Chemical Interconversion of the β-Lactam Antibiotics

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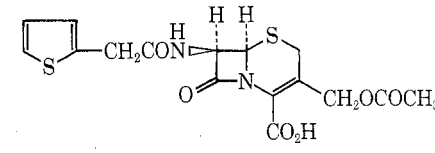
In 1955, a new antibiotic was isolated by Newton and Abraham[1] from *Cephalosporium acremonium*. This antibiotic, cephalosporin C, had a relatively weak antimicrobial spectrum which was, however, distinguished by an effectiveness against penicillin-resistant organisms. In 1961, when structure 1 was determined by both chemical[2] and X-ray[3] techniques and when its structural relationship to penicillin was realized, a world-wide interest in this molecule was generated.

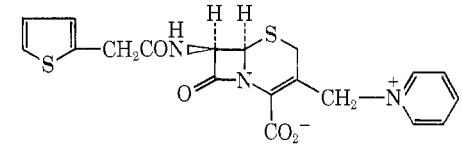
The penicillins, which were the first medically accepted antibiotics, were a powerful stimulus to chemical and microbiological research. The chemistry of the penicillins, a continuing 30-year research program from which has evolved many clinically effective antibiotics, was dependent on the successful modification of the fermentation to allow isolation of the penicillin nucleus, 6-aminopenicillanic acid (6-APA) (2). Acylation of 2 furnished the many variations of the penicillin molecule. Because of their broad clinical utility, the production of penicillins has become a major manufacturing business in many countries of the world. Moreover, modern technology allows the organic chemist to consider the penicillin molecule as a useful, economical starting material for the synthesis of a variety of derivatives.

The activity of cephalosporin C, although possessing some intriguing features, was not sufficient for the compound to become a candidate for clinical medicine. In the hope of achieving a success story with this new structure parallel to that of the penicillins, efforts were made to isolate the nucleus, 7-aminocephalosporanic acid (7-ACA) (3). In spite of intensive investigation, enzymatic cleavage of cephalosporin C has not been achieved and the microbiologist has had to rely on the chemist for synthesis of 3. Using nitrosyl chloride, Morin, *et al.*,[4] in 1962 generated 7-ACA in practical amounts for use in structure modification. Since that time, four cephalosporin antibiotics have been developed for clinical use.

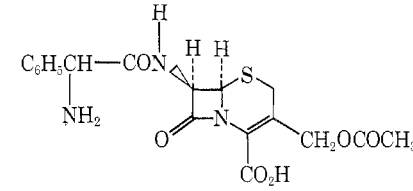
Chart I
Clinical Cephalosporins



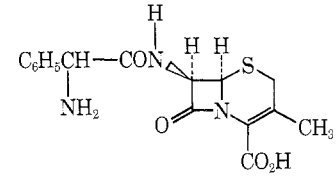
cephalothin



cephaloridine



cephaloglycin



cephalexin

The cephalosporin or "cephem" system generally is two oxidation levels above that of the penicillin or "penam" system. An exception is cephalexin, which is at an oxidation level midway between the penam and "normal" cephem structures. This deacetoxy cephem structure has been synthesized from 7-ACA by catalytic reduction.[5] However, the use of large amounts of noble metal catalyst makes this route to the antibiotic economically unrealistic.

Another possible approach evolved from the structural similarity of the cephalosporins and penicillins and, thus, the possibility of achieving an economic synthesis of cephalexin from penicillin.

Attempting a chemical transformation presented formidable problems; the published research on penicillin furnished no precedent for opening the thiazo-

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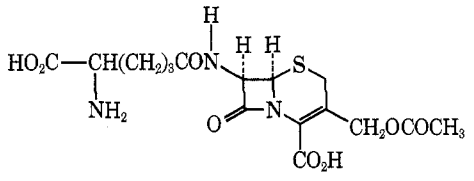
L. D. Hatfield did undergraduate work at Berea College and received the Ph.D. degree from Ohio University in 1966 under Professor W. D. Huntsman. He joined Eli Lilly and Company in 1966 as a Senior Organic Chemist and was promoted to Research Scientist in 1970. Dr. Hatfield's responsibilities at Eli Lilly and Company include the design of manufacturing processes for penicillin and cephalosporin compounds.

D. O. Spry received a B.S. degree from Iowa State University in 1960 and was employed by Goodrich Gulf Chemicals until entering graduate school at Michigan State University, receiving a M.S. in 1963 under Professor G. J. Karabatsos. He joined Eli Lilly and Company in 1965 and has worked on prostaglandins and β-lactam antibiotics.

(1) G. G. F. Newton and E. P. Abraham, *Nature (London)*, 175, 548 (1955).
(2) E. P. Abraham and G. G. F. Newton, *Biochem. J.*, 79, 377 (1961).
(3) D. C. Hodgkin and E. N. Maslen, *Biochem. J.*, 79, 393 (1961).
(4) R. B. Morin, B. G. Jackson, E. H. Flynn, and R. W. Roeske, *J. Amer. Chem. Soc.*, 84, 3400 (1962).
(5) C. W. Ryan, R. L. Simon, and E. M. Van Heyningen, *J. Med. Chem.*, 12, 310 (1969).



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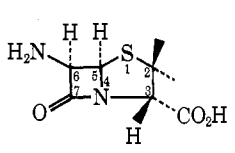

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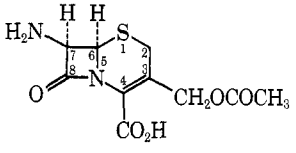

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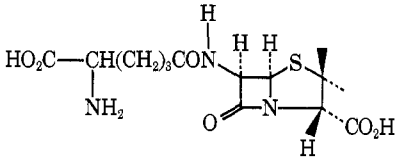

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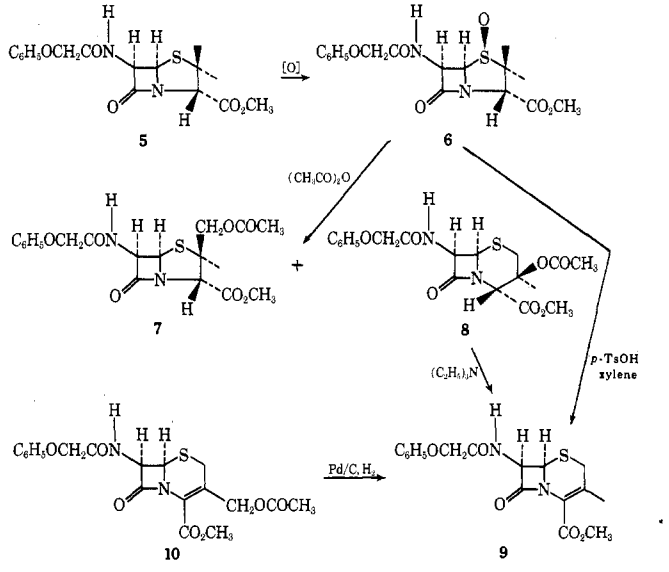
lidine ring and carrying out the requisite changes while still retaining the sensitive β-lactam function. An attraction was the economic availability of a molecule (penicillin) which possessed the correct asymmetry and most of the functionality.

