Tetrahedron. Vol. 31, pp. 2321 to 2345. Pergamon Press 1975. Printed in Great Britain

TETRAHEDRON REPORT

REARRANGEMENTS OF PENICILLANIC ACID DERIVATIVES

R. J. STOODLEY*
Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU

(*Received for publication* 8 *July* 1975)

INTRODUCTION

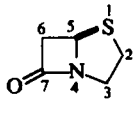
The quest for antibacterial agents which are more effective than the penicillins and cephalosporins is a major objective of contemporary β-lactam research. Some measure of the phrenetic activity currently devoted to the chemistry of β-lactam derivatives is provided by the publication of a monograph[1] and three reviews[2-4] in this area during the past three years.

An intriguing facet of the chemistry of penicillins and related molecules is their propensity to undergo reorganization reactions. Indeed, in the history of molecular rearrangements, few compounds can boast such an extensive repertoire. The understanding of this behaviour is, therefore, not only of vital importance to the specialist, who seeks to control how penicillins react, but it is also of inherent general interest.

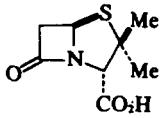
The purpose of this review is to assess the current interpretations of the rearrangements undergone by penicillanic acid derivatives. Only those reorganizations in which the bonds of the bicyclic framework are cleaved will be discussed. As far as possible, the reactions will be classified according to the bond-breaking processes by which they are considered to be triggered.

Nomenclature

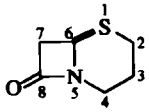
The fused thiazolidine-azetidinone system (1), which comprises the framework of penicillins, is denoted by the trivial name *penam*. When this structure bears Me groups at position 2 and a carboxy-moiety at position 3, it is referred to as *penicillanic acid* (2). The bicyclic units (3) and (4) are named *cepham* and *ceph-3-em*, respectively. The terms 1,2-*secoceph*-3-*em* and 1,2-*secoceph*-2-*em* are proposed for the respective structures (5) and (6).



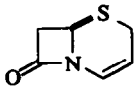
1



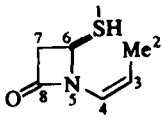
2



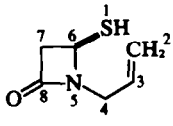
3



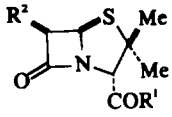
4



5



6

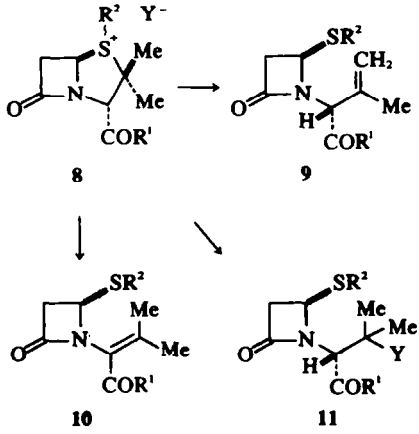


7

Although two stereoisomers are possible for penam, cepham, ceph-3-em and 1,2-secoceph-2-em, and four stereoisomers for penicillanic acid and 1,2-secoceph-3-em, in this review the names refer to compounds depicted by the formulae (1–6). The stereochemistry of substituents is designated by the α,β-notation. Accordingly, natural penicillins are derivatives of 6β-formamidopenicillanic acid (7; $R^1 = OH$, $R^2 = NH{\cdot}CHO$); for example, benzylpenicillin is 6β-phenylacetamidopenicillanic acid (7; $R^1 = OH$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$).

1-2 BOND CLEAVAGES

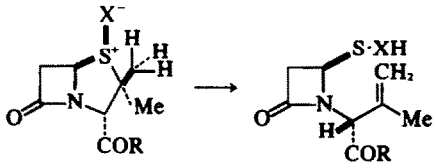
The sulphonium salt (8), derived from the reaction of a penicillanoyl derivative with an electrophilic reagent, R^2Y, is potentially activated for a 1–2 bond heterolysis. The expected primary products of such a reaction are the derivatives (9–11).



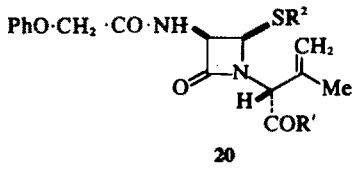
8 9 10 11

There appears to be only one example in which all three products are formed concurrently. This involves[5] the reaction of the imino-chloride (12; R = F) with silver(I) perchlorate in aqueous NN-dimethylformamide to afford a mixture of the thiazolines (15–17). The products are probably derived from the tertiary carbenium ion (14), formed by a 1–2 bond cleavage and cyclization of the intermediate (13; R = F).

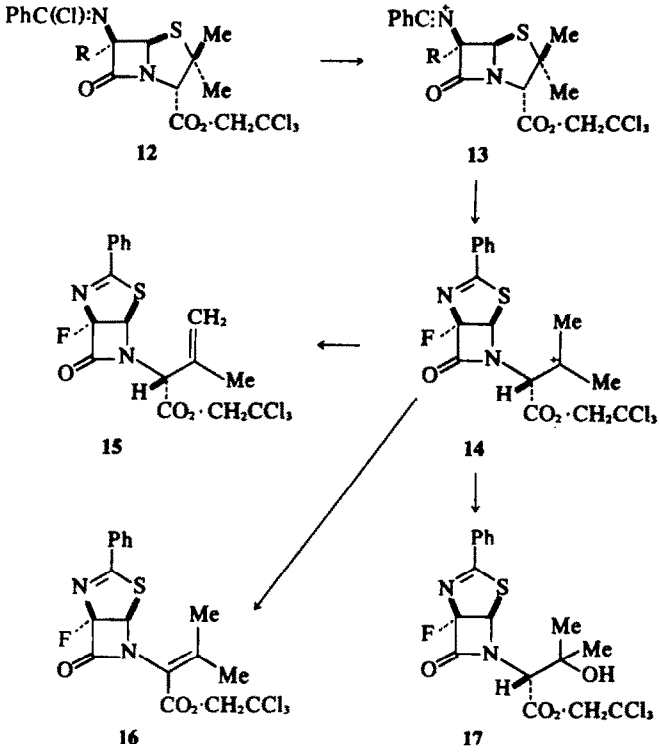
Under comparable conditions the imino-chloride (12; R = H) undergoes hydrolysis to give the 6β-benzamidopenicillanate (7; $R^1 = O{\cdot}CH_2CCl_3$, R^2 = NH·COPh), suggesting that the electrophilicity of the nitrilium ion (13) is an important factor in the reorganization.



18 19



20



12 13 14 15 16 17

In general, reactions involving a 1–2 bond rupture give rise to either a secoceph-2-em (9) or a secoceph-3-em intermediate (10). Products originating from the former species are usually obtained when the substituent, R^2, of the sulphonium salt (8) is capable of sustaining an anionic change. Products derived from a secoceph-3-em intermediate are typically formed when a penicillanoyl derivative is treated under basic conditions; these reactions are probably triggered by the removal of the 3-H atom as a proton.

Rearrangements involving secoceph-2-em derivatives

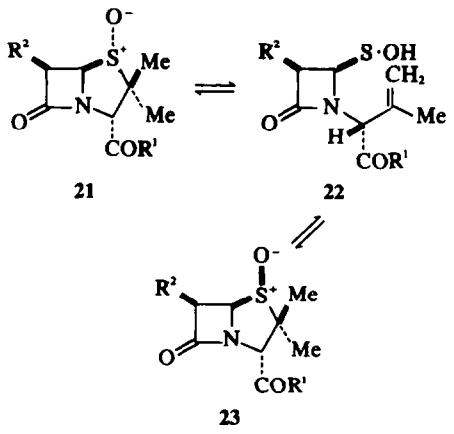
The formation of a secoceph-2-em derivative (19) probably involves an intramolecular, [1,4]-H shift of an ylide (18). Such reactions have been observed when the substituent, X, is a C- or N-bearing group or oxygen.

With a C- or N-containing substituent, the ylide (18) is not isolable; it is, however, believed to be generated as an intermediate when an azo-compound is thermolysed in the presence of a penicillanoyl derivative.[6,7] Thus, the secoceph-2-em [20; R^1 = OMe, R^2 = $CH(CO_2Me)_2$ or NH·CO_2Et] is produced when the penicillanate (7; R^1 = OMe, R^2 = NH·CO·CH_2·OPh) is heated with dimethyl azomalonate or ethyl azidoformate and a copper(II) salt.

The thermal rearrangements of penicillanoyl 1-oxides (18; X = O) to secoceph-2-em 1-oxides (19; X = O) have been extensively studied; these reactions will now be considered in detail.

Interconversion of penicillanoyl 1-oxides and secoceph-2-em 1-oxides. The first indication that a penicillanoyl 1-oxide could equilibrate with a secoceph-2-em 1-oxide was noted in 1969 by two groups.[8,9] The 1α-oxide (21; R^1 = OMe, R^2 = NH·CO·CH_2Ph or NH·COMe) was converted into the 1β-oxide (23; R^1 = OMe, R^2 = NH·CO·CH_2Ph or NH·COMe) in refluxing benzene and the sulphenic acid (22; R^1 = OMe, R^2 = NH·CO·CH_2Ph or NH·COMe) was proposed as the reaction intermediate. Since that time such isomerizations have been investigated on several occasions and both their thermodynamic and kinetic aspects have been clarified.

Thermodynamic aspects. With a penicillanoyl derivative bearing a 6β-amido-substituent, the 1β-oxide is



21 22 23

thermodynamically preferred—none of the 1α-oxide is detectable at equilibrium.[10–15] A similar situation prevails with a 6α-amidopenicillanoyl 1-oxide.[15] In the case of a derivative possessing the phthalimido-group at position 6, the 1α-oxide is overwhelmingly favoured when the substituent occupies the 6β-site,[11] whereas the 1β-oxide predominates (*ca.* 9:1) when the group resides at the 6α-position.[16] These results indicate that, unless a bulky group is present at the 6β-position, there is a marked preference for the 1β-oxide. Although the amido-H atom of a 6β-amidopenicillanoyl 1β-oxide is strongly H bonded with the sulphinyl-O atom,[9,17] this is evidently not the overriding feature in determining the thermodynamic stability.

Until recently it was generally assumed that secoceph-2-em 1-oxides were fleeting intermediates in the foregoing isomerizations. However, in 1974 Chou *et al.*[18] reported that the sulphenic acid (22; $R^1 = O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$-*p*, R^2 = phthalimido) comprised *ca.* 20% of the mixture obtained by brief heating of the 1α-oxide (21; $R^1 = O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$-*p*, R^2 = phthalimido) in ethyl acetate. The sulphenic acid, which was isolated in crystalline form, slowly reverted to the starting oxide at 38°.

Kinetic aspects. Barton *et al.*[12] observed that when the isomerization of the 1α-oxide (21; $R^1 = O{\cdot}CH_2CCl_3$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$) to the 1β-oxide (23; $R^1 = O{\cdot}CH_2CCl_3$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$) was conducted in 2-methylpropan-2-[$^2H_1$]ol (80° for 3 hr), the 1β-oxide contained deuterium (60% $^2H_1$) in the 2β-Me group. Cooper[11] also noted that the 1β-oxide (23; R^1 = OMe, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) incorporated deuterium (43% $^2H_1$, 11% $^2H_2$) in the 2β-Me group when it was heated in benzene containing deuterium oxide (80° for 24 hr). Evidently, the formation of a penicillanoyl 1-oxide from a secoceph-2-em 1-oxide involves a *syn*-addition. Therefore, the converse reaction is an example of a *syn*-elimination—in present-day terminology a sigmatropic, [1,4]-H shift—of the type first studied by Kingsbury and Cram.[19]

On the basis of deuterium-incorporation studies,[11,12,14,15] the free-energy change for the conversion of a 6β- or a 6α-amidopenicillanoyl 1α-oxide into the corresponding 1β-oxide possesses a profile similar to that depicted in Fig. 1. Thus, a 1α-oxide affords a secoceph-2-em 1-oxide more readily than does a 1β-oxide and there is a kinetic preference for the intermediate to isomerize to the 1β-oxide.

