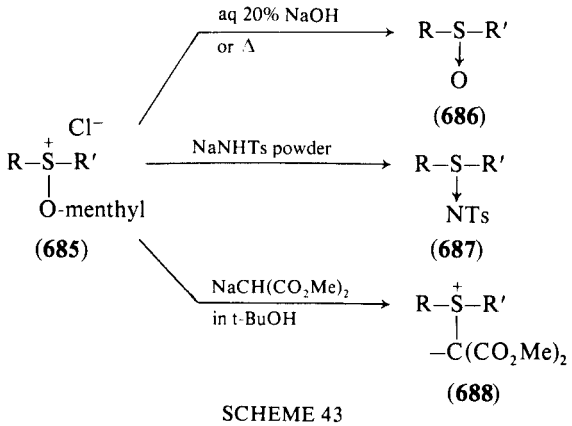
Optical activity of the unreacted sulfilimines



(**684**)

	R^1	R^2	$[\alpha]_{546}^{25}$
1a	CH_3	C_6H_5	+4.20
1b	CH_3	$C_6H_4CH_3(p)$	+5.40
1c	CH_3	$C_6H_4Cl(p)$	+5.94
1d	C_2H_5	C_6H_5	−5.16

The first examples[158] of optically active diaryl sulfimides have been obtained upon treatment of menthylsulfoxonium salts (**658**), with *N*-sodio *p*-toluenesulfonamide. Sulfoxides (**686**) and sulfonium ylides (**688**) may also be obtained from (**685**) as shown in Scheme 43. The ylides showed low optical stability even at room temperature. The thermolysis of (**685**) gave sulfoxides with retention of configuration, whereas the basic hydrolysis gave inverted sulfoxides.

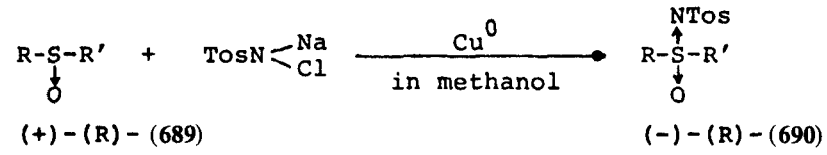


SCHEME 43

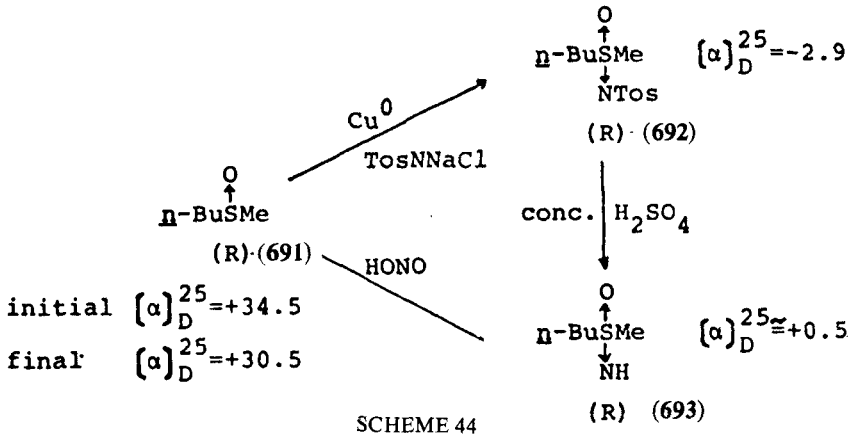
Optically active sulfoximides (**690**) were obtained[159] from the corresponding chiral sulfoxides (**689**) with chloramine T-copper in methanol. The reaction was shown to proceed with retention of configuration at sulfur by means of a stereochemical correlation involving the hydrolysis and deimidation reaction shown in Scheme 44.

The stable (*R*)-*S*-methyl-*S*-*p*-tolylsulfimide (**694**) isoelectronic with the corresponding sulfoxide, was obtained[160] upon resolution with (+)-α-bromo-π-camphorsulfonic acid. Treatment of (**694**) with chloroamine T gave the chiral sulfodiimide (−)-(**695**), which reacted with nitrous acid to give (*S*)-(**696**) in 84% optical purity. On the assumption that the reaction (**695**)→(**696**) proceeds with retention, then (−)-(**695**) possesses (*S*)-configuration.

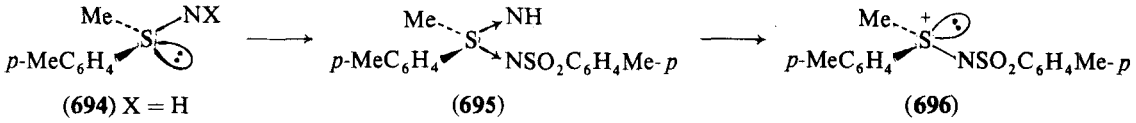
A simple one step method for the preparation of highly optically pure "free" sulfoximides (**697**) isoelectronic with the corresponding sulfones involves[161] the reaction of optically active sulfoxides with *O*-mesitylsulfonylhydroxylamine (MSH) (Table IV).