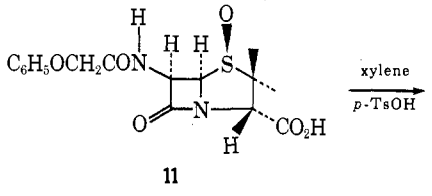
Morin and coworkers[5,6] approached this problem by activation of the sulfur to cleave the S–C_2 bond. Since the overall process was an oxidative one, they investigated the chemistry of penicillin sulfoxide derivative 6, obtained by oxidation of sulfide 5 with sodium metaperiodate. One additional advantage of using 6 for any chemical transformations was that the sulfoxide bond imparted considerable acid stability to the previously sensitive β-lactam bond.



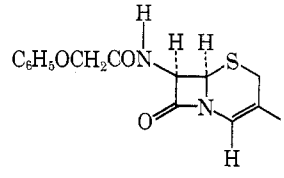
Sulfoxides possessing α-hydrogen atoms normally react with acetic anhydride to give α-acetoxy sulfides (Pummerer reaction); however, Morin, *et al.*,[6] found that 6 was stable under these conditions. They presumed that this stability was due to the unfavorable introduction of a C_5–sulfur double bond because of the steric requirements of the fused-ring system. However, treatment of 6 with refluxing acetic anhydride gave a 2:1 mixture of β-lactam-containing materials 7 and 8 in 60% yield. Compound 7 was shown by nmr and other physical chemical techniques to be the 2β-acetoxymethylpenicillin, whereas, 8 was the 3-acetoxycepham.

Treatment of 8 with base caused elimination of acetic acid to give the deacetoxycephem derivative 9, which could also be obtained by a palladium-catalyzed hydrogenation of cephalosporin 10.[6] This was the first chemical correlation between the penicillin and cephalosporin families of antibiotics.

Compound 9 was also obtained more directly from the penicillin sulfoxide in 10–15% yield by heating 6 in xylene containing *p*-toluenesulfonic acid. Under these reaction conditions the penicillin sulfoxide acid (11) underwent rearrangement of the thiazolidine ring with concomitant decarboxylation to give 12 as the major product.



11



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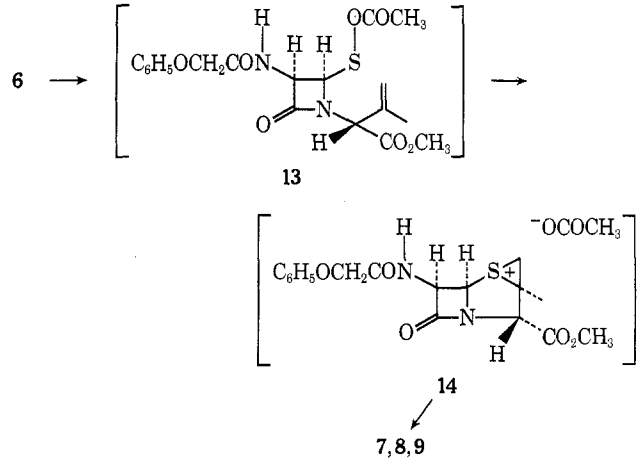
The mechanism originally postulated to explain these unusual products involved initial formation of a sulfenic anhydride (13) followed by addition to the double bond to give an episulfonium ion (14), from which the observed β-lactam products are easily accessible. This mechanism, daring in its originality, has stood up remarkably well to the sophisticated probes of other groups of investigators.



The need for an economic synthesis to cephalexin, a potentially valuable addition to the clinical arsenal, and the lure of the intriguing possibilities

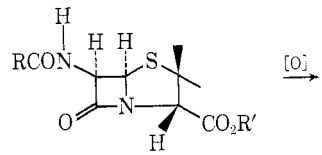
(6) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 85, 1896 (1963); 91, 1401 (1969).

opened by Morin and coworkers have been the basic driving forces of the work summarized in this Account.

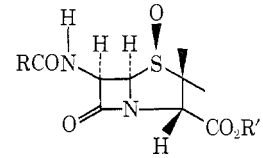
Structure of Penicillin Sulfoxides

Synthesis. Sykes and Todd, the first to oxidize a penicillin derivative to the sulfoxide, converted **15** to **16** using sodium metaperiodate.[7] More recently the oxidation has been reported by several groups with considerable variation in the penicillin derivative and the oxidizing agent employed. Chow, *et al.*,[8] extended sodium metaperiodate oxidation to other penicillin esters, and Essery, *et al.*,[9] used sodium metaperiodate in aqueous solutions for direct oxidation of the acids. Other workers have used hydrogen peroxide in acetic acid,[10] *m*-chloroperbenzoic acid,[11,12] iodobenzene dichloride in aqueous pyridine,[13] ozone,[11,14,15] and aqueous bromine.[16]

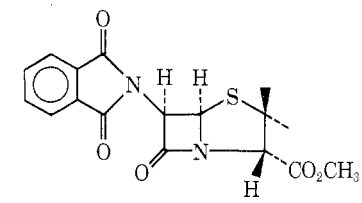
Many variations of penicillin substitution have been successfully utilized, and, in general, the oxidation is a facile process proceeding in high yields. The theoretical possibility of two sulfoxide isomers exists; until 1969, however, the possibility of more than one isomer from all the oxidation variations had not been mentioned. Then Cooper and coworkers[11] reported the peracid oxidation of various penicillin derivatives under different conditions when attempting to obtain two isomeric sulfoxides. They also attempted several unsuccessful methods of sulfoxide epimerization. They determined by nmr arguments that when the penicillin contained a secondary amido side chain, the sulfoxide stereochemistry was *S*,[11] whereas, when the amide was tertiary, the *R* stereochemistry resulted,[12] *i.e.*, **17** → **18** and **19** → **20**.



15, R = $C_6H_5CH_2$; R′ = CH_3
17, R = $C_6H_5OCH_2$; R′ = CCl_3CH_2



16, R = $C_6H_5CH_2$; R′ = CH_3
18, R = $C_6H_5OCH_2$; R′ = CCl_3CH_2



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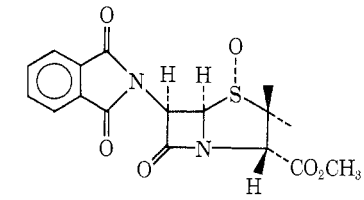

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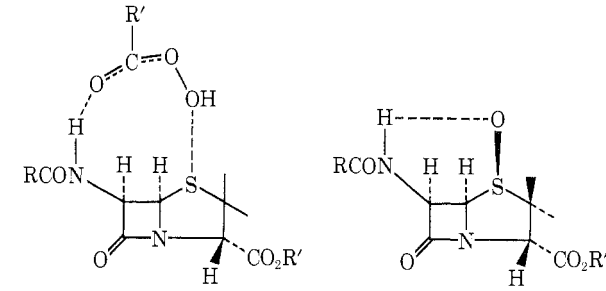