The conversion of sulphoxides into sulphenic acids and olefins is considered to occur by way of the co-planar

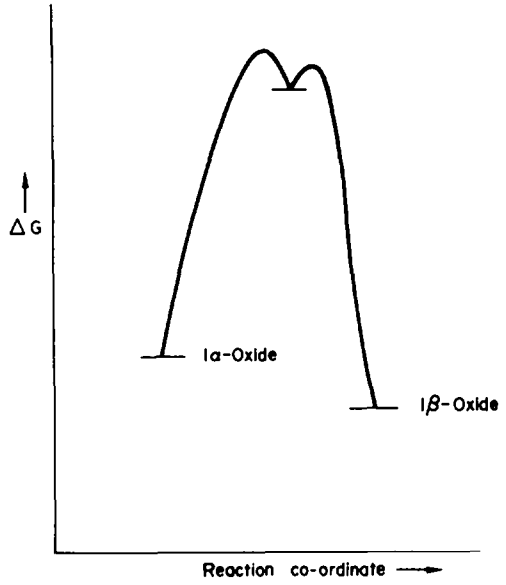
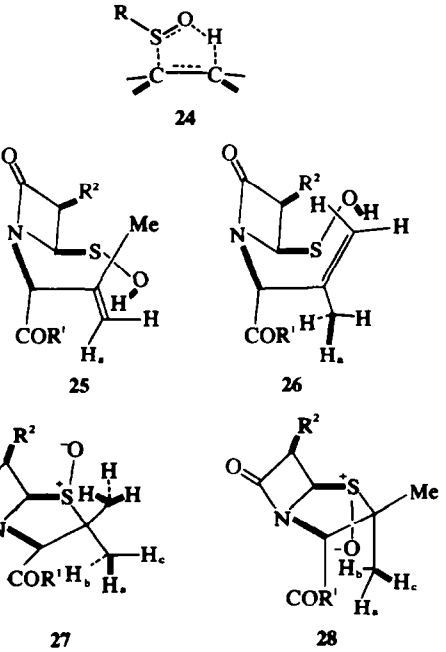


Fig. 1. Free-energy profile for the isomerization of a 6-amidopenicillanoyl 1α-oxide to the 1β-oxide.

transition state (24).[19] Consequently, the geometries (25) and (26) should provide approximate models for the transition states leading to the 1α- and 1β-oxides, respectively. An important difference between these geometries is that in the former the CO substituent is eclipsed with the methylene group whereas in the latter it is eclipsed with the Me moiety. Dreiding models reveal that there is a greater steric interaction in the former situation (the internuclear distance between the CO-C atom and H_a in *ca.* 2·4 Å) than in the latter (the internuclear distance between the CO-C atom and H_a is *ca.* 2·9 Å). This interaction may be responsible for the higher energy of geometry (25) and, therefore, the preferential formation of the 1β-oxide from the sulphenic-acid intermediate.



24 25 26 27 28

For sulphenic acid formation to occur from a penicillanoyl 1β-oxide, it is necessary for the 2β-Me group and the sulphinyl-O atom to be eclipsed. The attainment of this geometry (**27**) necessitates the eclipsing of the 2α-Me group and the 3-CO moiety (the internuclear distance between the CO–C atom and H_a is *ca.* 2·2 Å). In the conformer (**28**), required for sulphenic acid formation from the 1α-oxide, the 2α-Me group and the sulphinyl-O atom are eclipsed. Since the C–H_b bond must be co-planar with the S(1)–C(2) bond, H_a must approach close to the 3-substituent (the internuclear distance between the CO–C atom and H_a is *ca.* 1·7 Å). It is clear that sulphenic acid formation from either a 1β- or a 1α-oxide relieves compression between the 2α-Me group and the 3-CO substituent. In the case of the 1β-oxide this relief may be approximated with the change in the internuclear distance between the CO–C atom and H_a (from 2·2 to 2·9 Å). With the 1α-oxide the relief may be equated with the corresponding change in internuclear distance (from 1·7 to 2·4 Å). The increase in the rate of sulphenic acid formation from a 1α-oxide compared with the corresponding 1β-oxide may, therefore, be due to the greater alleviation of strain in the former instance.

A prediction of the foregoing model is that the rate of sulphenic acid formation from a given penicillanoyl 1-oxide is expected to increase with the size of the 3-substituent. Although no quantitative studies are available, there is some qualitative support for this proposal. Thus, Allan *et al.*[20] have noted that the conversion of the penicillanoyl 1β-oxides (**23**; R^2 = NH·CO·CH_2Ph) into the 1-tosylsecoceph-2-em derivatives (**20**; R^2 = SO_2·C_6H_4·Me-*p*)—reactions which probably involve the rate-determining formation of the sulphenic-acid intermediates (**22**; R^2 = NH·CO·CH_2Ph)—occurred more rapidly with a bulky substituent, R^1 (i.e. R^1 = NPr^i·NHPr^i > R^1 = NMe·NMe_2 > R^1 = O·CH_2CCl_3).

The rate of sulphenic acid formation is also expected to be sensitive to the acidity of the migrating H atom. A possible illustration of this effect is provided[10] by the recovery of the derivative (**29**) under conditions in which the 1α-oxide (**31**) was converted into the isomer (**30**).

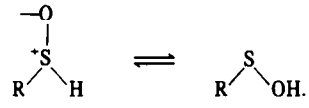
It is possible to convert 6β-amidopenicillanoyl 1β-oxides into the thermodynamically less stable 1α-oxides by UV irradiation in acetone.[9,10] A cleavage of the 1–2 bond is implicated since a mixture of the four isomers (**29–32**) was produced when the 1β-oxide (**32**) was photolysed.

Reactions of secoceph-2-em intermediates. The possibility of intercepting secoceph-2-em intermediates is of intrinsic interest and, moreover, the products of such reactions are of potential value for the construction of β-lactam antibiotic analogues. Three types of interception have been observed; these involve reactions with dienophiles, electrophiles and nucleophiles.

Cycloaddition reactions. The tendency for secoceph-2-em 1-oxides to undergo intramolecular *syn*-additions has already been discussed (p. 2323). The first indication that a sulphenic acid could be trapped by an external olefin was provided by Barton *et al.*[13,21] who obtained the adduct (**33**), as one major isomer, from the pyrolysis of the 1β-oxide (**23**; R^1 = OMe, R^2 = NH·CO·CH_2Ph) in benzene containing norbornadiene. Analogous cycloadducts were subsequently obtained with dimethyl acetylenedicarboxylate,[21,22] ethyl propiolate[22] and diethyl azodicarboxylate.[23] In the case of 4-methyleneoxetan-2-one,[21] the cycloaddition was accompanied by an isomerization of the double bond to give the secoceph-3-em derivative (**34**).

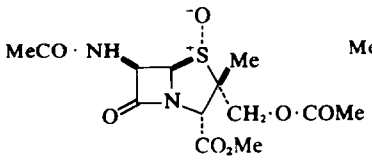
In some instances the expected cycloadducts were not obtained. Thus, pyrolysis of the penam 1β-oxide (**35**; R = CO·C_6H_4·NO_2-*o*) in the presence of dimethyl acetylenedicarboxylate[22] afforded the derivative (**36**)—the product of allylic rearrangement of the expected material. Thermolysis of the penam 1β-oxide (**35**; R = H) in the presence of acrylaldehyde[21] gave the cepham 1-oxide (**38**), as a mixture of stereoisomers; evidently, the initially formed cycloadduct (**37**) loses 2-methylpropenal and then undergoes cyclization.

Reactions with electrophiles. In principle a sulphenic acid may exist in two tautomeric forms.

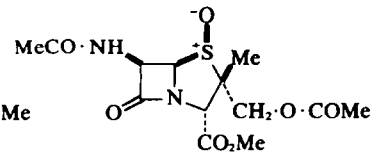


Spectroscopic studies have shown[18] that the O-protonated form is preferred for the derivative (**22**; R^1 = O·CH_2·C_6H_4·NO_2-*p*, R^2 = phthalimido). A sulphenic acid may also behave as an ambident nucleophile, reacting with an electrophilic species at either the O or the S atom. Secoceph-2-em 1-oxides display both types of reactivity.

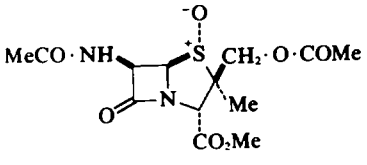
Possible examples of the interception of the S atom of a sulphenic acid by an electrophilic C atom are supplied by the thermal reactions of the penam 1β-oxide (**35**; R = CO·C_6H_4·NO_2-*o*) and the penicillanoyl 1α-oxide (**21**; R^1 = CHN_2, R^2 = phthalimido). Pyrolysis of the former compound yields the ceph-3-em 1-oxide (**39**), as a mixture of isomers, presumably by a S_N2'-like reaction of the sulphenic-acid intermediate.[22] The 1α-oxide (**21**;



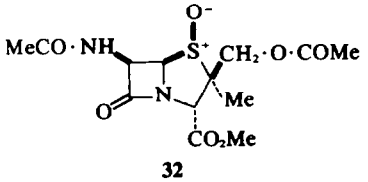
29



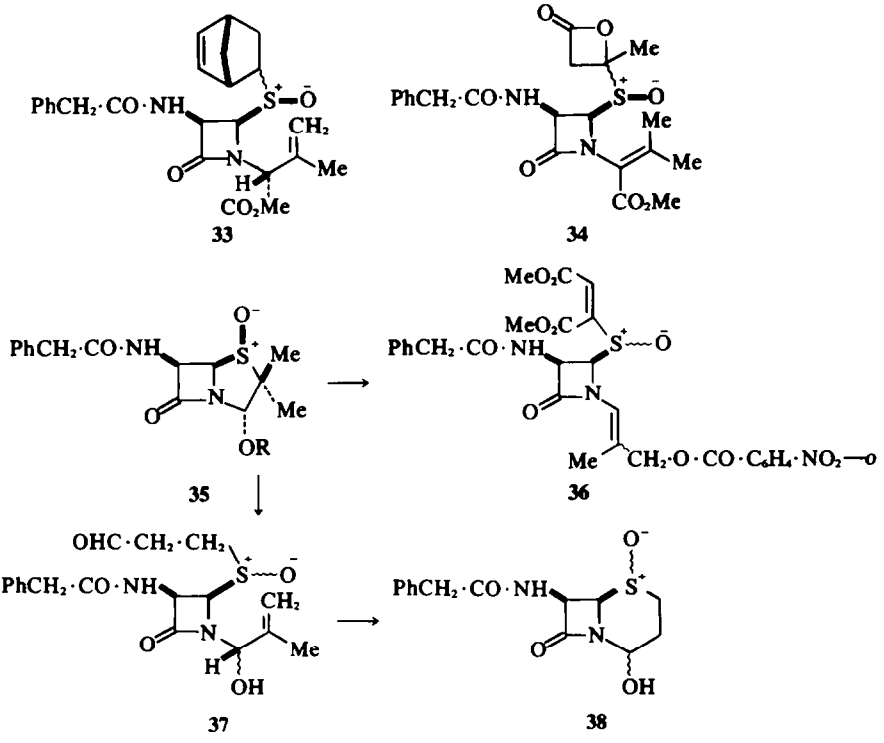
30



31

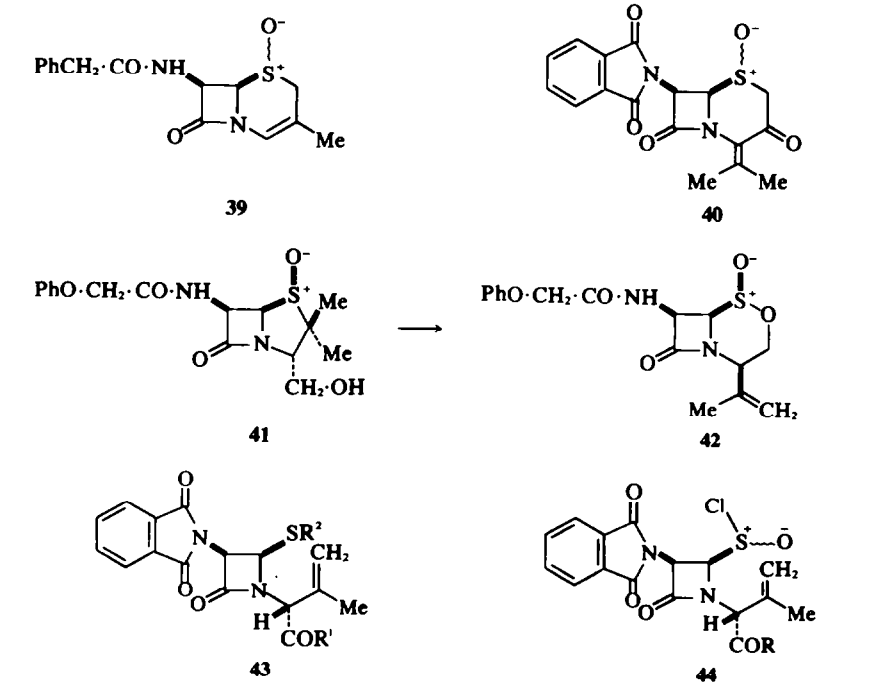


32



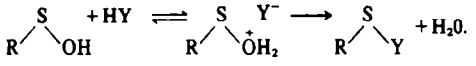
$R^1 = CHN_2$, R^2 = phthalimido) affords the cepham 1-oxide (**40**), as a mixture of isomers, when heated in the presence of copper(II) sulphate.[24] Treatment of the alcohol (**41**) with lead tetra-acetate and iodine gives the sultine (**42**); this reaction possibly involves the interception of the S atom of the sulphenic-acid intermediate by an electrophilic O atom.[25]

Although the foregoing examples illustrate that the S atom of a sulphenic acid displays nucleophilic properties, their intramolecular nature precludes them from being a reliable indication of the relative nucleophilicity of the S and O atoms. The ambident nucleophilic character of sulphenic acids is demonstrated in certain intermolecular reactions. For example, pyrolysis of the penicillanoyl 1α-oxide (**21**; $R^1 = O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$-*p*, R^2 = phthalimido) in benzene containing NO-bis(trimethylsilyl)acetamide yields the O-silyl derivative (**43**; $R^1 = O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$-*p*, $R^2 = O{\cdot}SiMe_3$) in high yield.[26] Moreover, the lithium sulphenate (**43**; $R^1 = O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$-*p*, R^2 = OLi), obtained by treating



the sulphenic acid (43; $R^1 = O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$-*p*, $R^2 = OH$) with lithium di-isopropylamide in tetrahydrofuran at −126°, undergoes exclusive O-alkylation with methyl fluorosulphonate.[27] Sulphuryl chloride reacts[28] with the 1β-oxide (21; $R^1 = OMe$, R^2 = phthalimido) to give the sulphinyl chloride (44; R = OMe); a sulphenic-acid intermediate is indicated since the sulphinyl chloride (44; $R = O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$-*p*) is formed in almost quantitative yield[18] from the secoceph-2-em 1-oxide (43; $R^1 = O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$-*p*, $R^2 = OH$).