(+)-(R)-(689) (-)-(R)-(690)



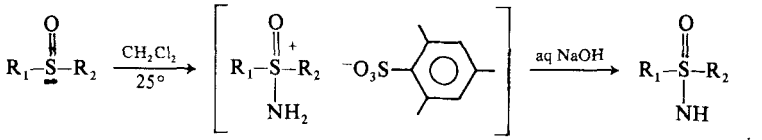
SCHEME 44



(694) X = H (695) (696)

TABLE IV

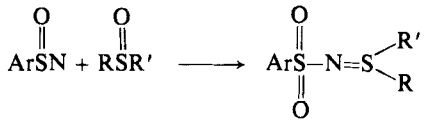
Reactions of Sulfoxides with MSH



(697) a–h

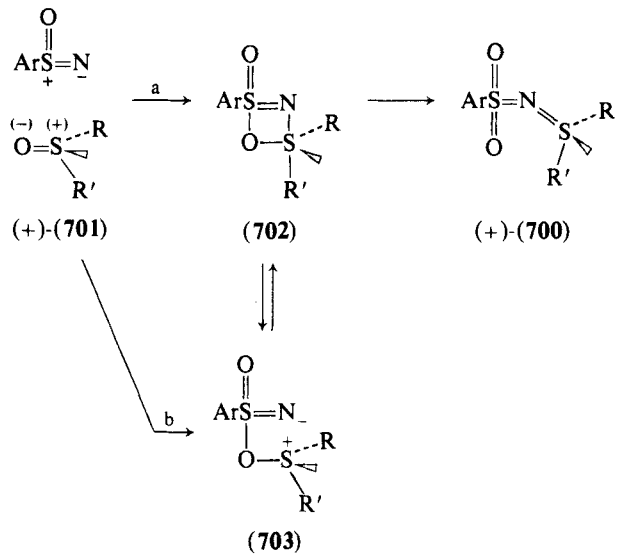
		Sulfoxide			Sulfoximine			
R_1	R_2	$[\alpha]_D^{25}$, deg (c, acetone)	Absolute confign.	Optical purity, %	$[\alpha]_D^{25}$, deg (c, acetone)	Absolute confign.	Optical purity, %	Reaction yield, %
CH_3	*p*-Tolyl	+145.0 (1.00)	*R*	99	−31.9 (3.00)	*R*	98.5	80
C_2H_5	*p*-Tolyl	+188.0 (1.10)	*R*	100	−22.0 (1.00)	*R*	99	70
$CH(CH_3)_2$	*p*-Tolyl	+191.1 (1.255)	*R*	100	−17.1 (1.005)	*R*	99	79
$(CH_2)_3CH_3$	*p*-Tolyl	+193.8 (1.430)	*R*	100	−17.2 (1.530)	*R*	99	77
$C_6H_5CH_2$	*p*-Tolyl	+234 (1.00)	*R*	93	+ 4.7 (1.26)	*R*	92	60
C_6H_5	*p*-Tolyl	+ 21.0 (1.090)	*R*	99.5	+ 5.0 (1.075)	*R*	99	19
C_6H_5	CH_3	−137.0 (1.20)	*S*	94	+34.1 (2.00)	*S*	93.5	70
CH_3	$(CH_2)_3CH_3$	−110.3 (1.985)	*R*	92	− 5.00 (1.209)	*R*	91.5	78

In their investigation on the properties of sulfinyl azides, Maricich and Hoffman[162] prepared *p*-toluenesulfinyl azide (**698**) which when thermally decomposed in the presence of (+)-*R*-methyl-*p*-tolylsulfoxide, (+)-(**701**), 99% optically pure, gave (+)-*R*-*N*-(*p*-tosyl)methyl-*p*-tolylsulfimide, (+)-(**700**), of 92.1% optical purity, resulting in an overall 96.5% retention of configuration. Two alternative plausible paths (a and b) are suggested for the formation of (+)-(**700**), both of which go through a cyclic sulfurane (**702**) (Scheme 45).



(698) (699) (700)

	Ar	R	R′
(+)-(700)	*p*-$CH_3C_6H_4$	CH_3	*p*-$CH_3C_6H_4$

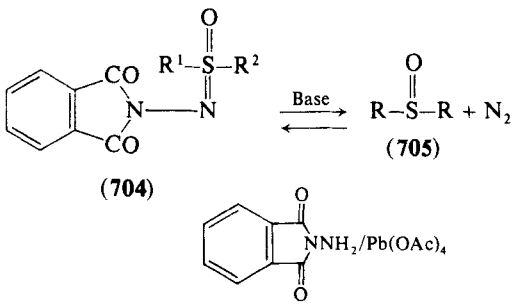


(+)-(701) (702) (+)-(700)