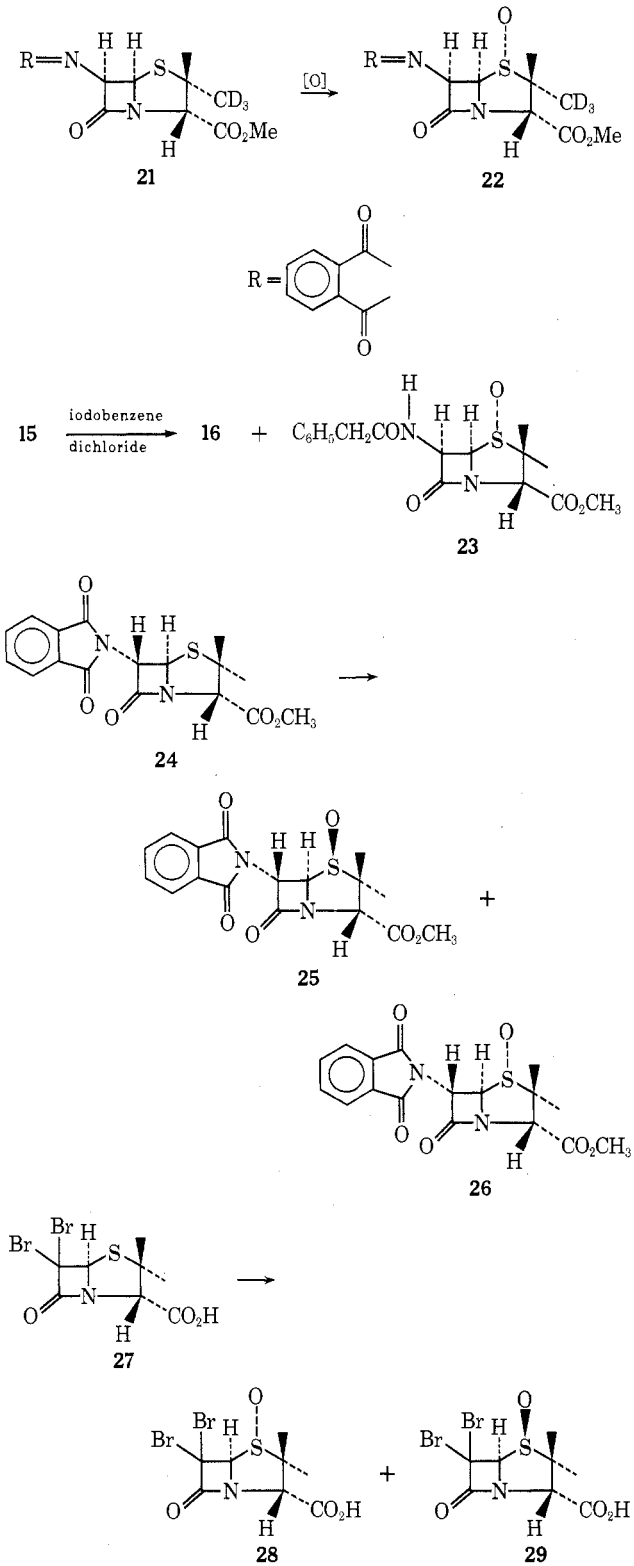
Figure 1

The reason suggested for this remarkable stereochemical control was that the amide NH, involved in hydrogen bonding to the peracid, establishes a "reagent approach control" to the sulfoxide stereochemistry (see **Figure 1**). It was also noted that, though the (*S*)-sulfoxide was the more sterically hindered, it possessed a strong internal hydrogen bond to the amide NH which also caused it to be more thermodynamically stable product. However, the oxidations were carried out under kinetic control, and the hydrogen bonding explanation was favored. The phthalimidopenicillin oxidation was sterically controlled and, thus, furnished the *R* stereochemistry.

An alternative explanation for obtaining only the *R* stereochemistry assumed that a stereochemical mixture was obtained on oxidation. The (*S*)-sulfoxide, however, then isomerized to the more thermodynamically stable (*R*)-sulfoxide *via* a sulfenic acid intermediate. This was elegantly disproved by Spry[14] who oxidized α-trideuteriomethyl sulfide (**21**) to the (*R*)-sulfoxide (**22**). The trideuteriomethyl group had the α stereochemistry, which would be predicted from steric control of oxidation, whereas thermodynamic control should result in a mixture of α- and β-CD_3 configurations. Confirmation of the nmr arguments for the structure of **11** was obtained by an X-ray crystallographic study.[11]

Similar arguments have also allowed others to assign sulfoxide stereochemistry in the penicillins. Barton, *et al.*,[13] developed an oxidizing procedure which gave a 1:1 mixture of isomers **16** and **23** when treating **15** with iodobenzene dichloride. An isomeric mixture of sulfoxides was also obtained when the proposed directing influences were removed; *i.e.*, where the steric interaction was decreased, 6-epiphthalimidopenicillin methyl ester (**24**) gave a mixture of **25**

(7) P. Sykes and A. R. Todd in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, pp 156, 946, and 1008.
(8) A. W. Chow, N. M. Hall, and J. R. E. Hoover, *J. Org. Chem.*, 27, 1381 (1962).
(9) J. M. Essery, K. Dadabo, W. J. Gottstein, A. Hallstrand, and L. C. Cheney, *J. Org. Chem.*, 30, 4388 (1965).
(10) E. Guddal, P. Morch, and L. Tybring, *Tetrahedron Lett.*, 381 (1962).
(11) R. D. G. Cooper, P. V. Demarco, J. C. Cheng, and N. D. Jones. *J. Amer. Chem. Soc.*, 91, 1408 (1969).
(12) R. D. G. Cooper, P. V. Demarco, and D. O. Spry, *J. Amer. Chem. Soc.*, 91, 1528 (1969).
(13) D. H. R. Barton, F. Comer, and P. G. Sammes, *J. Amer. Chem. Soc.*, 91, 1529 (1969).
(14) D. O. Spry, *J. Org. Chem.*, 37, 793 (1972).
(15) D. O. Spry, *J. Amer. Chem. Soc.*, 92, 5006 (1970).
(16) J. P. Clayton, *J. Chem. Soc. C*, 2123 (1969).



and 26,[12] and 6,6-dibromopenicillin (27) gave sulfoxides 28 and 29.[16]

Spry has shown[14,15] that oxidation of 30 with ozone in a protic solvent results in a 1:1 ratio of isomeric sulfoxides 11 and 31 in quantitative yield.