Reactions with nucleophiles. In principle, the protonation of a sulphenic acid on the O atom renders the S atom susceptible to nucleophilic attack.



The first indication that a secoceph-2-em 1-oxide could undergo such a reaction (in which the nucleophile was the internal double bond) was provided by Morin *et al.*[29] In these pioneering studies it was noted that the 1β-oxide (23; $R^1 = OMe$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) was converted by refluxing acetic anhydride into a 2:1 mixture of the 2β-acetoxymethylpenam (45; $R^1 = OMe$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) and the 3β-acetoxycepham (46; $R^1 = OMe$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) in 60% yield. However, in xylene containing a trace of toluene-*p*-sulphonic acid, the ceph-3-em (47; $R^1 = OMe$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) was the only β-lactam-containing product (15%). The 3β-acetoxycepham (46; $R^1 = OMe$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) afforded the ceph-3-em (47; $R^1 = OMe$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) under mildly basic conditions.

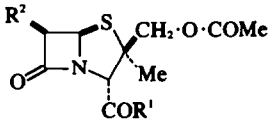
Because of the structural similarity of the ceph-3-em product with a cephalosporin (e.g. 48; $R^1 = OH$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) the foregoing rearrangements have been extensively studied. The outcome of the reaction is not only dependent on the structure of the penicillanoyl 1-oxide but also upon the solvent, the temperature and the Lewis acid.

Conceptions concerning the mechanisms of the reorganizations are based, in large measure, on the stereochemistry of the compounds isolated from the acetic-anhydride reactions;[10,12,14,29-32] such products are generally derived under kinetically controlled conditions. In the case of a 6β-amidopenicillanoyl 1-oxide,[12,14,29] the major product is typically a 2β-acetoxymethylpenam (45) and a 3β-acetoxycepham (46); a ceph-3-em (47) is often formed as a minor product. Decarboxylation is usually observed[33] with a 6β-amidopenicillanic acid 1-oxide (e.g. 23; $R^1 = OH$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$), resulting in the production of a ceph-3-em (e.g. 49; $R = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$). The usually proposed, common precursor of these derivatives is the thiiranium ion (50), which is considered to be formed from the sulphenic acid (22) by way of the sulphenic anhydride. In the reactions leading to the derivatives (45) and (46) the acetate anion behaves as a nucleophile, whereas in that affording the ceph-3-em (47) it acts as a base. It has been noted[14] in the case of the 1β-oxide (23; $R^1 = OMe$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$) that an increase in the acetate-ion concentration favours the elimination to give the ceph-3-em (47; $R^1 = OMe$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$). However, by reducing the acidity of the 3-H atom of the penicillanoyl derivative—as with the amide (23; $R^1 = NHBu^t$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$)—ceph-3-em formation can be excluded.[12,14]

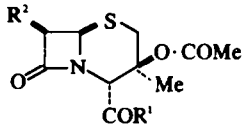
Thermolysis of the 1β-oxide (23; $R^1 = O{\cdot}CH_2CCl_3$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$) in tetrachloromethane containing pyridinium hydrochloride and pyridine gave a mixture of the 2β-chloromethylpenam (51; $R^1 = O{\cdot}CH_2CCl_3$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$) and the 3β-chlorocepham (52; $R^1 = O{\cdot}CH_2CCl_3$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$) in moderate yield.[34] Although stable in the solid state, the former product was converted into the latter in NN-dimethylformamide. Both derivatives afforded the ceph-3-em (47; $R^1 = O{\cdot}CH_2CCl_3$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$) when heated in benzene containing pyridine. It is evident, therefore, that the ceph-3-em is the most stable product and that the cepham is thermodynamically preferred to the penam.

The direct conversion of a penicillanoyl 1-oxide into the corresponding ceph-3-em—the thermodynamically stable product—can be effected with a wide range of reagents, including toluene-*p*-sulphonic acid,[29,32,35-37] methanesulphonic acid,[33,36] dipyridinium phosphate,[38,39] diethyl azodicarboxylate,[23] αα′-azobis(N-methylformamide)[23] and acetic anhydride (above 130°).[40]

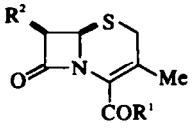
In contrast with an aryl- or alkyl-sulphonic acid, sulphuric acid and its esters[36] react with a penicillanoyl 1-oxide, (e.g. 23; $R^1 = O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$-*p*, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) to give a 3β-hydroxycepham (e.g. 53; $R^1 = O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$-*p*, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$). Moreover, whereas the former reagents induce the decarboxylation[29,33] of a penicillanic acid 1-oxide (e.g. 23;



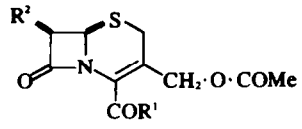
45



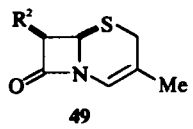
46



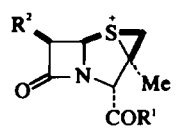
47



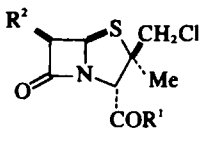
48



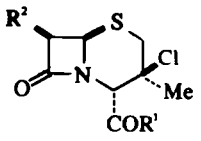
49



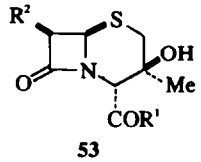
50



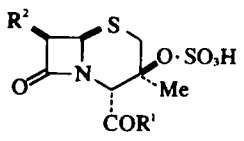
51



52



53



54

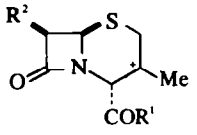
R^1 = OH, R^2 = NH·CO·CH_2·OPh) to a ceph-3-em (e.g. **49**; R = NH·CO·CH_2·OPh), the latter afford a 3β-hydroxycepham (e.g. **53**; R^1 = OH, R^2 = NH·CO·CH_2·OPh). The 3β-hydroxycepham is considered to be formed from the corresponding 3β-sulphate (**54**; R^1 = O·CH_2·C_6H_4·NO_2-*p* or OH, R^2 = NH·CO·CH_2·OPh) by the loss of sulphur trioxide.[36]

In contrast with the behaviour of 6β-amidopenicillanoyl 1β-oxides, the kinetic products derived from the rearrangements of 6β-phthalimidopenicillanoyl 1α-oxides[10,30,31,41] are subject to less rigorous stereochemical control. For example, the 1α-oxide (**21**; R^1 = OMe, R^2 = phthalimido) yields a mixture[10] of the 2β-acetoxymethylcepham (**45**; R^1 = OMe, R^2 = phthalimido) and the 2α-isomer (**55**; R^1 = OMe, R^2 = phthalimido), in addition[41] to the 3β-acetoxycepham (**46**; R^1 = OMe, R^2 = phthalimido) and the ceph-3-em (**47**; R^1 = OMe, R^2 = phthalimido), when heated in acetic anhydride. It has been suggested[42] that both the *endo*-thiiranium ion (**50**; R^1 = OMe, R^2 = phthalimido) and its *exo*-counterpart (**56**; R^1 = OMe, R^2 = phthalimido) intervene in this reorganization. Similar intermediates have been invoked[41] to account for the formation of the 2α-chloromethylpenam (**57**; R^1 = OMe, R^2 = phthalimido) and the 3β-chlorocepham (**52**; R^1 = OMe, R^2 = phthalimido) from the reactions of the 1α-oxide (**21**; R^1 = OMe, R^2 = phthalimido) and the 3β-hydroxycepham (**53**; R^1 = OMe, R^2 = phthalimido) with thionyl chloride; with these examples the 2β-chloromethylpenam (**51**; R^1 = OMe, R^2 = phthalimido) is apparently not formed.

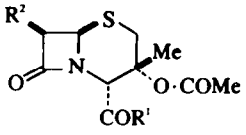
There are some reactions of phthalimido-derivatives which appear to require the formation of only the *endo*-thiiranium ion (**50**; R^1 = OMe, R^2 = phthalimido). Thus, treatment of the 3β-chlorocepham (**52**; R^1 = OMe, R^2 = phthalimido) with silver(I) acetate in acetic acid[41] leads to a mixture of the 2β-acetoxymethylpenam (**45**; R^1 = OMe, R^2 = phthalimido), the 3β-acetoxycepham (**46**; R^1 = OMe, R^2 = phthalimido) and the ceph-3-em (**47**; R^1 = OMe, R^2 = phthalimido) in high yield. The 3β-mesyloxycepham (**58**; R^1 = OMe, R^2 = phthalimido) is produced from the sulphenic acid (**43**; R^1 = OMe, R^2 = OH) and methanesulphonic acid at room temperature, whereas at *ca.* 80° the ceph-3-em (**47**; R^1 = OMe, R^2 = phthalimido) results.[18] Thermolysis of the penam 1α-oxide (**59**) in a mixture of acetic anhydride, NN-dimethylacetamide and toluene-*p*-sulphonic acid hydrate yields[10] the 3β-hydroxycepham (**60**), as the major product, and the ceph-3-em (**48**; R^1 = OMe, R^2 = phthalimido).

Although the thiiranium ions offer a convenient rationale of product stereochemistry,[42] their involvement is not obligatory. Thus, an alternative interpretation of the foregoing reorganizations is that the tertiary carbenium ion (**61**) is formed from the sulphenic-acid derivative and it is the common intermediate leading to the products. Although there may be a kinetic preference for the formation of this ion in one conformational form (e.g. **63**), it will be assumed that the energy barrier to the alternative conformer (e.g. **64**) is low in comparison with the activation energies of the reactions leading to the products.

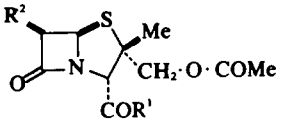
For penam formation, the 1–2 bond of the tertiary carbenium ion (**61**) must be *ca.* orthogonal with the trigonal centre at position 3. This geometry is present in both the conformers (**63** and **64**). Ring contraction of conformer (**63**) would yield a 2β-substituted methylpenam, possibly by way of the transition state (**65**). Ring-contraction of the conformer (**64**) would give the



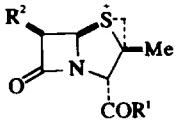
61



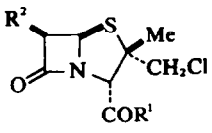
62



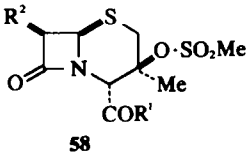
55



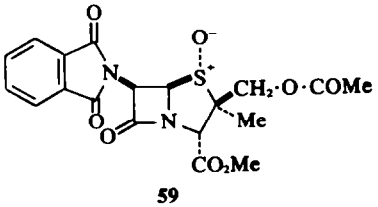
56



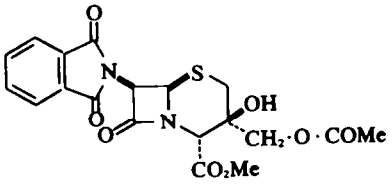
57



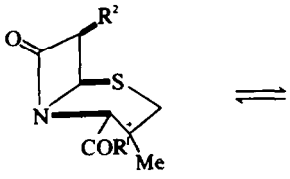
58



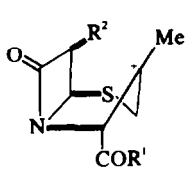
59



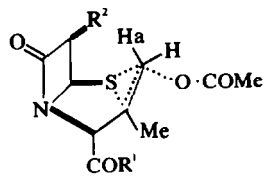
60



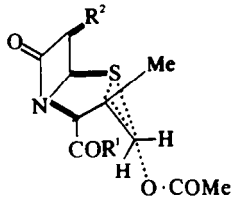
63



64



65



66

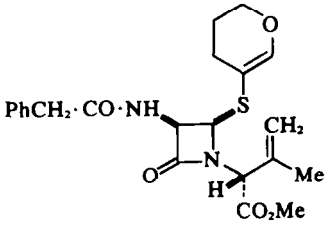
2α-substituted methylpenam, possibly via the transition state (66). Compared with the latter, the former ring contraction involves the relief of $A^{(1,2)}$ strain[43] between the eclipsed Me and CO moieties but an increase in compression between H_a and the substituent, R^2. Therefore, providing the substituent is not a bulky one, the reaction leading to the 2β-substituted methylpenam is likely to be favoured.

A prediction of the foregoing model is that an increase in the bulk of the CO substituent should increase the interaction with the Me group and promote the ring contraction. Although no systematic study has been reported, there is one observation which is consistent with this proposal. Thus, Barton *et al.*[14] noted that the ratio of the 2β-acetoxymethylpenam (45; R^2 = NH·CO·CH_2Ph) to the 3β-acetoxycepham (46; R^2 = NH·CO·CH_2Ph), obtained from the reaction of the 1β-oxide (23; R^2 = NH·CO·CH_2Ph) with acetic anhydride, was altered from 2:1 to 1:3 when the substituent, R^1, was changed from the methoxy-moiety to the t-butylamino-group. Another forecast, relating to the reactions of the 1α-oxides (21; R^2 = phthalimido) with acetic anhydride, is that an increase in the size of the substituent, R^1, is expected to inhibit the formation of the 2α-substituted methylpenam.