(703)

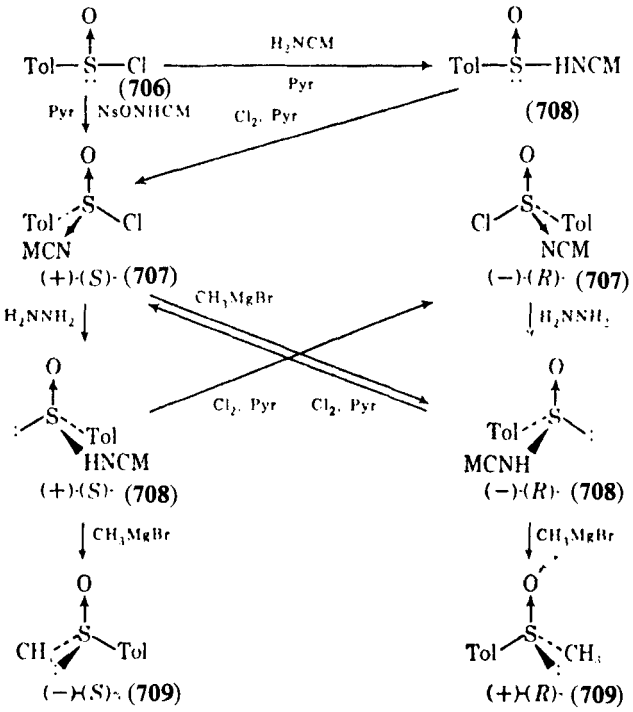
SCHEME 45

Optically active sulfoximides (**704**) have been obtained[164] upon reaction of chiral sulfoxides with *N*-aminophthalimide and lead tetracetate. The sulfoxides (**705**) could be regenerated in high optical purity when the sulfoximides were treated with a base such as sodium ethoxide or hydrazine in ethanol. Both reactions proceed with retention of configuration.



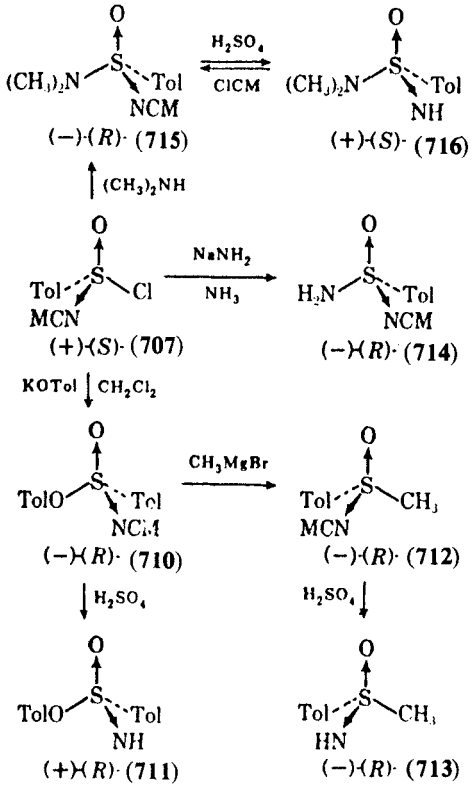
(704) (705)

The synthesis of *N*-carbomethoxy-*p*-toluenesulfonimidoyl chloride (**706**) and a study of the stereochemical course of its reactions has been described by Jones and Cram.[164] In Schemes 46 and 47 are shown the variety of the reactions studied and the stereochemical assignments of the products obtained. Tentative absolute configurations were made on the basis of analogies with previously known compounds and reactions, where substitutions taking place at the sulfur center proceed with inversion whereas those at one of the ligands without involvement of the sulfur proceed with retention.

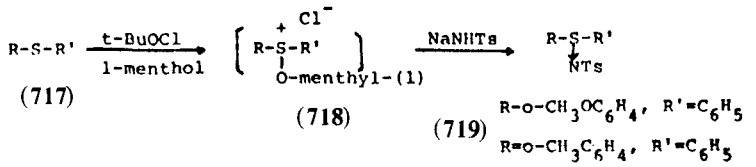


[a] Tol = *p*-$CH_3C_6H_4$; NCM = NCO_2menthyl-(−); Ns = *p*-$NO_2C_6H_4SO_2$.