Nmr Studies on Penicillin and Penicillin Sulfoxides. The initial assignment of the sulfoxide stereochemistry in phenoxymethylpenicillin sulfoxide ester 6 as β or *S* was made by Morin, *et al.*,[6] from consideration of the shielding effects of the S–O

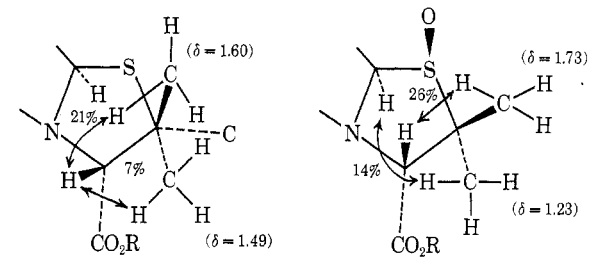
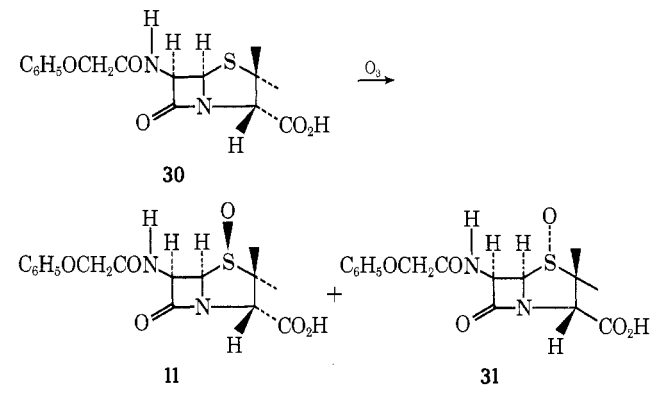


Figure 2. Nuclear Overhauser effects in penicillin esters and penicillin sulfoxide esters.



bond. Cooper, *et al.*,[11,12] conducted a more detailed study which initially involved a rigorous assignment of spectral signals. The protons at C-3, C-5, and C-6 were self-evident from their multiplicity; however, the two methyl-signal assignments were questionable and were resolved by application of nuclear Overhauser effects,[11] a well-substantiated method for defining which protons in a molecule are spatially proximal. The values obtained are shown in Figure 2 and, in addition, show an interesting conformational change between sulfide 5 and sulfoxide 6.

Once the signal assignments were proven, the authors measured the aromatic-induced solvent shifts (ASIS) in deuteriochloroform and benzene (d_6) for both 5 and 6. They reasoned that the observed shift differences for 5 and 6 were caused by the introduction of the sulfoxide bond into the molecule (see Table I). Only two signals were significantly shield-

Table I
Benzene-Induced Solvent Shifts[a] for Penicillin Methyl Ester (5) and Its Sulfoxide 6

	H_3	H_5	H_6	2α-CH_3	2β-CH_3
5 ($CDCl_3$)	4.47	5.58	5.74	1.49	1.60
(C_6D_6)	4.39	5.11	5.54	1.13	1.20
Δ^1	+0.08	+0.47	+0.20	+0.36	+0.40
6 ($CDCl_3$)	4.69	5.03	6.10	1.23	1.73
(C_6D_6)	4.65	3.77	5.93	0.51	1.23
Δ^2	+0.04	+1.26	+0.17	+0.72	+0.50
Δ^2-Δ^1	−0.04	+0.79	−0.03	+0.36	+0.10

[a] In parts per million.

ed: those of H_5 and the 2α-methyl group. Together with the previously known characteristics of benzene bonding to the positive end of the sulfur–oxygen dipole, this indicated the *S* stereochemistry. Application of ASIS to 19 and 20 gave no readily interpretable results. The configuration of 20 was assigned by

epimerization of the side chain to the 6-episulfoxide **26**, identical with one of the sulfoxides obtained by oxidation of the 6-epipenicillin sulfide **24**. Interpretable solvent shifts of sulfoxides **25** and **26** allowed stereochemical assignment. The *R* stereochemistry of **20** prevented the simple solute–solvent interaction.

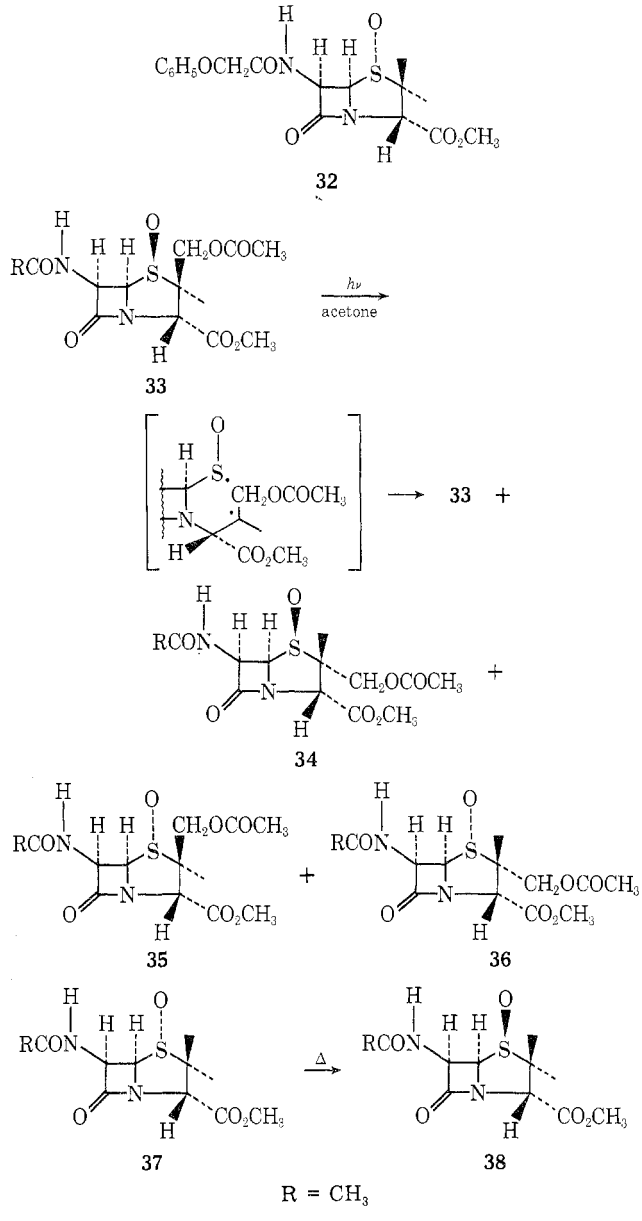
A simple technique was evolved by Cooper, *et al.*,[11] to determine sulfoxide stereochemistry in cases where a secondary amido side chain was present. The internuclear distance between the amido NH proton and the oxygen of a (*S*)-sulfoxide is 1.6 Å, and the downfield shift of the NH proton of a (*S*)-sulfoxide compared to the sulfide or (*R*)-sulfoxide demonstrated the formation of an intramolecular –NH---O–S hydrogen bond. Changing the solvent from $CDCl_3$ to DMSO (d_6) confirmed this hydrogen bonding. In cases where hydrogen bonding existed, *e.g.*, (*S*)-sulfoxide, there was little or no shift of the NH signal. Substantial shifts (>1 ppm) were observed where there was no internal hydrogen bond, *e.g.*, sulfide or (*R*)-sulfoxide.

Anistropy changes on oxidation of the penicillins to sulfoxides have been studied by several investigators.[11,12,13,17] The general observation has been that a syn-axial effect causes deshielding of the protons at C-3 in (*S*)-sulfoxides, and that this allows assignment of *S* stereochemistry in some instances. A more detailed examination by Cooper, *et al.*,[11] has shown that any attempted stereochemical assignments based on shielding effects of a sulfoxide bond should be treated with caution, since the knowledge of the screening environment around a sulfoxide bond is somewhat nebulous. Attempts to correlate this with an acetylenic bond and calculate the expected shifts for the various protons in the (*S*)- and (*R*)-sulfoxides indicated a good qualitative agreement for the (*S*)-sulfoxide, while no similar agreement for the (*R*)-sulfoxide was apparent.