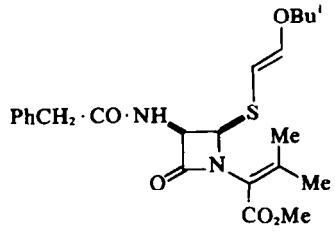
It is significant that 3α-substituted cephams (e.g. 62) have never been isolated from the foregoing rearrangements. Although such substances have been postulated to be unstable under the reaction conditions,[42] undergoing elimination to the ceph-3-ems (47), another possibility is that the activation energy for their formation is greater than that leading to the 3β-substituted cephams (e.g. 46). In principle, the derivatives (46 and 62) may be formed by attack of the acetate anion at the carbenium-ion site of either conformer (63 or 64). The most favourable pathway for the formation of the derivative (62) appears to involve nucleophilic attack from the α-face of conformer (64); the development of partial tetrahedral character at position 3 increases the steric interaction between the substituent, R^2, and the Me moiety. The 3β-acetoxy-derivative (46) is most likely to arise by nucleophilic attack from the β-face of conformer (63); the development of slight tetrahedral character at position 3 is expected to alleviate the unfavourable interaction between the 3 and 4 substituents. Consequently, the carbenium-ion model accounts for the preferential formation of 3β-substituted cephams.

According to the foregoing postulate, the ceph-3-em (47) may be considered to arise from the conformer (63) by the elimination of a proton, and the derivative (49) from the conformer (64; R^1 = OH) by the loss of carbon dioxide.

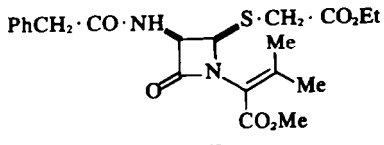
The possibility of intercepting secoceph-2-em 1-oxides with external nucleophiles was first demonstrated by Barton *et al.*[13,21] who obtained the derivative (67) from the thermolysis of the 1β-oxide (23; R^1 = O·CH_2CCl, R^2 = NH·CO·CH_2Ph) in the presence of dihydropyran and a catalytic quantity of aluminium bromide. With isobutyl vinyl ether and 1,1-diethoxyethane the respective secoceph-3-ems (68 and 69) were isolated.[21,44] There are several examples in which thiols serve as the nucleophilic traps for sulphenic-acid intermediates.[34,45,46] For example, pyrolysis of the 1β-oxide (22; R^1 = O·CH_2CCl_3, R^2 = NH·CO·CH_2Ph) in the presence of 2-mercaptobenzothiazole[34] gives the secoceph-2-em (70) in



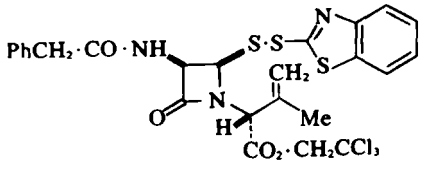
67



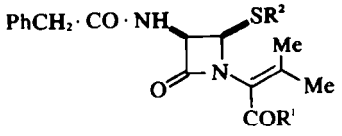
68



69



70



71

90% yield; the reaction is also successful with the acid (**23**; R^1 = OH, R^2 = NH·CO·CH_2·OPh). Related reactions occur[20] when the 1β-oxides (**23**; R^2 = NH·CO·CH_2Ph) are heated with toluene-*p*-sulphinic acid; a secoceph-2-em (e.g. **20**; R^1 = NMe·NMe_2, R^2 = SO_2·C_6H_4·Me-*p*) results when the starting material is an amide (e.g. **23**; R^1 = NMe·NMe_2, R^2 = NH·CO·CH_2Ph), whereas a secoceph-3-em (e.g. **71**; R^1 = O·CH_2CCl_3, R^2 = SO_2·C_6H_4·Me-*p*) is formed in the case of an ester (e.g. **24**; R^1 = O·CH_2CCl_3, R^2 = NH·CO·CH_2Ph).

The reduction of sulphenic acids was first effected by Cooper and José, by heating penicillanoyl 1-oxides with trimethyl phosphite.[47] The outcome of the reaction depends upon the nature of the 6β-substituent. In the case of an amido-derivative[39,45,47,48] (e.g. **23**; R^1 = O·CH_2CCl_3, R^2 = NH·CO·CH_2·OPh), a thiazoline-azetidinone (e.g. **73**; R^1 = O·CH_2CCl_3, R^2 = CH_2·OPh) is formed, presumably by an intramolecular condensation of a secoceph-2-em intermediate (e.g. **72**; R^1 = O·CH_2CCl_2, R^2 = NH·CO·CH_2·OPh). The thiol (**72**) is probably formed by the Arbusov rearrangement.

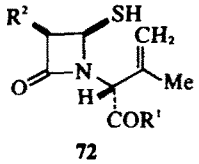
$$\text{RS·OH} + \text{P(OMe)}_3 \longrightarrow \text{RS·}\overset{+}{\text{P}}\text{(OMe)}_3\overset{-}{\text{O}}\text{H}$$
$$\Downarrow$$
$$\text{RSH} + \text{PO(OMe)}_3 \longleftarrow \text{RS·P(OMe)}_3\text{OH}$$

When the formation of a thiazoline-azetidinone (**73**) is precluded or inhibited—as in the case of the 1α-oxide (**21**; R^1 = O·CH_2CCl_3, R^2 = phthalimido or NH·CO·CMe_2·OPh)—the 1-methylsecoceph-2-em (**74**; R^1 = O·CH_2CCl_3, R^2 = phthalimido or NH·CO·CMe_2·OPh) is the predominant product,[49] probably originating from the reaction of the thiol (**72**; R^1 = O·CH_2CCl_3, R^2 = phthalimido or NH·CO·CMe_2·OPh) with trimethyl phosphate. The phosphorus derivative (**75**) has been isolated[49] as a minor product from the reaction involving the 1α-oxide (**21**; R^1 = O·CH_2CCl_3, R^2 = phthalimido).

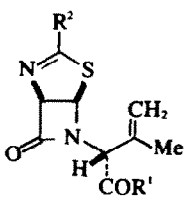
When the foregoing reductions are performed in the presence of acetic anhydride, 1-acetylsecoceph-2-ems (e.g. **76**; R^1 = O·CH_2CCl_3, R^2 = NH·CO·CH_2·OPh) are the major constituents;[50] evidently, the thiol intermediates (**72**) preferentially react with the acylating agent.

An interesting, internal, redox reaction occurs when the 1β-oxide (**23**; R^1 = NH·NHPr^i, R^2 = NH·CO·CH_2Ph) is heated in the presence of dipyridinium phosphate.[38] Instead of the expected ceph-3-em (**47**; R^1 = NH·NHPr^i, R^2 = NH·CO·CH_2Ph), the penam (**78**; R = NH·CO·CH_2Ph) is the predominant product. It is possibly formed from the sulphenic acid (**22**; R^1 = NH·NHPr^i, R^2 = NH·CO·CH_2Ph) by way of the intermediates (**77** and **72**; R^1 = N:N·Pr^i, R^2 = NH·CO·CH_2Ph).

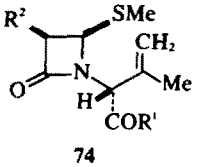
Ring-opening reactions. In certain reactions, in which secoceph-2-em 1-oxides may be invoked as primary intermediates, non-β-lactam products are formed. Thus, Morin *et al.*[29] isolated the isothiazolones (**79**; R^1 = OMe, R^2 = NH·CO·CH_2·OPh) and (**80**; R^1 = OMe, R^2 = NH·CO·CH_2·OPh) and the thiazinone (**82**; R^1 = OMe, R^2 = NH·CO·CH_2·OPh), as minor components, from the reaction of the 1β-oxide (**23**; R^1 = OMe, R^2 = NH·CO·CH_2·OPh) with acetic anhydride. In boiling pyridine the compound (**80**; R^1 = OMe, R^2 = NH·CO·CH_2·OPh) was obtained as the major product (50%). It appears[51] that the isothiazolone (**79**; R^1 = OMe, R^2 = NH·CO·CH_2·OPh) is the precursor of the derivatives (**80**; R^1 = OMe, R^2 = NH·CO·CH_2·OPh) and (**82**; R^1 = OMe, R^2 = NH·CO·CH_2·OPh), the latter material being formed by way of the intermediate (**81**; R^1 = OMe, R^2 = NH·CO·CH_2·OPh). Analogous isothiazolones[22,35] and thiazinones[45] have also been reported by other workers.



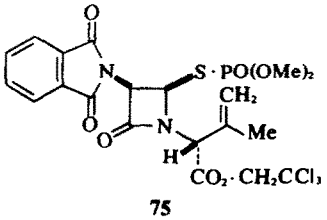
72



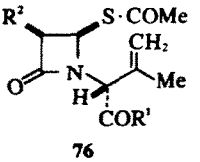
73



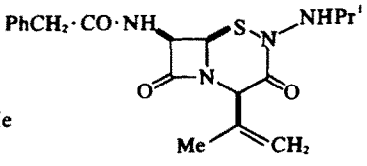
74



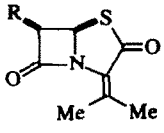
75



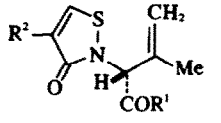
76



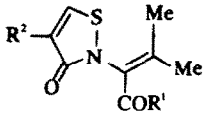
77



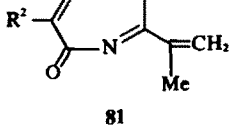
78



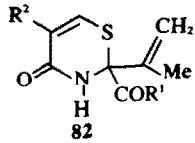
79



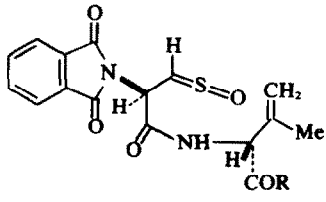
80



81



82



83

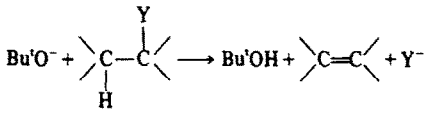
Corroboration that the isothiazolone (**80**) is derived from the secoceph-2-em 1-oxide (**22**) by a base-catalysed reaction comes from the observation that the isothiazolone (**80**; R^1 = OMe or O·CH_2·C_6H_4·NO_2-*p*. R^2 =

phthalimido) is produced in excellent yield when the sulphenic acid (43; R^1 = OMe or O·CH_2·C_6H_4·NO_2-*p*, R^2 = OH) is treated with a weak base.[18,27] The sulphene (83; R = OMe or O·CH_2·C_6H_4·NO_2-*p*)—formed by a β-elimination of the sulphenate (43; R^1 = OMe or O·CH_2·C_6H_4·NO_2-*p*, R^2 = O^-)—is evidently an intermediate, since the reorganization does not occur with the trimethylsilyl derivative (43; R^1 = OMe, R^2 = O·$SiMe_3$).

Rearrangements involving secoceph-3-em derivatives

The 3-H atom of a penicillanoyl derivative is acidified by the adjacent CO moiety. Its removal as a proton may, in principle, initiate the elimination of the S atom to give a secoceph-3-em derivative. Although such a product has never been isolated, there is persuasive evidence that it is formed as an intermediate in certain base-initiated reactions of penicillanoyl derivatives.

In simple systems,[52] the ease of the elimination



is in the order Y = SR < Y = SOR < Y = SO_2R. Penicillanoyl 1-oxides and 1,1-dioxides are, therefore, expected to undergo base-induced β-eliminations to the secoceph-3-em isomers more readily than penicillanoyl derivatives. Although there is evidence for the isomerization of penicillanoyl 1-oxides, the corresponding reaction of penicillanoyl 1,1-dioxides has not been reported.

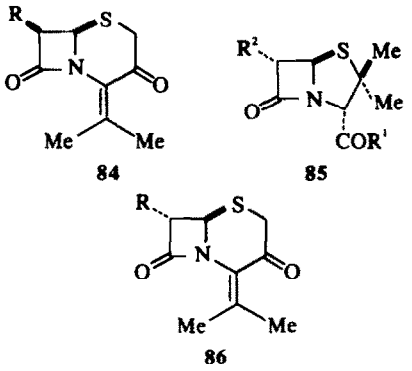
Reactions of secoceph-3-em intermediates. As in the case of secoceph-2-ems, the interception of secoceph-3-em intermediates is of interest because of the possible utility of the products for the synthesis of biologically active β-lactams. The two types of interception, which have been observed, involve the reaction of the thiol moiety with an internal electrophile and with an external electrophile.

Intramolecular reactions. Wolfe *et al.*[53,54] first showed that treatment of a penicillanoyl chloride (7; R^1 = Cl) with triethylamine in dichloromethane resulted in the formation of the corresponding 3-isopropylidene-2-oxopenam (78). It is clear that the chlorocarbonyl substituent plays a dual role—it acidifies the H atom, permitting the β-elimination to a secoceph-3-em intermediate (72; R^1 = Cl), and its serves as an intramolecular trap for the derived thiol function.

Although the yields of penams (78) are low (*ca.* 20–30%), the reaction is of general applicability, occurring with a wide range 6β-amidopenicillanoyl chlorides (7; R^1 = Cl, R^2 = NH·COR) or mixed anhydrides (7; R^1 = O·CO_2Et or O·SO_2Me, R^2 = NH·COR). Moreover, epimerisation at position 6 (pp. 2341–2343) is evidently not a competing reaction since the 6β-phthalimidopenam (78; R = phthalimido) is obtained from 6β-phthalimidopenicillanoyl chloride (7; R^1 = Cl, R^2 = phthalimido).