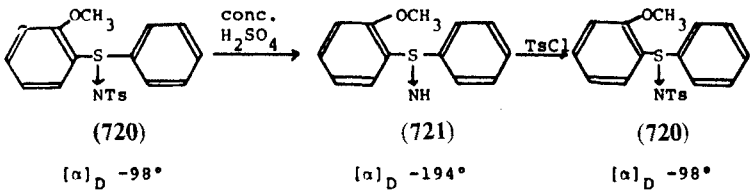
SCHEME 46



SCHEME 47

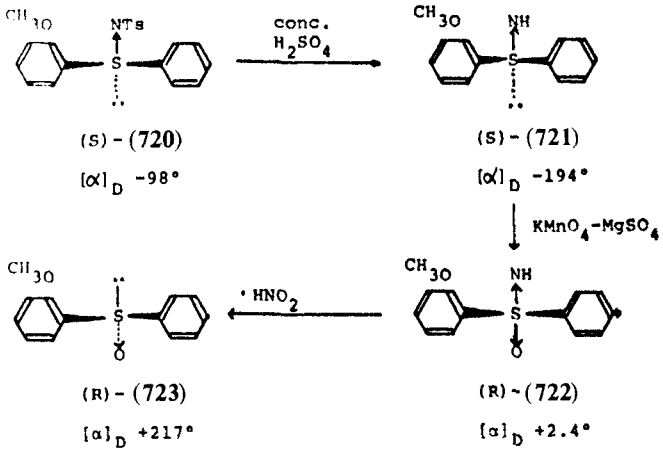


SCHEME 48

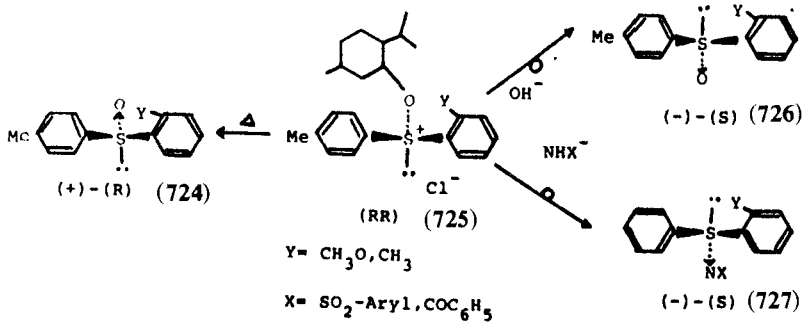


SCHEME 49

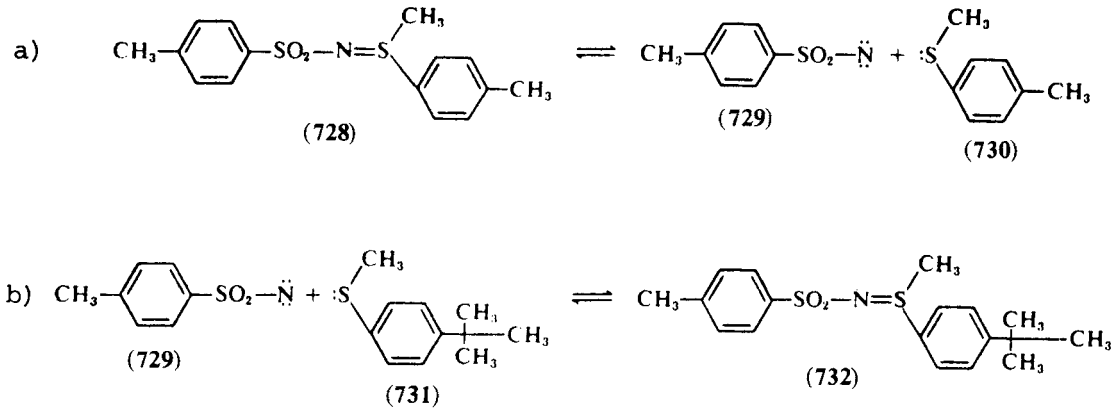
Optically active *o*-substituted diphenyl sulfimides have been prepared by Oae *et al.*[165,166] from the corresponding sulfides by a two step asymmetric induction sequence of reaction (Scheme 48). The thus obtained *N*-substituted sulfimide (**720**) could be converted into the corresponding free sulfimides (**721**) by acid hydrolysis (Scheme 49) and these in turn could be *N*-resubstituted. Oxidation of the free sulfimides (**721**) gave sulfoximides (**722**) which were deiminated with nitrous acid to the sulfoxides (**723**) (Scheme 50). The menthoxysulfonium salt (**725**) intermediate in the formation of the sulfimides was also converted to either one of the enantiomeric sulfoxides depending on the reaction conditions (Scheme 51). Extensive cd studies on these compounds show that sulfoxides and sulfimides free or substituted having the same configuration at sulfur have similar cd curves.