Epimerization of Penicillin Sulfoxides. Previous to the reported oxidation of the sulfides by agents capable of producing both sulfoxide isomers, attempts were made to obtain **32** by epimerization of the (*S*)-sulfoxide **6**. Cooper, *et al.*,[11] reported unsuccessful application of the standard procedures using trimethyloxonium fluoroborate and acetyl chloride.

A successful method was reported by Archer and Demarco[17] who subjected the (*S*)-sulfoxide **6** to irradiation in acetone using a Pyrex filter to give a mixture of **6** and **32**. Spry[15] applied this procedure to **33** and obtained a mixture of isomers **33**, **34**, **35**, and **36**. This experiment also established that photochemical racemization proceeds through a homolytic cleavage of the $S–C_2$ bond to a diradical.

It has been reported that (*R*)-sulfoxide **37** thermally epimerizes in refluxing benzene to the more thermodynamically stable (*S*)-sulfoxide (**38**)[17] and that under similar conditions (*R*)-sulfoxide **26** epimerizes to an equilibrium of (*R*)- and (*S*)-sulfoxides (**26** and **25**).[18] Furthermore, Spry has also reported that **35** thermally epimerizes to **34**.[15] The possibilities that these facile sulfoxide epimerizations proceed through pyramidal inversion or homolytic scission–recombination mechanisms were considered unlikely owing to the far greater energy requirements of these mechanisms, and a sulfoxide–sulfenic acid equilibrium was invoked as the explanation.[15,19]



Rearrangements of Penicillin Sulfoxides

Penicillin Sulfoxide–Sulfenic Acid Equilibrium. Morin, *et al.*,[6] proposed that the rearrangement of a penicillin sulfoxide proceeds through a sulfenic anhydride, followed by an intramolecular trans addition to the double bond, to an episulfonium ion (**14**). The logical precursor of **13** was regarded by Morin and by Cooper and Jose[19,20] to be a sulfenic acid thermally generated from the sulfoxide in a reversible six-electron electrocyclic rearrangement. Cooper[19] demonstrated the existence of this equilibrium by heating sulfoxide **18** in the presence of D_2O to give deuteration in the β-methyl group (see Figure 3). The phthalimidopenicillin sulfoxide ester (**20**) incorporat-

(17) R. A. Archer and P. V. Demarco, *J. Chem. Soc. C*, 91, 1530 (1969).
(18) D. O. Spry, unpublished results.
(19) R. D. G. Cooper, *J. Amer. Chem. Soc.*, **92**, 5010 (1970).
(20) R. D. G. Cooper and F. L. Jose, *J. Amer. Chem. Soc.*, **92**, 2575 (1970).

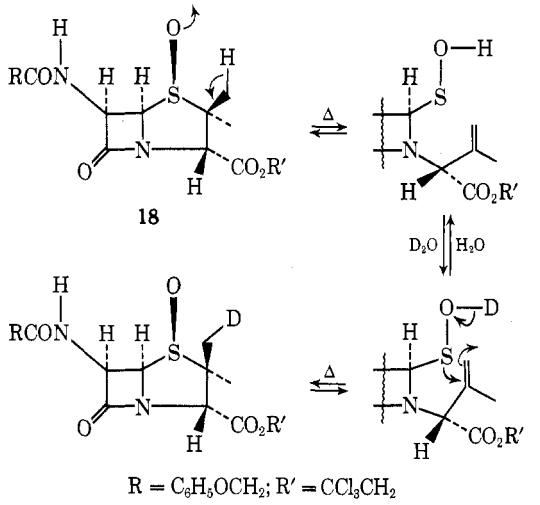
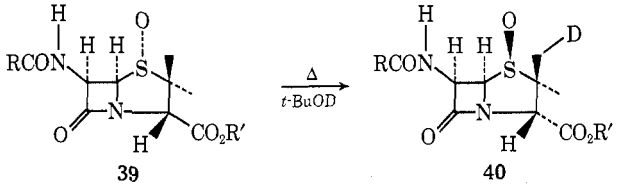


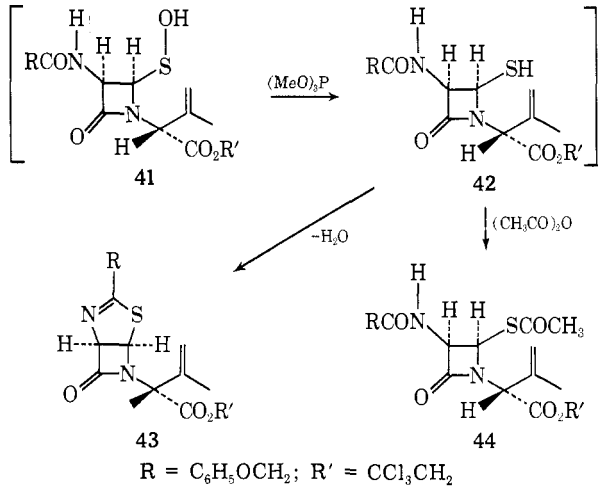
Figure 3

ed deuterium only in the α-methyl group. The deuterium incorporation of both **18** and **20** was a stereospecific process. The sulfenic acid addition to the double bond on the basis of the postulated mechanism requires the sulfoxide bond to be cis to the deuterated methyl group.[19] Theoretically, both the β-sulfoxide–β-deuteriomethyl and the α-sulfoxide–α-deuteriomethyl isomers can result; however, the more thermodynamically stable β isomer is produced. The involvement of a sulfenic acid in the facile epimerization of (*R*)-sulfoxide **39** to (*S*)-sulfoxide **40** was demonstrated by Barton, *et al.*,[21] by thermally epimerizing **39** to **40** in the presence of *tert*-butyl alcohol-*O*-*d*. The incorporation of a deuterium atom into the β-methyl group of the resultant (*S*)-sulfoxide and the lack of this incorporation in the (*S*)-sulfoxide when subjected to identical conditions clearly showed the presence of an energy profile for the sulfoxide isomers.

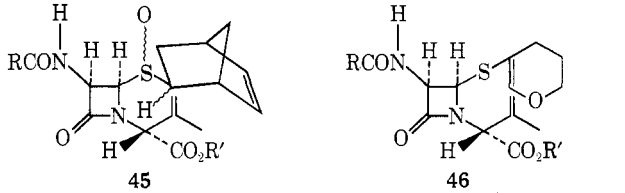
For phthalimidopenicillin **20** the situation is reversed, with the *R* isomer the more thermodynamically stable.[12,15]



Trapping of the Sulfenic Acid. Several recently reported reactions have been explained by a trapping of the sulfenic acid. Cooper and Jose[20] achieved this reductively by using trimethyl phosphite, when a reduction of sulfenic acid **41** to thiol **42** was proposed. The isolated product, thiazolidine **43**, was derived by an intramolecular condensation. Alternatively, the thiol, if generated in the presence of acetic anhydride,[22] could be acylated to *S*-acetyl derivative **44**. Reaction of the sulfenic acid with external olefins



has been accomplished by Barton, *et al.*,[23] who obtained products **45** and **46** by trapping with norbornadiene and dihydropyran, respectively.