The principle embodied in the foregoing reorganization has been extended to penicillanoylmethyl halides, resulting in a synthesis of 4-isopropylidene-3-oxocephams.[55,56] Thus, treatment of the chloro-ketone (7; R^1 = CH_2Cl, R^2 = phthalimido) with 1,5-diazabicyclo[4.3.0]non-5-ene in dimethyl sulphoxide yields a 1·7:1 mixture of the cephams (84; R = phthalimido) and (86; R = phthalimido) in high yield. The latter product arises from the epimeric chloroketone (85; R^1 = CH_2Cl, R^2 = phthalimido), which is formed by a competitive, irreversible, base-catalysed isomerization (pp. 2341–2342) of the starting material.

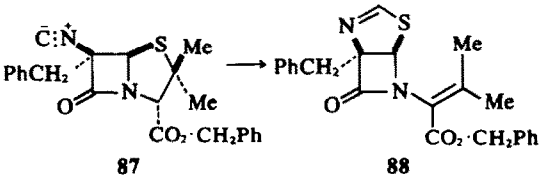
In view of the potential utility of the ring-expansion reaction, efforts were made to eliminate the epimerization. When the chloro-ketone (7; R^1 = CH_2Cl, R^2 = phthalimido) was treated with a deficiency of 1,5-diazabicyclo[4.3.0]non-5-ene in dimethyl sulphoxide containing deuterium oxide, the chloromethyl protons of the unreacted starting material were completely replaced by deuterium; however, there was no observable exchange of the 3-proton. Consequently, the base-induced removal of the 3-proton of derivative (7; R^1 = CH_2Cl, R^2 = phthalimido) represents the slow step in the formation of the cepham (84; R = phthalimido).



84 85 86

The substituent, R^1, in the penicillanoyl derivative (7; R^2 = phthalimido) is expected to exert a greater effect on the acidity of the 3-H atom than on the 6-H atom. A change in this substituent is, therefore, likely to influence the ratio of the cephams produced. In the case of the iodo-ketone (7; R^1 = CH_2I, R^2 = phthalimido), for example, the reaction proceeds at least 10 times faster and a 4·3:1 mixture of cephams (84; R = phthalimido) and (86; R = phthalimido) is obtained in high yield.

The ring-expansion can be extended[56] to the chloro-ketone (7; R^1 = CH_2Cl, R^2 = NH·CO·CH_2·OPh) and to the tosyloxy-ketone (7; R^1 = CH_2·O·SO_2·C_6H_4·Me-*p*, R^2 = NH_2), resulting in a synthesis of the cephams (84; R = NH·CO·CH_2·OPh and NH_2). In these instances, epimerization of the 6β-substituent does not occur.

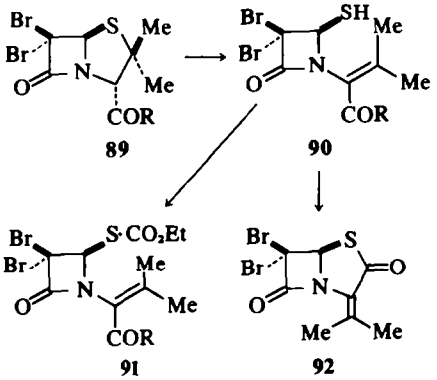


87 88

It was noted earlier (p. 2329) that 6β-amidosecoceph-2-em intermediates (e.g. 72; R^1 = O·CH_2CCl_3, R^2 = NH·CO·CH_2·OPh), prepared by reduction of the corresponding sulphenic acids with trimethyl phosphite, undergo intramolecular condensations to give thiazoline-azetidinones (e.g. 73; R^1 = O·CH_2·CCl_3, R^2 = CH_2·OPh). The corresponding reaction of *in situ* generated 6β-amidosecoceph-3-ems (e.g. 71; R^1 = OMe, R^2 = H) has not been observed. However, an example in which the thiol moiety is trapped intramolecularly by the isocyano-function is provided[57] by the conversion of the penicillanate (87) into the thiazoline-azetidinone (88) in the presence of potassium carbonate.

Intermolecular reactions. The first indication that a

secoceph-3-em could be trapped by an external electrophile was provided by Clayton[58] during a study of the reaction of the mixed anhydride (**89**; R = O·CO_2Et) with triethylamine in dichloromethane. In addition to the expected product (**92**), the 1-ethoxycarbonylsecoceph-3-em (**91**; R = OEt) was isolated in 15% yield. The latter product is probably derived from the anhydride (**91**; R = O·CO_2Et), formed by an intermolecular, ethoxycarbonyl-group transfer from the starting material to the intermediate (**90**; O·CO_2Et).



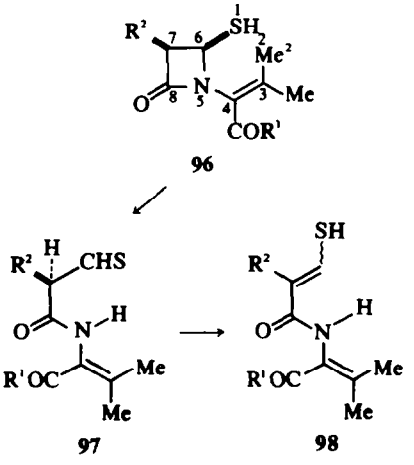
89 **90** **91** **92**

Clayton *et al.* have shown[59] that 6β-triphenylmethylaminopenicillanates (e.g. **7**; R^1 = O·CH_2Ph, R^2 = NH·CPh_3) react with methyl iodide in the presence of sodium hydride and tetrahydrofuran to give 1-methylsecoceph-3-ems (e.g. **93**; R^1 = O·CH_2Ph, R^2 = NH·CPh_3). The acidity of the 3-H atom is an important factor in promoting such isomerizations since under corresponding conditions the diethylamide (**7**; R^1 = NEt_2, R^2 = NH·CPh_3) is recovered unchanged.[60]

Although other electrophilic C sources—such as allylic, benzylic and propargylic halides[61]—can function as the trapping agent, 6,6-dibromopenicillanates (e.g. **89**; R = OMe), are the only other compounds which undergo the reaction.[32] Non-β-lactam materials are produced (pp. 2331–2333) with other penicillanates.[32,60]

It was noted earlier (p. 2330) that a pencillanoyl 1-oxide is expected to isomerize to the corresponding secoceph-3-em 1-oxide under basic conditions. Although the reaction has not been extensively studied, the 1β-oxide (**23**; R^1 = O·CH_2Ph, R^2 = NH·CPh_3) does afford the 1-methylsecoceph-3-em 1-oxide (**95**), as one major isomer, when treated with potassium t-butoxide and methyl iodide;[62] the sulphenate (**94**) is a likely intermediate. This result contrasts with that observed (p. 6) for the lithium sulphenate (**43**; R^1 = O·CH_2·C_6H_4·NO_2-*p*, R^2 = OLi), which undergoes O-alkylation with methyl fluorosulphonate.

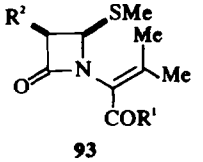
Ring-opening reactions. In many reactions, in which the secoceph-3-ems may be invoked as primary intermediates, non-β-lactam products are also formed. The enethiols (**98**), which are the likely precursors of these products, probably arise from the secoceph-3-ems (**96**) by a β-elimination pathway. In principle, such a process may be induced by the removal of either the 1-proton or the 7-proton and followed by the cleavage of the 5–6 bond. The former mechanism, involving the intermediacy of the thioaldehyde (**97**), is preferred on stereoelectronic grounds. Thus, in the thiolate intermediate an electron pair on the S atom can readily adopt the antiperiplanar geometry with respect to the 5–6 bond. By contrast, in the enolate-like intermediate the electron pair, located formally in a *p*-type orbital at position 7, is *ca.* orthogonal with the 5–6 bond.



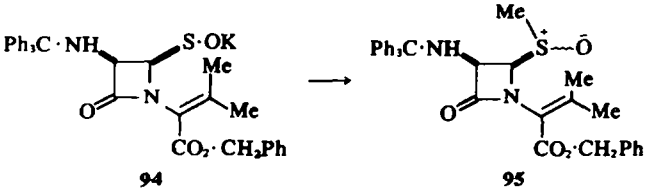
96 **97** **98**

In a careful study[63] of the reaction of 6β-phenoxyacetamidopenicillanoyl chloride (**7**; R^1 = Cl, R^2 = NH·CO·CH_2·OPh) with triethylamine in dichloromethane, the oxazolinones (**101**; X = S and S_2) were isolated in addition to the penam (**78**; R = NH·CO·CH_2·OPh). Compounds (**101**; X = S and S_2) probably originate from the oxazolinone (**100**; R^1 = H, R^2 = NH·CO·CH_2·OPh), which in turn is formed from the enethiol (**99**; R^1 = Cl, R^2 = NH·CO·CH_2·OPh). The oxazolinone (**100**; R^1 = H, R^2 = NH·CO·CH_2·OPh) was characterized as the initial hydrolysis product of the penam (**78**; R = NH·CO·CH_2·OPh) at pH 9·8;[64] it was subsequently converted into a mixture of the oxazolinones (**101**; X = S and S_2). Moreover, under mildly acidic conditions, the oxazolinone (**100**; R^1 = H, R^2 = NH·CO·CH_2·OPh) underwent cyclization to the thiazole (**102**), implying that it possesses the (*Z*)-configuration.[64]

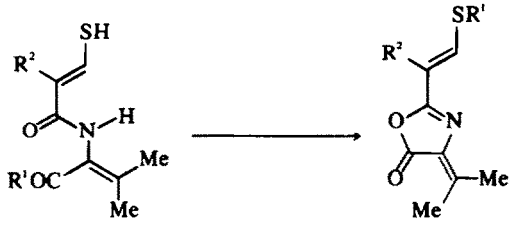
The enethiol (**100**; R^1 = H, R^2 = NH·CO·CH_2·OPh) is



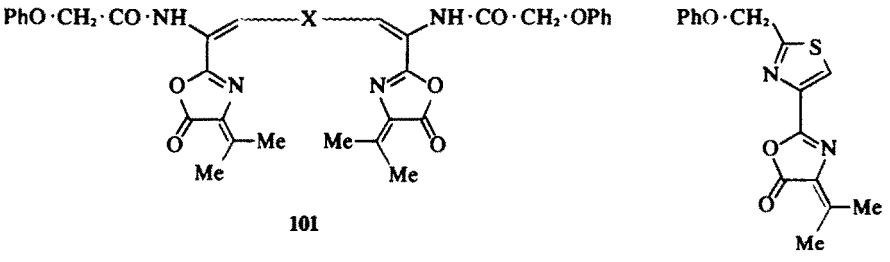
93



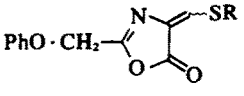
94 **95**



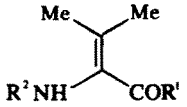
99 100



101 102



103

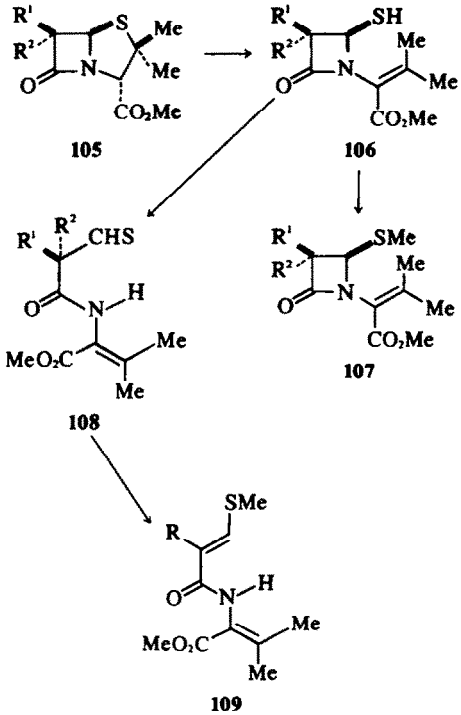


104

also implicated in the conversion of 6β-phenoxyacetamidopenicillanic acid (7; R^1 = OH, R^2 = NH·CO·CH_2·OPh) into the oxazolinones (**100**; R^1 = Me, R^2 = NH·CO·CH_2·OPh) and (**101**; X = S), which occurs in NN-dimethylformamide containing methyl chloroformate and triethylamine.[63] It seems likely that the oxazolinone (**100**; R^1 = Me, R^2 = NH·CO·CH_2·OPh) possesses the (*Z*)-configuration since this geometry has been proven[65] for the analogous oxazolinone (**100**; R^1 = Me, R^2 = NH·CO·CH_2Ph), obtained from the acid (7; R^1 = OH, R^2 = NH·CO·CH_2Ph) under corresponding conditions.

When the acid (7; R^1 = OH, R^2 = NH·CO·CH_2·OPh) is heated in acetic anhydride, the oxazolinone (**100**; R^1 = COMe, R^2 = NH·CO·CH_2·OPh) and its diastereoisomer (one isomer predominating), the oxazolinone (**103**; R = COMe) (a single isomer) and the crotonic acid (**104**; R^1 = OH, R^2 = COMe) are produced.[63,66] The species (**100**; R^1 = H, R^2 = NH·CO·CH_2·OPh)—the likely precursor of the oxazolinone (**100**; R^1 = COMe, R^2 = NH·CO·CH_2·OPh) and its diastereoisomer—is probably derived from the enethiol (**99**; R^1 = O·COMe, R^2 = NH·CO·CH_2·OPh) by a cyclization reaction. The enethiol (**99**; R^1 = O·COMe, R^2 = NH·CO·CH_2·OPh) may also give rise to the products (**103**; R = COMe) and (**104**; R^1 = OH, R^2 = COMe), by way of the respective intermediates (**103**; R = H) and (**104**; R^1 = O·COMe, R^2 = H).