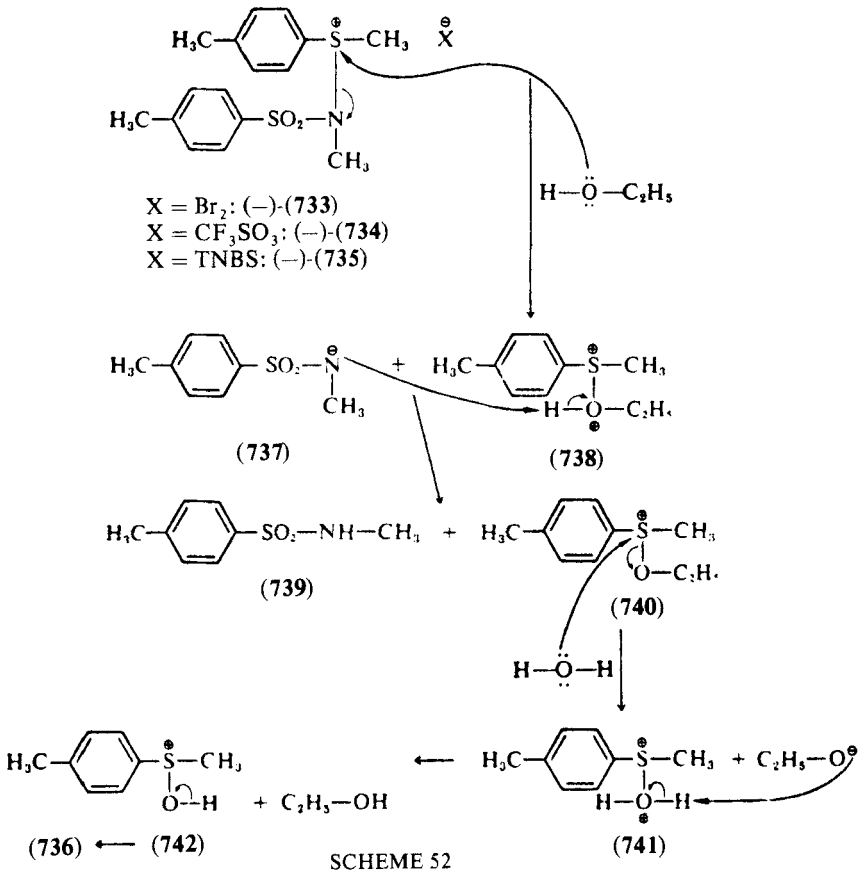
SCHEME 50



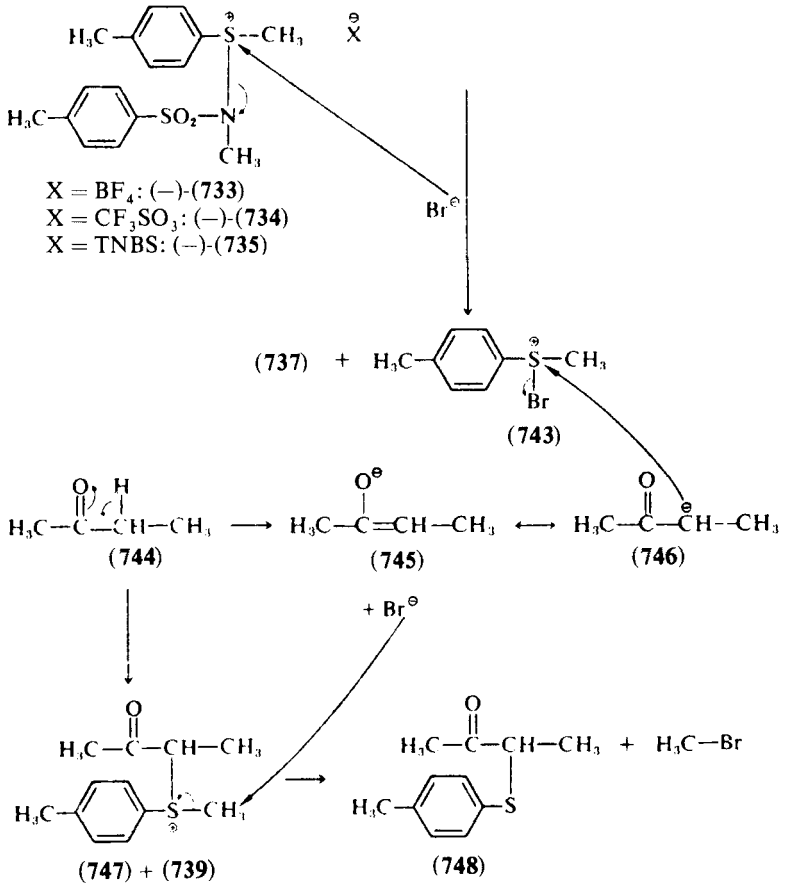
SCHEME 51



The first order polarimetric rate constants for the racemization of (−)-(**728**) have been determined by Darwish and Datta.[167] Two plausible mechanistic paths were considered: (a) dissociation-recombination via nitrene (**729**) and sulfide (**730**) or (b) pyramidal inversion. The fact that upon addition of sulfide (**731**) none of (**732**) was obtained after ten half lives of racemization, and the quantitative recovery of (**728**) strongly points to a pyramidal inversion process. Kinetic studies indicate that the barrier to pyramidal inversion in sulfimides is somewhat higher than that for sulfonium salts and sulfonium ylides but much lower than for sulfoxides. The sulfonium salts (−)-(**733**), (−)-(**734**) and (−)-(**735**) decomposed into sulfonamide (**739**) and methyl *p*-toly-sulfoxide (**736**) (Scheme 52), when treated with ethanol. In the presence of tetra-*n*-butylammonium bromide the products of decomposition were (**739**) and (**748**) (Scheme 53).