Mechanism of Penicillin–Deacetoxycephalosporin Interconversion. The intramolecular olefinic trapping of the sulfenic acid was the mechanism proposed by Morin, *et al.*,[6] for the formation of **7** and **8**. However, the original proposal did not offer a satisfactory explanation for the stereochemical control of the reaction. In addition, further experiments by Spry[15] indicated that in the case of phthalimidopenicillin sulfoxide **20** rearrangement with acetic anhydride gave both the α- and β-acetoxymethylpenicillin isomers (**47** and **48**) together with the 3β-acetoxycepham (**49**) and Δ^3-cephem product (**50**); *i.e.*, a lack of stereochemical control was now evident. Several other seemingly inconsistent observations were also reported, namely, that rearrangement of ester **18** with methanesulfonic acid in dimethylacetamide (DMAC) gave Δ^3-cephem **51**[24] in excellent yields, whereas use of sulfuric acid gave 3β-hydroxycepham **52**.[25,26] Rearrangement of acid **11** also presented a mechanistic problem because, with acetic anhydride or methanesulfonic acid in DMAC, the decarboxylated product (**12**) was formed in 62% yield with only a minor amount of 3-hydroxycepham acid **53** present.[24] Use of sulfuric acid–DMAC, however, changed the product composition to 47% **53** and only a trace of **12**.

As a more complete explanation of this somewhat

(21) D. H. R. Barton, F. Comer, D. G. T. Greig, G. Lucente, P. G. Sammes, and W. G. E. Underwood, *Chem. Commun.*, 1059 (1970).

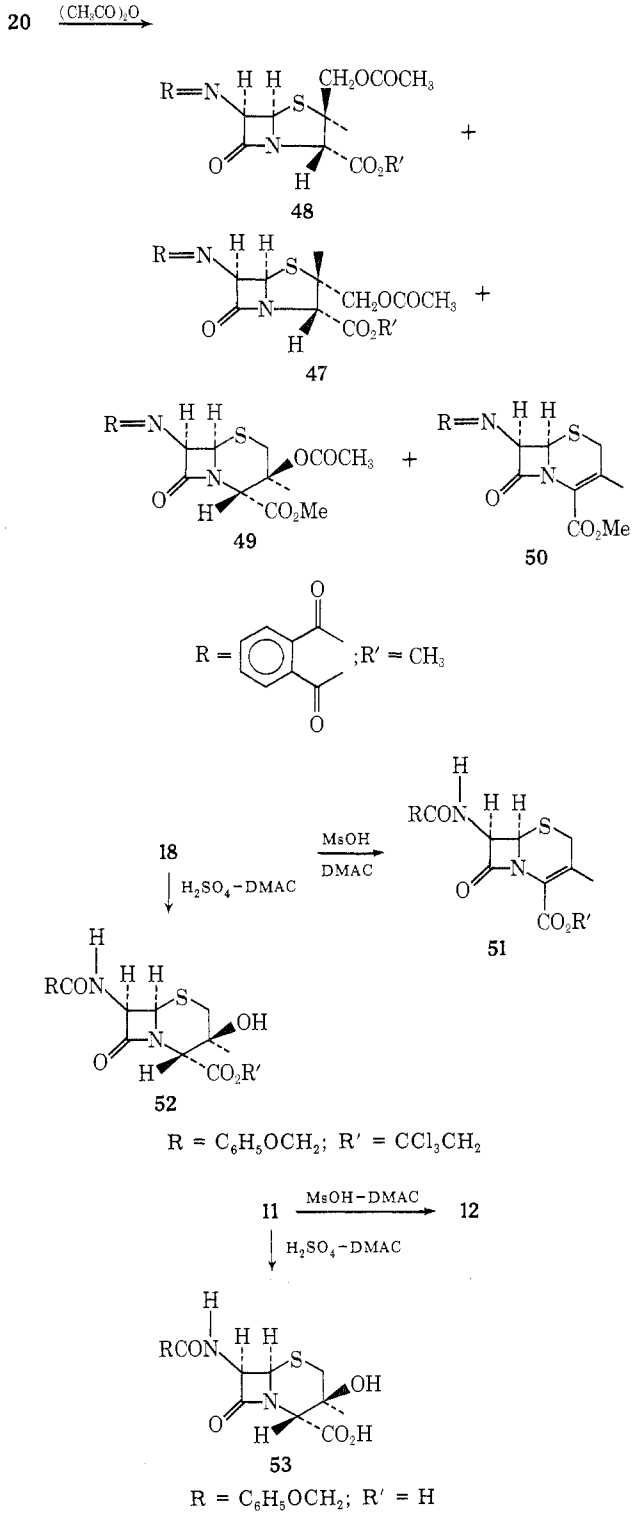
(22) L. D. Hatfield, J. Fisher, F. L. Jose, and R. D. G. Cooper, *Tetrahedron Lett.*, 4897 (1970).

(23) D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *Chem. Commun.*, 1683 (1970).

(24) L. D. Hatfield, J. W. Fisher, F. L. Jose, W. L. Garbrecht, and R. D. G. Cooper, in preparation.

(25) G. E. Gutowski, C. J. Daniels, and R. D. G. Cooper, *Tetrahedron Lett.*, 3429 (1971).

(26) G. E. Gutowski, B. J. Foster, C. J. Daniels, L. D. Hatfield, and J. W. Fisher, *Tetrahedron Lett.*, 3433 (1971).



R = $C_6H_5OCH_2$; R′ = CCl_3CH_2

R = $C_6H_5OCH_2$; R′ = H

complex series of rearrangements, we propose that the initial step is an electrocyclic ring opening of the sulfoxide to the sulfenic acid, the sulfur atom no longer being chiral. The second stage is the reaction of the sulfenic acid with the acidic reagent present, *e.g.*, acetic anhydride, sulfonic acid, or sulfuric acid, to form a mixed anhydride (Figure 4).[5,6,26] Consequently, the sulfur changes from a good nucleophile to an electrophile such that now it can undergo an internal S_N2 displacement by the olefinic double bond.

The approach of the double bond must be orthogonal and from the side opposite to the leaving group.