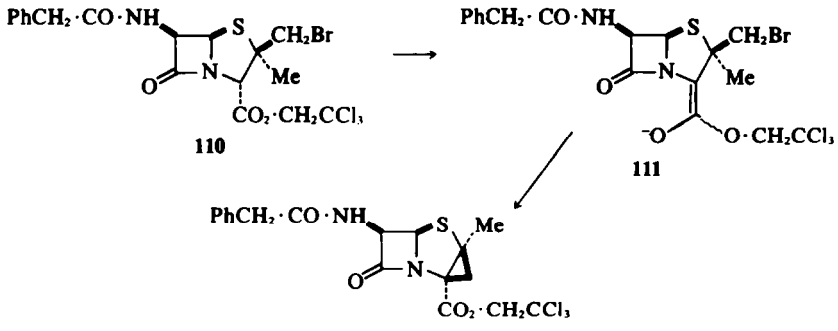
In contrast with the penicillanates (**105**; R^1 = NH·CPh_3, R^2 = H and R^1 = R^2 = Br) which afford[32,59] the 1-methylsecoceph-3-ems (**107**; R^1 = NH·CPh_3, R^2 = H and R^1 = R^2 = Br), the derivatives (**105**; R^1 = R^2 = H: R^1 = H, R^2 = Br and R^1 = NH·CO·CH_2·OPh, R^2 = H) yield the ring-opened products (**109**; R = H, Br and NH·CO·CH_2·OPh) when treated with methyl iodide and sodium hydride.[32,60] This differing behaviour may be attributed to the ease of methylation of the secoceph-3-em (**106**) to give the 1-methylsecoceph-3-em (**107**) compared with its isomerization to the thioaldehyde (**108**). In the



105 106 107 108 109

series (**108**; R^1 = R^2 = H: R^1 = H, R^2 = Br and R^1 = R^2 = Br), the dipolar interaction between the thioaldehyde function and the attached C moiety is increasing; consequently, the ease of formation of these derivatives from the secoceph-3-ems (**106**) is expected to decrease in the same order.

It was noted earlier (pp. 2329–2330) that secoceph-2-em 1-oxides show a tendency to undergo ring-opening reactions under basic conditions. Secoceph-3-em 1-oxides



110 111 112

exhibit a similar behaviour. Thus, treatment of the penicillanoyl 1-oxide (**23**; $R^1 = O{\cdot}CH_2Ph$, $R^2 = NH{\cdot}CPh_3$) with potassium t-butoxide[62] and of the chloro-ketone (**7**; $R^1 = CH_2Cl$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) with lithium hydridotri-t-butoxyaluminate[67] yields the isothiazolones (**80**; $R^1 = O{\cdot}CH_2Ph$, $R^2 = NH{\cdot}CPh_3$ and $R^1 = CH_2Cl$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) as the major products. The isothiazolone (**80**; $R^1 = OMe$, $R^2 =$ phthalimido) is also formed when the secoceph-3-em (**106**; $R^1 = H$, $R^2 =$ phthalimido)—prepared by total synthesis—is treated with dimethyl sulphoxide at pH 7·4.[68]

Mechanism of formation of secoceph-3-em derivatives. Although it is evident from the foregoing discussion that penicillanoyl derivatives can isomerize to the corresponding secoceph-3-ems under basic conditions, very little is known about the mechanism of these reactions. In principle, the removal of the 3-proton either precedes the elimination of the thiol moiety (*E*1*cB* pathway) or it is coupled with the elimination (*E*2 pathway).

Deuterium-exchange studies (p. 2330) have established[55] that the rate-limiting step in the formation of the cepham (**84**; R = phthalimido) involves the removal of the 3-H atom of the chloro-ketone (**7**; $R^1 = CH_2Cl$, $R^2 =$ phthalimido). This result is consistent with either the slow formation of the enolate followed by its rapid isomerization to the secoceph-3-em (**96**; $R^1 = CH_2Cl$, $R^2 =$ phthalimido) or the slow generation of the secoceph-3-em (**96**; $R^1 = CH_2Cl$, $R^2 =$ phthalimido) by an *E*2-like process. The former pathway is preferred by analogy with a recent report which claims that the cyclopropanes (e.g. **112**), are produced when the penams (e.g. **110**) are treated with 1,5-diazabicyclo[5.4.0]undec-5-ene.[69] Intramolecular reactions of enolate-like intermediates (e.g. **111**) best account for the products.

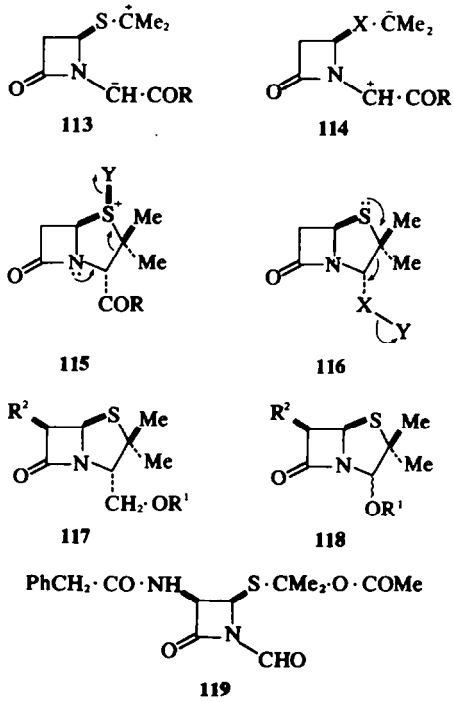
Reversibility of the penicillanoyl → secoceph-3-em transformation. The final issue which will be considered in this section is whether the penicillanoyl → secoceph-3-em transformation is reversible. There are three reports which suggest that it is. First, in 1969 Wolfe *et al.*[70] claimed that hydrolysis of the penam (**78**; R = phthalimido) at pH 7·4 afforded the penicillanic acid (**7**; $R^1 = OH$, $R^2 = NH{\cdot}CO{\cdot}C_6H_4{\cdot}CO_2H$-*o*). Second, a bioactive substance, corresponding chromatographically with the penicillanic acid (**7**; $R^1 = OH$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$), was observed by Thomas[71] when the penam (**78**; $R = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) was incubated at pH 2. Third, Chou isolated the ester (**7**; $R^1 = OMe$, $R^2 =$ phthalimido) from the reduction of methyl 6β-phthalimido-1-trimethylsilyloxysecoceph-3-em with trimethyl phosphite.[26]

Nevertheless, there are some observations which suggest that further experimentation is needed before the results are accepted. Thus, Baldwin and Kitchin[72] have been unable to substantiate Wolfe's claim. The yield of methyl 6β-phthalimidopenicillanate obtained by Chou was very low (1–2%); moreover, the possibility that this was a precontamination of the starting material was not excluded.[73] Furthermore, attempts to effect the ring closure of secoceph-3-ems—prepared by total synthesis—to penicillanates have been unrewarding.[68,74]

In summary, the evidence for the secoceph-3-em → penicillanoyl transformation is insubstantial. The observations of Wolfe, Thomas and Chou may possibly be ascribed to the use of samples which already contained the penicillanoyl derivatives.

2-3 BOND CLEAVAGES

The 2–3 bond of a penicillanoyl derivative is potentially activated for heterolysis. For example, the cationic centre of the ion pair (**113**) is stabilized inductively by the *gem*-dimethyl group and mesomerically by the S atom; the carbanionic centre is mesomerically stabilized by the CO group. In the case of a penicillanoyl 1-oxide and 1,1-dioxide, heterolysis in the alternate manner may be possible; thus, the negative charge of the ion pair (**114**; X = SO or SO_2) is stabilized by the S moiety and the positive charge by the N function. A consideration of the pathways leading to the species (**113** and **114**; X = SO or SO_2) suggests that their stereoelec-



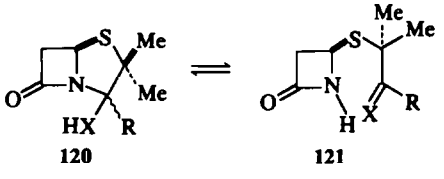
113 114 115 116 117 118 119

tronic requirements are satisfactory. As yet, products arising from these hypothetical intermediates have not been reported.

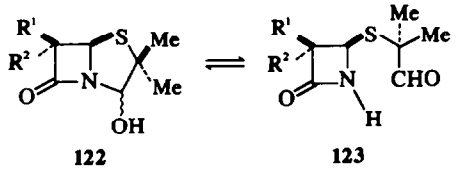
The fragmentations (**115** and **116**; X = CO) provide possible means of rupturing the 2–3 bond of a penicillanoyl derivative. The stereoelectronic requirements of these processes appear to be favourable, since orbital overlap can be maintained throughout.[75] Attempts to ionize the halogen atom of penicillanoyl halides (e.g. **7**; R^1 = Cl) have not been reported and the only documented reactions[76,77] of penicillanyl tosylates (e.g. **117**; R^1 = O·SO_2·C_6H_4·Me-*p*, R^2 = NH·CPh$_3$ or NH·CO·CH_2Ph) involve the cleavage of the β-lactam bond (p. 20). However, an example which possibly involves the fragmentation (**116**; X = O) is provided by the conversion of the 3-hydroxypenam (**118**; R^1 = H, R^2 = NH·CO·CH_2Ph) into the azetidinone (**119**) with lead tetra-acetate in benzene.[78]

3-4 BOND CLEAVAGES

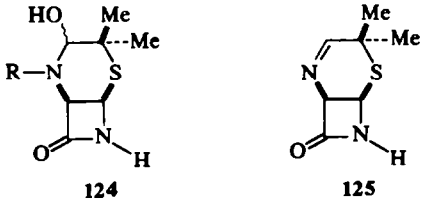
Fission of the 3–4 bond of a penicillanic acid derivative is not expected to occur unless the 3-H atom or the 3-carboxy-group is replaced by the amino- or hydroxy-moiety. In such an event, the derivative (**120**; R = COR', X = NR' or O) may isomerize to the azetidinone (**121**; R = COR', X = NR' or O). Although there is no known method for the replacement of the H atom, the carboxy-group can be converted into the required moiety.[78–81] Several 3α-alkoxyamido-6β-amido-2,2-dimethylpenams have been prepared but there is no record of their isomerization to the ring-opened forms. By contrast, 6β-substituted derivatives of 3-hydroxy-2,2-dimethylpenams do exhibit ring-chain tautomerism.



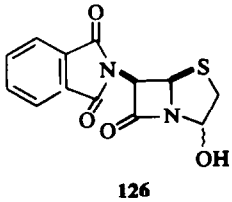
120 **121**



122 **123**



124 **125**



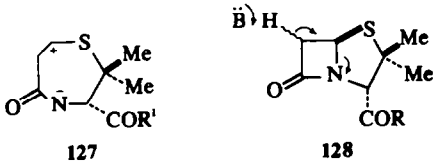
126

The equilibrium between the penam (**122**) and the azetidinone (**123**) is sensitive[78] to the size of the substituent, R^1. With the amido-group, the 3-hydroxypenam (e.g. **122**; R^1 = NH·CO·CH_2Ph, R^2 = H) comprises *ca.* 90% of the mixture. However, with a bulkier group—such as the phthalimido-moiety—the ring-opened form (**123**; R^1 = phthalimido, R^2 = H) predominates (*ca.* 70%). The bicyclic tautomer is also preferred in the case of 6β-amido-3-hydroxy-2,2-dimethylpenam 1-oxides[45,80] and 1,1-dioxides.[82,83] The equilibrium constant is probably determined by the magnitude of the compressional interaction between the 6β-substituent and the 2β-Me group. In accord with this viewpoint, the 3-hydroxypenam tautomers (**122**; R^1 = H, R^2 = phthalimido)[84] and (**126**)[85] are favoured.

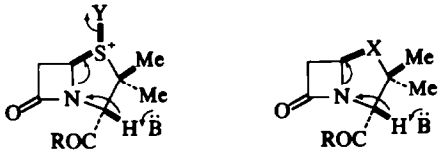
In principle, an azetidinone (**123**) bearing a 6β-amido-substituent may isomerize to the carbinolamine (**124**; R = COR'). Although there is no evidence for this tautomeric form, derivative (**125**) is formed[86] from the amino-azetidinone (**122**; R^1 = NH_2, R^2 = H).

4-5 BOND CLEAVAGES

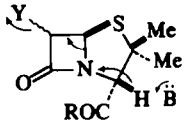
Several processes are feasible, in theory, for the rupture of the 4–5 bond of a penicillanoyl derivative. Thus, direct heterolysis could afford the ion pair (**127**). A consideration of the pathway leading to this species suggests that the cationic charge can be stabilized by the S atom; however, the carbanionic centre is developing in a geometry which is *ca.* orthogonal with the π-electrons of the CO group.