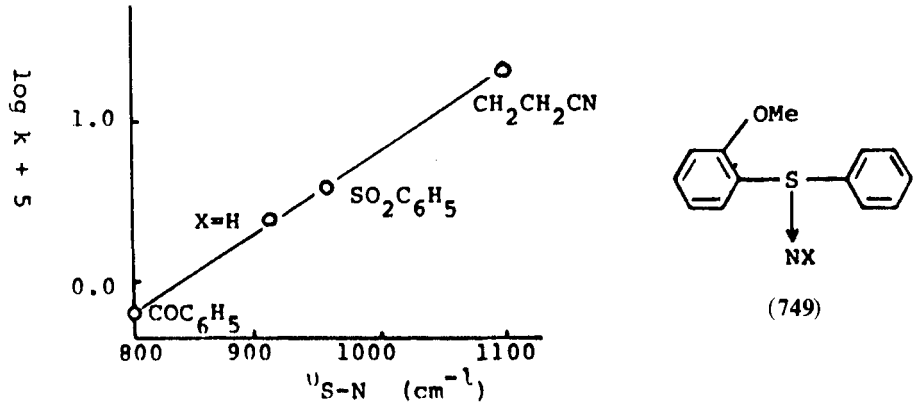


SCHEME 52



SCHEME 53

Subsequent studies[168] on the rate of thermal racemization of various *S*-*o*-anisyl *S*-phenyl *N*-(substituted)-sulfimides (**749**) explored the nature of the factors which affect the pyramidal inversion of the trivalent sulfur compounds. The rates of the racemization were clearly first order and the sulfimides did not undergo any decomposition. Electronic effects indicate that electron withdrawing groups on the nitrogen atom retard the rate of pyramidal inversion. In addition a decrease in the frequency of the infrared spectrum corresponds to a decrease in the rate of inversion. By plotting the log *k* versus the *S*—*N* stretching frequency it is possible to predict *S*—*N* stretching frequencies from the rate constants of racemization and vice versa (Scheme 54).

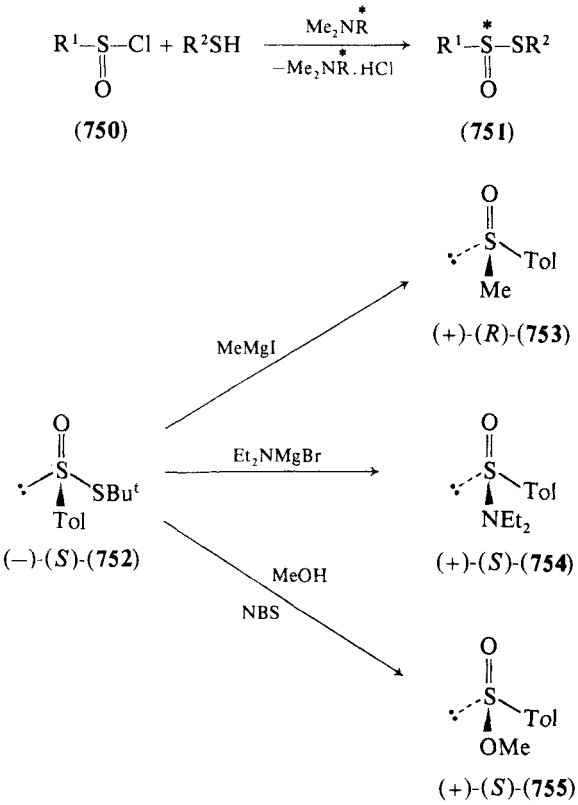


SCHEME 54

The x-ray structure of *S*-(+)-*N*-phthalimido-*p*-tolyl-α-naphthyl sulfoximide has been obtained by Sgarabotto and coworkers.[169]