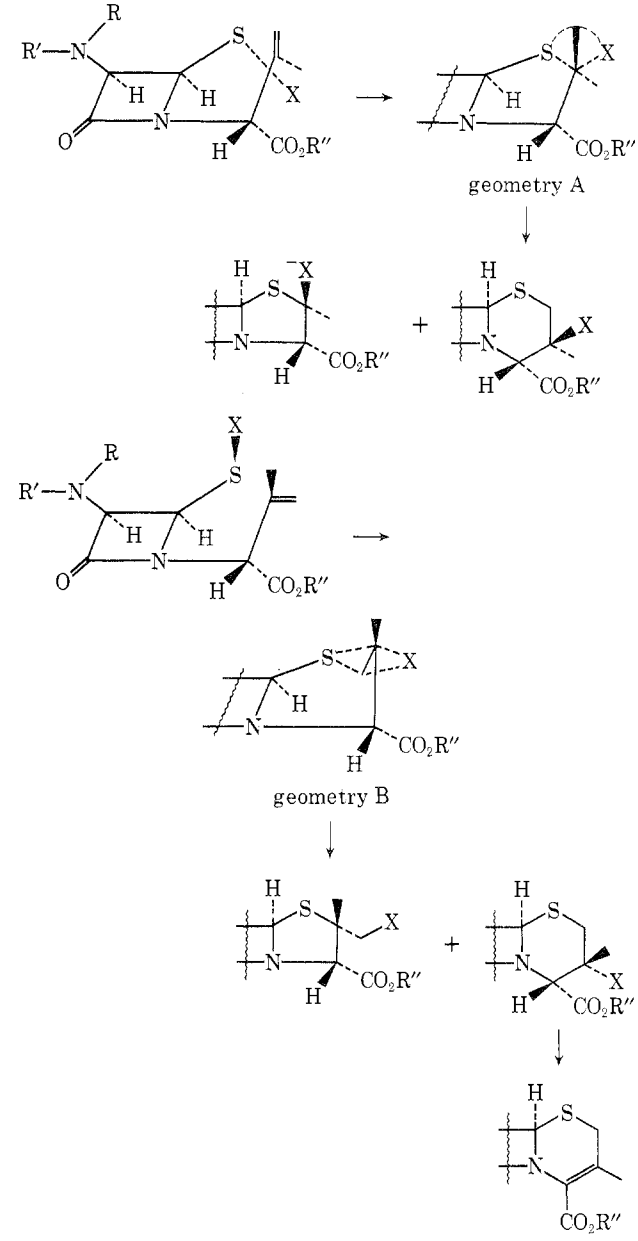


Figure 4

Concurrent trans addition of the available anion to the double bond results in an episulfonium ion pair, its geometry controlling the product stereochemistry. This ion pair has two possible geometries, A and B (see Figure 4). Geometry A would give the β-acetoxymethylpenicillin and β-acetoxycepham products and B, the α-acetoxymethylpenicillin and α-acetoxycepham products. This latter product has never been observed; however, it would be expected to undergo a facile trans elimination of acetic acid to a Δ^3-cephem, a product which is observed. Obviously, when the penicillin side chain is $C_6H_5CH_2CONH$, only geometry A is operative, but for phthalimidopenicillin, both A and B are involved.

We reason that the formation of the sulfenic anhydride has given the sulfur a leaving group with a considerable steric requirement, *i.e.*, the sulfur now possesses an intramolecularly induced chirality. Due to the sulfenic anhydride interaction with the β-amido side chain, it leaves in the α direction, the

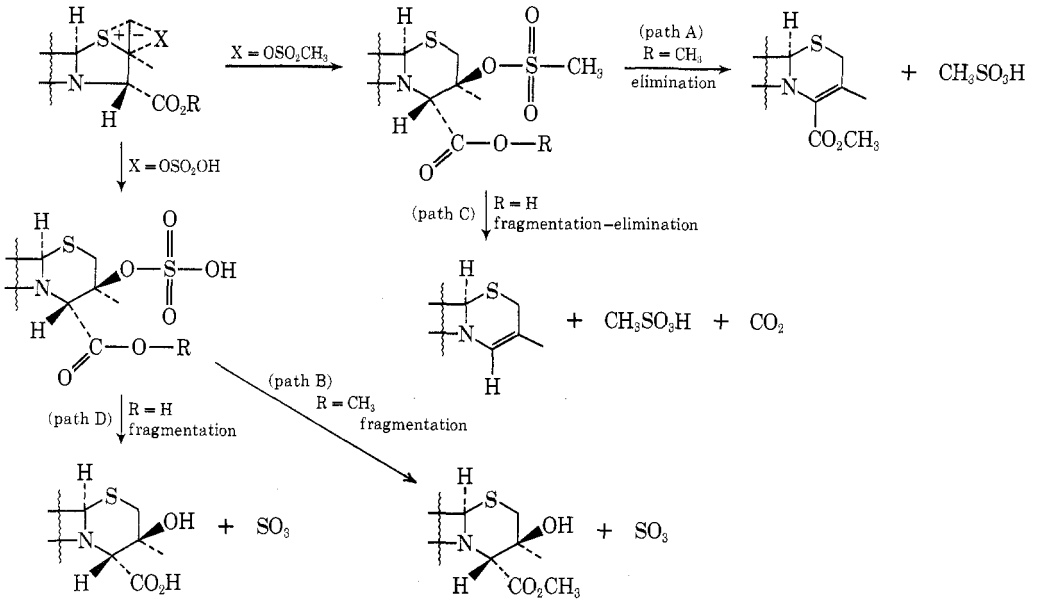


Figure 5

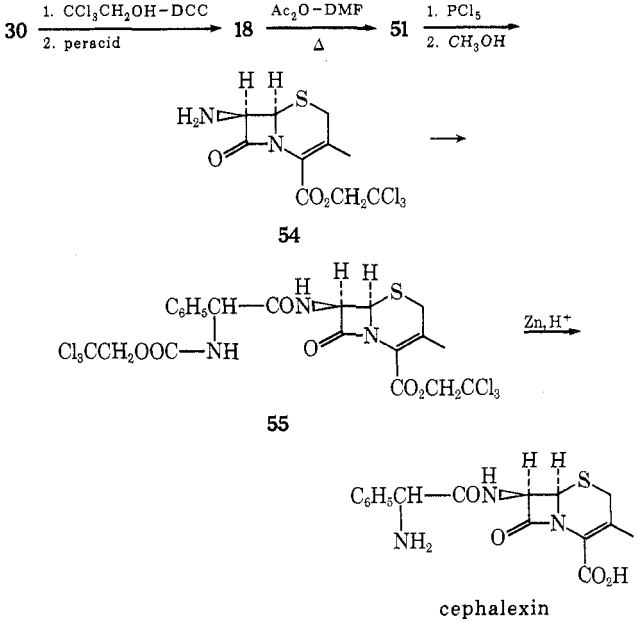
double bond then approaching from the β face, resulting in geometry A. However, in the phthalimido case the greater bulk of this group establishes a competing steric repulsion between the side chain and the approaching double bond, thus making possible the formation of a small amount of geometry B; hence the observed formation of **47** and **48**. The observation that the only conditions in which five-membered-ring rearrangement products are formed is acetic anhydride can be directly attributed to the nucleophilicity of the anion (acetate *vs.* bisulfate *vs.* methanesulfonate). Also, with methanesulfonic acid the anion is a more effective leaving group than either bisulfate or acetate, thus giving the Δ^3-cephem product *via* a facile internal cis elimination (path A, Figure 5).