127 **128**



129 **130**



131

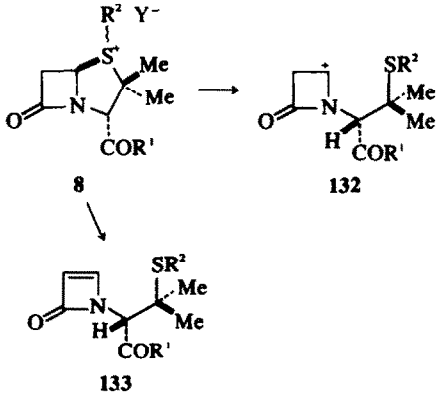
Four eliminations may be considered—process (**128**) involves the removal of the 6-H atom as a proton and processes (**129–131**) require the removal of the 3-H atom as a proton. Whereas the stereoelectronic requirements of the eliminations (**128** and **131**) are unfavourable, those of the processes (**129**) and (**130**; X = SO or SO_2) may be acceptable.

As yet, however, there is no direct evidence that the 4–5 bond is ever cleaved in a primary reaction of a penicillanoyl derivative.

1-5 BOND CLEAVAGES

In principle, two processes warrant consideration for the cleavage of the 1–5 bond. The sulphonium salt (**8**), derived from the reaction of a penicillanoyl derivative

with an electrophilic agent, R^2Y, may undergo a 1–5 bond heterolysis to give the azetidinyl cation (**132**), which is mesomerically stabilized by the N moiety. Alternatively, the 1–5 bond rupture may be coupled with or may follow the removal of the 6-H atom as a proton; in this instance the azetinone (**133**) may be considered to be the reaction intermediate.



8 **132** **133**

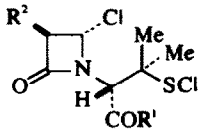
Rearrangements involving azetidinyl-cation intermediates

The first demonstration that the 1–5 bond of a penicillanoyl derivative could be selectively cleaved was provided by Kukolja in 1971.[87] Treatment of the ester (**7**; R^1 = OMe, R^2 = phthalimido) with a molar equivalent of chlorine at −78° gave a 4:1 mixture of the chloro-azetidinones (**134**; R^1 = OMe, R^2 = phthalimido) and (**135**; R^1 = OMe, R^2 = phthalimido) in high yield; these derivatives underwent further reaction with chlorine affording the compounds (**136**; R^1 = OMe, R^2 = phthalimido) and (**137**; R^1 = OMe, R^2 = phthalimido). The corresponding reaction of the 6β-phenylacetamidopenicillanate (**7**; R^1 = $O{\cdot}CH_2CCl_3$; R^2 = $NH{\cdot}CO{\cdot}CH_2Ph$) gave the chloro-azetidinone (**136**; R^1 = $O{\cdot}CH_2CCl_3$, R^2 = $NH{\cdot}CO{\cdot}CH_2Ph$) in 90% yield;[88] the product stereochemistry suggests that the oxazoline-azetidinone (**138**; R^1 = $O{\cdot}CH_2CCl_3$, R^2 = Cl) intervenes.

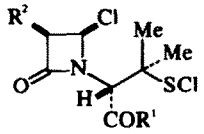
It seems likely that other reagents, which are a source of electrophilic chlorine, react with penicillanates by an initial 1–5 bond heterolysis. Thus, 1-chlorobenzotriazole[89] converts the penicillanate (**7**; R^1 = $O{\cdot}CH_2CCl_3$, R^2 = phthalimido) initially into the chloro-azetidinone (**139**; R^1 = $O{\cdot}CH_2CCl_3$, R^2 = phthalimido), which subsequently affords the derivative (**136**; R^1 = $O{\cdot}CH_2CCl_3$, R^2 = phthalimido). N-Chloro-N-sodio-toluene-*p*-sulphonamide[90] reacts with the penicillanate (**7**; R^1 = OMe, R^2 = $NH{\cdot}CO{\cdot}CH_2Ph$) to give the thiadiazine-azetidinone (**140**), possibly by way of the oxazoline-azetidinone (**138**: R^1 = OMe, R^2 = $NH{\cdot}SO_2{\cdot}C_6H_4{\cdot}Me$-*p*). In certain instances, oxazoline-azetidinones[8,14,90–92] can be isolated from such reactions. Thus, the derivative (**141**; R = OMe) is formed from the penicillanate (**7**; R^1 = OMe, R^2 = $NH{\cdot}CO{\cdot}CH_2Ph$) and t-butyl hypochlorite[91] or iodobenzene dichloride.[8,14]

Chlorine reacts with 2-oxo-3-isopropylidenepenams (e.g. **78**; R = phthalimido or $NH{\cdot}CO{\cdot}CH_2Ph$) to give mixtures of the chloro-azetidinones (**136**; R^1 = Cl, R^2 = phthalimido or $NH{\cdot}CO{\cdot}CH_2Ph$) and (**137**; R^1 = Cl, R^2 = phthalimido or $NH{\cdot}CO{\cdot}CH_2Ph$); the reaction is probably triggered by a 1–5 bond fission.[93,94]

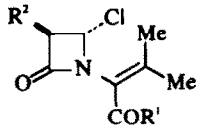
Mercury(II) acetate in acetic acid is also a versatile



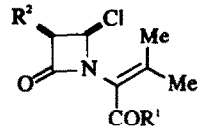
134



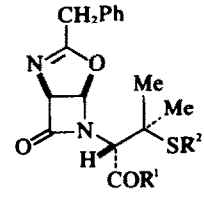
135



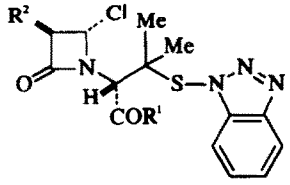
136



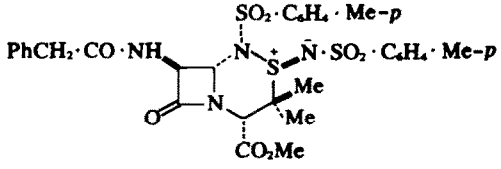
137



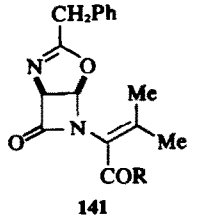
138



139

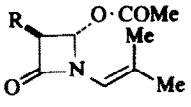


140

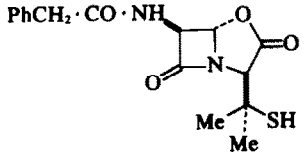


141

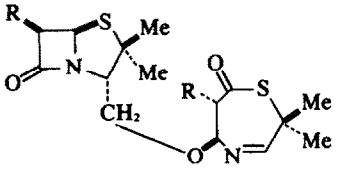
reagent for inducing the selective 1–5 bond cleavage of penicillanic acid derivatives. The products of such reactions depend upon the experimental conditions—at room temperature the oxazoline-azetidinones (e.g. **138**; $R^1 = R^2 = Hg{\cdot}O{\cdot}COMe$) are formed,[95] whereas at 80° a decarboxylative elimination and an opening of the oxazoline ring take place[96] to give the acetoxy-azetidinones (e.g. **142**; $R = NH{\cdot}CO{\cdot}CH_2Ph$). Attempts to isolate the acid (**138**; $R^1 = R^2 = H$) were thwarted by its facile rearrangement[97] to the oxazolidine-azetidinone (**143**).



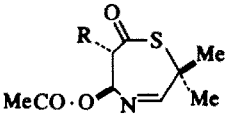
142



143



144



145

Treatment of the penicillanyl alcohol (**117**; $R^1 = H$, R^2 = phthalimido or $NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) with lead tetra-acetate in benzene[25] affords a product which is formulated as the penicillanyloxy-thiazepinone (**144**; R = phthalimido or $NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$). The thiazepinone (**145**; R = phthalimido) is also formed in low yield in the case of the 6β-phthalimidopenicillanyl alcohol. Although the sequence of reactions leading to these products has not been elucidated it is likely that they are initiated by a 1–5 bond cleavage of the penicillanyl alcohol.

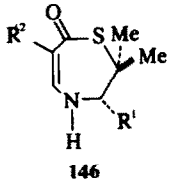
Rearrangements involving azetinone intermediates

The first indication that a penicillanoyl derivative could rearrange to a thiazepinone was provided by Kovacs *et al.*[98] who isolated the derivative (**146**; $R^1 = CO_2Me$, R^2 = phthalimido) from the reaction of the penicillanate (**7**; $R^1 = OMe$, R^2 = phthalimido) with triethylamine in dichloromethane; the 6α-phthalimidopenicillanate (**85**; R = OMe, R^2 = phthalimido) was an accompanying product, which was stable under the reaction conditions. It was subsequently shown that the product ratio was independent of temperature (between 25 and 50°), suggesting that the products were derived by a common, rate-determining process.[99]

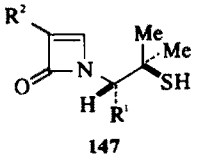
Thiazepinone formation requires the cleavage of the 1–5 and 4–7 bonds of the penicillanoyl precursor, bond formation between the S atom and the CO moiety, and a proton transfer from position 6 to the N atom. In principle, the reaction may proceed by way of the azetinone (**147**; $R^1 = CO_2Me$, R^2 = phthalimido) or the ketene (**148**; $R^1 = OMe$, R^2 = phthalimido). The formation of the latter intermediate is unlikely on stereoelectronic considerations, since the C(6)-H and 4–7 bonds of the penicillanoyl precursor are *ca.* orthogonal. Moreover, in methanol containing a trace of sodium methoxide,[100] the penicillanate (**7**; $R^1 = O{\cdot}CH_2{\cdot}OMe$, $R^2 = N{:}CH{\cdot}C_6H_4{\cdot}NO_2$-*p*) rapidly equilibrated with the epimer (**85**; $R^1 = O{\cdot}CH_2{\cdot}OMe$, $R^2 = N{:}CH{\cdot}C_6H_4NO_2$-*p*), and the mixture was quantitatively isomerized to the thiazepinone (**146**; $R^1 = CO_2{\cdot}CH_2{\cdot}OMe$, $R^2 = N{:}CH{\cdot}C_6H_4{\cdot}NO_2$-*p*). If the ketene (**148**; $R^1 = O{\cdot}CH_2{\cdot}OMe$, $R^2 = N{:}CH{\cdot}C_6H_4{\cdot}NO_2$-*p*) had intervened, it would have been expected to react with the solvent to give the derivative (**149**)—a product which was shown to be stable under the reaction conditions. It is evident, therefore, that the azetinones (**147**) are the precursors of the thiazepinones (**146**).

A study of the reaction of methyl 6β-phthalimidohomopenicillanate (**150**; R^1 = phthalimido, $R^2 = H$) with organic bases reveals that the formation of the thiazepinone (**146**; $R^1 = CH_2{\cdot}CO_2Me$, R^2 = phthalimido) increases at the expense of the epimer (**150**; $R^1 = H$, R^2 = phthalimido), as the strength of the base decreases.[101]

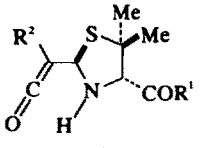
In certain instances, thiazepinones undergo further base-induced rearrangements.[102] For example, treatment of the methoxymethyl ester (**7**; $R^1 = O{\cdot}CH_2{\cdot}OMe$, R^2 = phthalimido) with triethylamine in dichloromethane yields a 5:2 mixture of the thiazinone (**153**) and the epimer (**85**; $R^1 = O{\cdot}CH_2{\cdot}OMe$, R^2 = phthalimido) in high yield—the products are stable under the reaction conditions. The thiazinone (**153**) is almost certainly derived from the



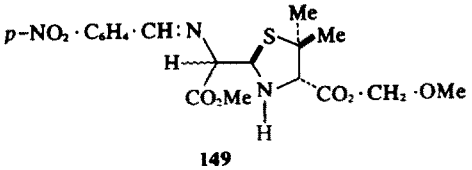
146



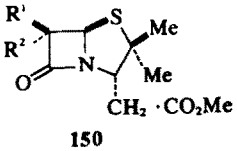
147



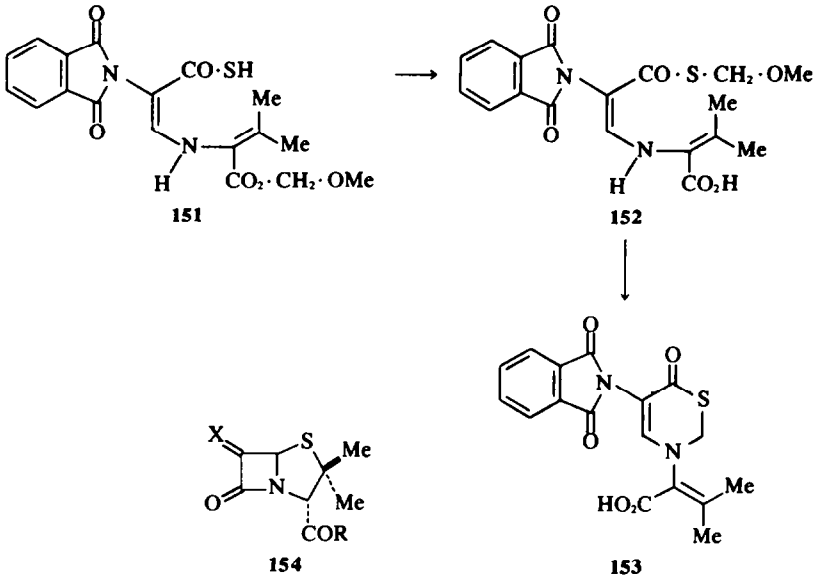
148



149



150



151 152 153 154

thiazepinone (**146**; $R^1 = CO_2{\cdot}CH_2{\cdot}OMe$, R^2 = phthalimido), probably by way of the intermediates (**151** and **152**).