VI THIOSULFINATES AND SULFINAMIDES

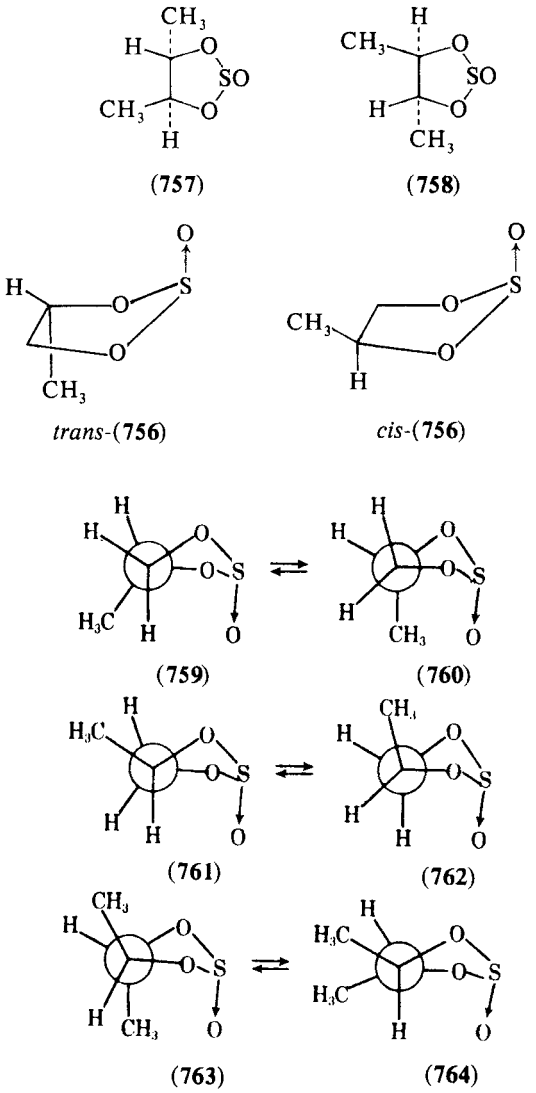
A novel method[170] for the asymmetric synthesis of chiral thiosulfinates (**751**) involves the reaction of sulfinyl chlorides and thiols in the presence of optically active tertiary amines. The absolute configuration of the thiosulfinates (**752**) were obtained upon conversion to the known sulfoxides (**753**) with the reasonable assumption that the reaction proceeded with inversion at sulfur. Other reactions afforded sulfinamides (**754**) and sulfinates (**755**).



VII SULFITES

Sarel *et al.*[171] have applied chiroptical methods in the configurational assignment of chiral sulfites. Three optically pure glycols (*S*)-(+)-1,2-propylene glycol, (*S,S*)-(–)-2,3-butylene glycol and (*R,R*)-(+)-2,3-butylene glycol, were converted in the corresponding *cis* and *trans* sulfites, (**756**), (**757**), (**758**), upon treatment with thionyl chloride. The sulfites show in the uv spectrum only one maxima at (**213**)–(**218**) nm. The two (**756**) diastereomers although identical with (**757**) in the alkyl moiety configuration differ in the chiroptical properties, and they do not exhibit antipodal relationship in the cd curves. The chirality of the ring may be the factor determining the sign of the Cotton effect in the cyclic sulfites. The equilibrium conformation of the respective compounds are shown in Scheme 55. In the case of *cis*-(**756**) the preferred configuration should be (**759**) due to lower interaction between the methyl and S–O group. In the *trans*-(**756**) where this interaction is greatly diminished approximately equal populations of (**761**) and (**762**) are to be expected. Sulfite (**757**) conformation (**763**) is expected to be more populated. Increasing solvent polarity should lead to an increase in the intensity of

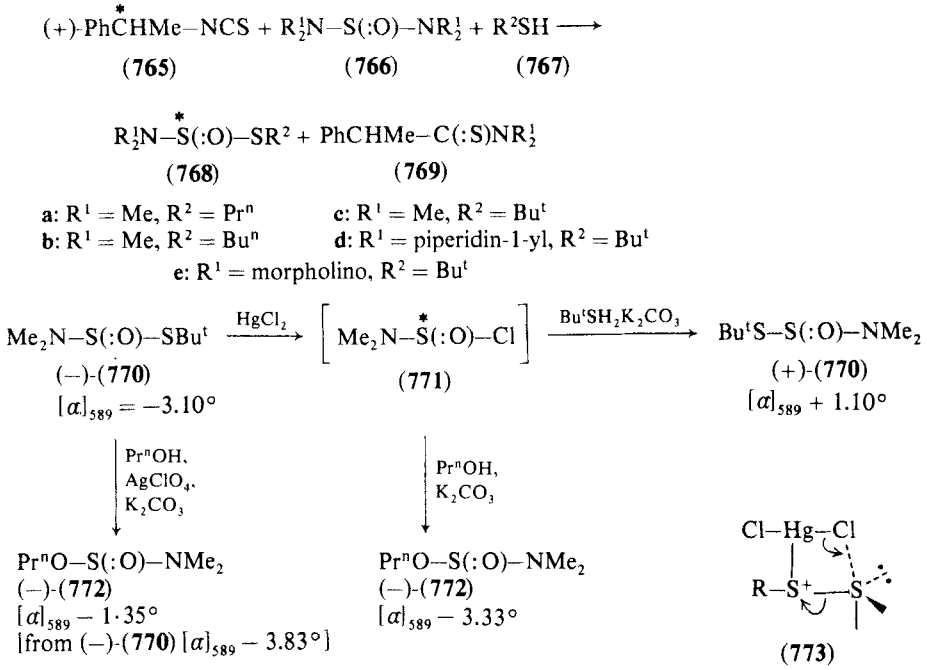
the long-wavelength dichroic band in *cis*-(**756**) since owing to solvation there is a stronger non-bonded interaction between the S—O group and the methyl, and the dihedral angle is increased, which is the observed situation. In *trans*-(**756**) no solvent effect is observed as expected.