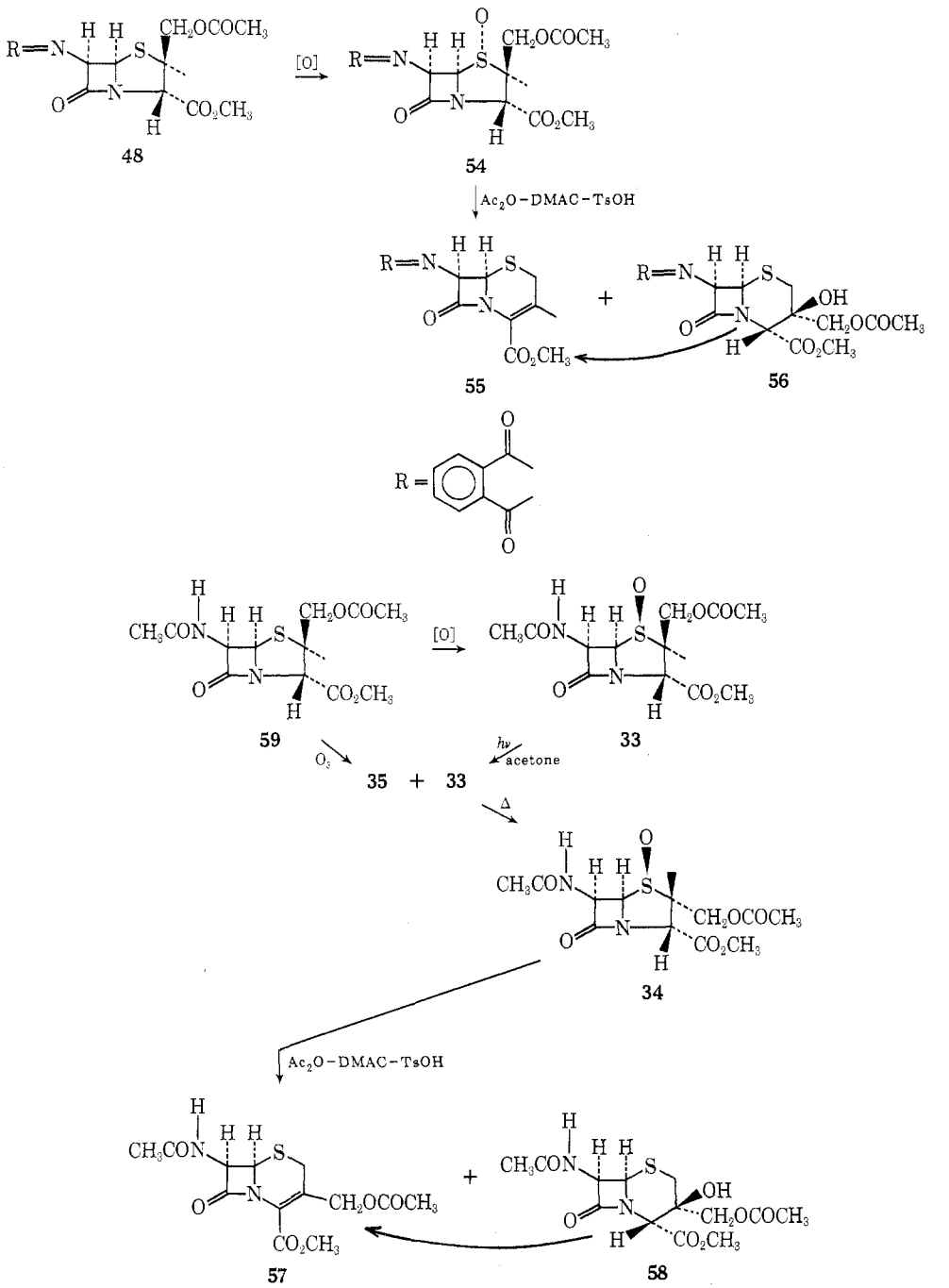
Bisulfate has two possible modes of collapse: by a cis elimination or, more preferably, by a fragmentation to the 3β-hydroxycepham (path B). The explanation for the rearrangement products of acid **11** with methanesulfonic or -sulfuric acids can be seen from Figure 5 to be a direct result of the leaving group qualities of the anion; *i.e.*, mesylate is a much better leaving group and induces predominantly a fragmentation–elimination pathway (path C), whereas bisulfate undergoes an internal fragmentation (path D) to the hydroxy acid.

Penicillin–Cephalosporin Conversion

The utility of the rearrangements of penicillin sulfoxide has been aptly demonstrated by Spry,[15] who, using two consecutive sulfoxide rearrangements, converted a penicillin into a cephalosporin. Previously, other workers[6] had tried unsuccessfully to rearrange the acetoxymethylpenicillin sulfoxide; presumably the lack of reactivity was due to the cis relationship between the acetoxymethyl and sulfoxide groups. Spry[15] circumvented this by using the phthalimidopenicillin derivative (**48**) obtained by acetic anhydride rearrangement of penicillin **20**. Oxidation of **48** gave the α-sulfoxide **54** with a trans sulfoxide–acetoxymethyl relationship which rearranged under ring expansion conditions to give a mixture of cephem **55** and 3-hydroxycepham **56**. Recyclization of **56** under the rearrangement conditions caused dehydration to yield **55**. Accomplishment of this reaction sequence on penicillins containing secondary amide side chains was then achieved by using the photochemical sulfoxide epimerization of **33** to obtain **35**. Thermal epimerization of **35** gave **34** which then rearranged to a mixture of cephem **57** and hydroxycepham **58**. A more facile route to **34** was to use the nonstereoselective oxidation properties of ozone in polar solvents. Oxidation of **59** gave the α- and β-sulfoxides (**35** and **33**) in a 2:1 ratio.[15]

The attainment of the initial goal of this research has been demonstrated by Chauvette and coworkers who have used the penicillin sulfoxide to deacetoxycephem ring expansion as the key step in the synthe-





sis of cephalexin from penicillin.[27] Penicillin V, a reasonably inexpensive penicillin produced by fermentation, was converted to its ester sulfoxide 18 by reaction with dicyclohexylcarbodiimide–trichloroethanol followed by peracid oxidation. Rearrangement of 18 in DMF containing acetic anhydride followed by cleavage of the phenoxyacetamido side chain realized the nucleus ester 54 in 60% overall yield from 18. Acylation of 54 with *N*-trichloroethoxycarbonyl-protected D-phenylglycine gave 55 and zinc removal of the protecting groups resulted in an economically feasible synthesis of cephalexin from penicillin.

(27) R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. Jose, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, 36, 1259 (1971).

Conclusion

Penicillin sulfoxides, derivatives of penicillin having low microbiological activity and no usefulness, rapidly are becoming valuable synthetic intermediates in β-lactam chemistry. We hope that we have shown some of this potential value here. Students of the recent literature[28] are well aware of the research vistas that are being developed from this molecule.

We wish to acknowledge our colleagues at Eli Lilly and Company for their many helpful criticisms.

(28) "Cephalosporins and Penicillins: Chemistry and Biology," E. H. Flynn, Ed., Academic Press, New York, N. Y., 1972.