SCHEME 55

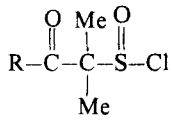
VIII AMIDOTHIOSULFITES

The first examples of the novel family of chiral amidothiosulfites (**768**) have been prepared by Mikolajczyk and Drabowicz.[172] Treatment of a mixture of (+)-α-phenylethylisocyanate (**765**) and the diamide (**766**) with an equimolar amount of an achiral thiol (**767**) gave optically active amido-sulfite (**768**). When (—)-(**770**) was treated with mercury chloride the optically active, unstable, amido sulfinyl chloride (**771**) was obtained which *in situ* was converted to (+)-(**770**). In order to determine the stereochemistry of these reactions both (—)-(**770**) and (**771**) were propanolyzed to the amidosulfite (—)-(**772**). Since the stereochemical course of reactions **c** and **d** is expected to be the same and to proceed with inversion it follows that reaction **a** proceeds with retention, by the proposed four-member transition state (**773**).



IX SULFINYL CHLORIDES

A family of novel β-ketosulfinyl chlorides (**774**) obtained by treating the isopropyl ketons with thionyl chloride has been described.[173] The magnitude of non-equivalence of the α-gem-dimethyl groups can be readily observed and was shown to be temperature and solvent dependent and is probably due to both intrinsic diastereoisomerism as well as to the presence of rotational conformers.

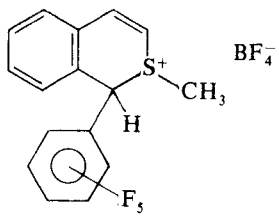


(774)

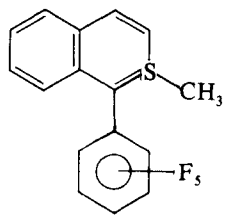
X THIABENZENES

The first example (**776**) of this new chiral sulfur family has been prepared upon deprotonation of compound (**775**) with brucine in anhydrous dimethyl sulfoxide.[174,175]

The optically active (**776**) was quite unstable in the presence of brucine hydrofluoroborate; however, it was stabilized upon treatment with sodium methoxide. The barrier for pyramidal inversion obtained from the decrease in intensity of the cd spectrum was at least 23.7 kcal/mol, suggesting an ylide-type character for the thiabenze molecule.



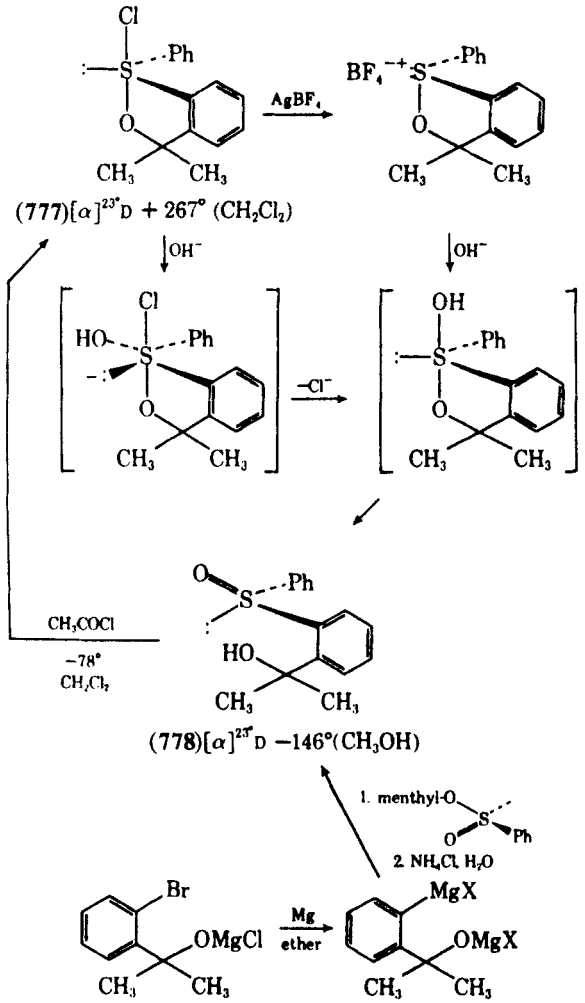
(775)



(776)

XI HALOSULFURANES

The first example[176] of a novel chiral halosulfurane (**777**) has been described by Martin *et al.* Compound (**777**) prepared as indicated, underwent basic hydrolysis with retention to sulfoxide (**778**). The enantiomeric purities of (**777**) and (**778**) were determined by their nmr spectra using (*S*)-(+)-1-(10-methyl-9-anthryl)-2,2,2-trifluoroethanol.



SCHEME 56

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