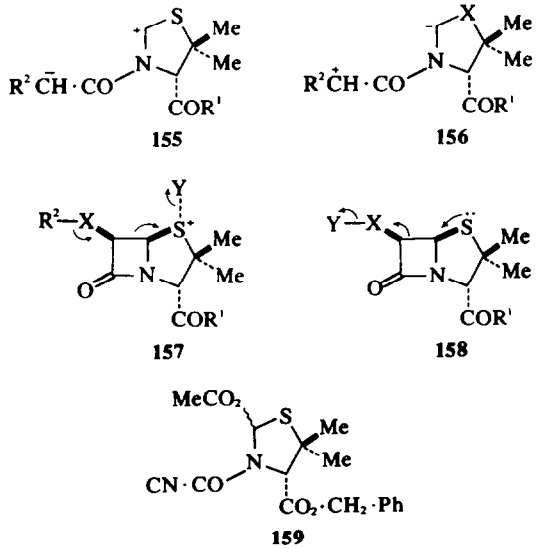
An unusual feature of the foregoing reactions is that 6α-phthalimidopenicillanates show little tendency to isomerize to thiazepinones—it has been estimated[103] that the rate of rearrangement of the derivative (**150**; R^1 = H, R^2 = phthalimido) to the thiazepinone (**146**; $R^1 = CH_2{\cdot}CO_2Me$, R^2 = phthalimido) in the presence of 1-methylpiperidine is *ca.* 300-times slower than the transformation of the 6β-isomer (**150**; R^1 = phthalimido, R^2 = H) into a mixture of the thiazepinone (**146**; $R^1 = CH_2{\cdot}CO_2Me$, R^2 = phthalimido) and the 6α-phthalimido-derivative (**150**; R^1 = H, R^2 = phthalimido). There is a dramatic thermodynamic preference[104] for the α-isomers of 6-phthalimidopenicillanates—more than 99% in the case of the methoxymethyl ester (**85**; $R^1 = O{\cdot}CH_2{\cdot}OMe$, R^2 = phthalimido). The instability of the 6β-isomer is attributed (p. 21) to the severe steric interaction between the 6β-phthalimido- and the 2β-Me groups. This large, ground-state energy difference is considered to be responsible for the slow rate of isomerization of 6α-phthalimidopenicillanates to thiazepinones, implying that the transition states of the two reactions are similar in energy.[101,105] Evidently, these transition states possess considerable trigonal character at position 6.

6-Amidopenicillanates are not isomerized to the corresponding thiazepinones in the presence of tertiary amines, possibly because of the lower acidity of the 6-H atom. However, prior treatment of the derivatives with NO-bis(trimethylsilyl)acetamide does induce the rearrangement;[106,107] the trimethylsilyl compounds [e.g. **7**; $R^1 = O{\cdot}CH_2Ph$, $R^2 = N{:}C(O{\cdot}SiMe_3)CH_2{\cdot}OPh$] are likely intermediates in the reactions.

There are a few examples of thiazepinone formation under non-basic conditions. Thus, antimony pentachloride[108] and phosphorus oxychloride[98] induce the rearrangement. Catalytic hydrogenation of the derivative (**154**; $R = O{\cdot}CH_2Ph$, $X = CH{\cdot}COPh$) yields the thiazepinone (**146**; $R^1 = CO_2{\cdot}CH_2Ph$, $R^2 = CH_2{\cdot}COPh$) as a minor product.[109]

5-6 BOND CLEAVAGES

The 5–6 bond of a penicillanoyl derivative is potentially activated for heterolysis. Thus, both the cationic and carbanionic sites of the ion pair (**155**) are mesomerically stabilized—the former by the S and N moieties and the latter by the CO function. In the case of a penicillanoyl 1-oxide and 1,1-dioxide, heterolysis in the alternate manner may be possible. The negative charge of the ion pair (**156**; X = SO or SO_2) is stabilized by the sulphinyl or sulphonyl group although the positive charge is probably destabilized by the CO moiety. In the generation of the ion pair (**155**), the developing carbenium ion is benefiting from the mesomeric stabilization of the S and N moieties; however, the carbanion is being formed *ca.* orthogonal to the π-system of the CO group. In the formation of the ion pair (**156**; X = SO or SO_2), the developing carbanion is likely to be stabilized by the sulphinyl or sulphonyl moeity; the carbenium ion, which is being formed *ca.* orthogonal to the π-system of the CO group, is expected to benefit from the presence at position 6 of a N- or O-containing substituent, R^2. As yet, there are no reported examples of a 5–6 bond cleavage by the foregoing pathways.

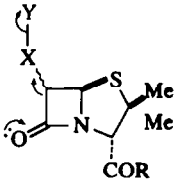


155 156 157 158 159

The fragmentation processes (**157** and **158**) provide possible means of effecting the 5–6 bond rupture. A consideration of the stereoelectronic requirements[75] of these processes suggests that continuous orbital overlap is feasible. A possible example is provided by the conversion of the aminopenicillanate (7; $R^1 = O{\cdot}CH_2Ph$, $R^2 = NH_2$) into the thiazolidine (**159**), which occurs in the presence of lead tetra-acetate in benzene;[110] the imine (**154**; $R = O{\cdot}CH_2Ph$, $X = NH$) is probably the species which undergoes the fragmentation.

6-7 BOND CLEAVAGES

The 6–7 bond of a penicillanoyl derivative is not directly activated for heterolysis. However, in principle, the bond cleavage may be achieved by the fragmentation process (**160**). Although stereoelectronically feasible,[75] there is, as yet, no reported instance of its occurrence.



160

4-7 BOND CLEAVAGES

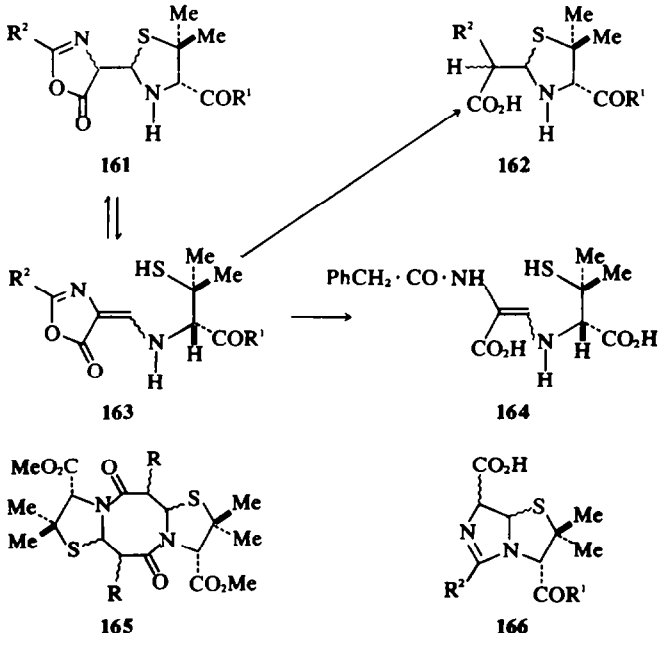
The 4–7 bond of a penicillanoyl derivative is very susceptible to cleavage by nucleophiles.[111] In the case of a 6-amido-compound, there is the opportunity for intramolecular participation by the amido-moiety, resulting in the formation of a thiazolidinyl-oxazolinone (**161**).

Kinetic studies suggest[112–114] that the intramolecular reaction is important in the hydrolysis of a 6β-acetamidopenicillanic acid (7; $R^1 = OH$, $R^2 = NH{\cdot}COR$) in the pH 1–5 region, but not under neutral or alkaline conditions. Under acidic aqueous conditions the thiazolidinyl-oxazolinone (**161**; $R^1 = OH$) is not isolable, but rapidly rearranges to the penicillenic acid (**163**; $R^1 = OH$). In the early literature,[115] it was shown that hydrogen chloride in anhydrous ether induced the isomerization of the penicillanate (7; $R^1 = OMe$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$) to the hydrochloride salt of the thiazolidinyl-oxazolinone (**161**; $R^1 = OMe$, $R^2 = CH_2Ph$). The salt was extremely sensitive to moisture, hydrolysing to the penicilloic acid (**162**; $R^1 = OMe$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$), and it was converted into the penicillenate (**163**; $R^1 = OMe$, $R^2 = CH_2Ph$) by treatment with diazomethane.

It appears that under strongly acidic conditions the penicillenic acid (**163**; $R^1 = OH$) is the primary decomposition product. In some cases the compound can be isolated from such reactions,[116] although it is more conveniently prepared by treating a penicillanoyl derivative with mercury(II) chloride.[117] Penicillenic acids readily undergo further reactions, probably by way of low equilibrium concentrations of diastereoisomeric mixtures of the thiazolidinyl-oxazolinones (**161**). Thus, benzylpenicillenic acid (**163**; $R^1 = OH$, $R^2 = CH_2Ph$) preferentially affords[118] the penamaldic acid (**164**) at pH 1·0, the penillic acid (**166**; $R^1 = OH$, $R^2 = CH_2Ph$) at pH 3·0 and the penicilloic acid (**162**; $R^1 = OH$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$) at pH 6·0. An additional rearrangement product, so far observed[113] only in the case of the benzamido-derivative (7; $R^1 = OH$, R^2 = 2,6-dimethoxybenzamido) is the tricyclic compound (**165**; R = 2,6-dimethoxybenzamido); it is presumably formed by dimerization of the thiazolinyl-oxazolinone (**161**; $R^1 = OH$, R^2 = 2,6-dimethoxyphenyl). It should be stressed that the stereochemistry of the foregoing substances has not been defined. However, the penillic acid (**166**; $R^1 = OH$, $R^2 = CH_2Ph$) and the dimer (**165**; R = 2,6-dimethoxybenzamido) are apparently obtained as single isomers.

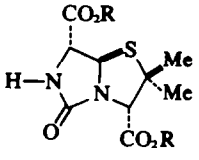
A decrease of the nucleophilicity of the amido-CO group is known to increase the acid stability of a 6β-amidopenicillanic acid.[119] In the case of the *para*-substituted benzamides (7; $R^1 = OH$, $R^2 = NH{\cdot}CO{\cdot}C_6H_4{\cdot}R\text{-}p$), a linear Hammett correlation (ρ − 1·60) is observed, in accord with the intramolecular pathway.[114]

When carbon dioxide is bubbled through an aqueous

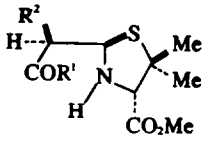


161 **162** **163** **164** **165** **166**

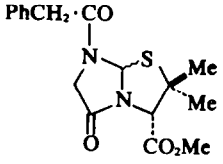
solution of 6β-aminopenicillanic acid (7; R^1 = OH, R^2 = NH_2) at pH 7, the diacid (167; R = H) is formed in good yield.[120–122] This reorganization—a reaction analogous to the conversion of a 6β-amidopenicillanate into a penillic acid—probably involves the intermediacy of the thiazolidinyl-oxazolinone (161; R^1 = R^2 = OH), formed by way of the carbamic acid (7; R^1 = OH, R^2 = NH·CO_2H). It seems unlikely that the penicillenic acid (163; R^1 = R^2 = OH) intervenes since no deuterium incorporation is observed at position 6 when the reaction is performed in deuterium oxide.[123] Moreover, the diester (167; R = Me) can be synthesized by treating the thiazolidine (168; R^1 = OMe, R^2 = NH_2) with phosgene.[122] Consequently, the chirality at positions 5 and 6 of the starting material is retained in the product.



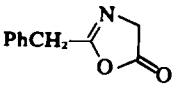
167



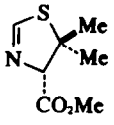
168



169



170



171

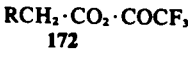
The rearrangement of methyl 6β-phenylacetamidopenicillanate (7; R^1 = OMe, R^2 = NH·CO·CH_2Ph) to methyl benzylpenillonate (169), which occurs in boiling toluene containing a trace of iodine,[124] formally requires a 5–6 bond heterolysis. However, it is unlikely that the reaction is triggered by this process since the phthalimidopenicillanate (7; R^1 = OMe, R^2 = phthalimido) is stable under the reaction conditions.[123] Derivative (7; R^1 = OMe, R^2 = phthalimido) would be expected to undergo a 5–6 bond rupture more readily because of the greater relief of steric strain and, possibly, the better stabilization of the developing carbanion. Although penillonate formation is precluded, the ion pair (155; R^1 = OMe, R^2 = phthalimido) would be expected to recyclize to give a diastereoisomer of the starting material, in which the S(1)–C(5) bond and the phthalimido-group are *trans* orientated.

Jansen and Robinson[125] have demonstrated that the penillonate (169) is formed by heating the oxazolinone (170) and the thiazoline (171) in benzene. They propose that the thiazolidinyl-oxazolinone (161; R^1 = OMe, R^2 = CH_2Ph) is the primary intermediate, which fragments to the oxazolinone (170) and the thiazoline (171); these fragments then afford the penillonate (169). In accord with this proposal, methyl benzylpenicillenate (163; R^1 = OMe, R^2 = CH_2Ph) can be detected as an intermediate.[124]

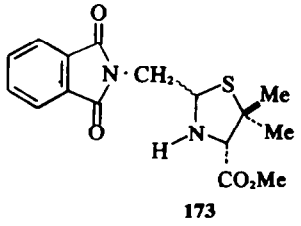
The thiazoline (171) and, probably, the anhydride (172; R = NH·CO·CH_2Ph) are produced when the penicillanate (7; R^1 = OMe, R^2 = NH·CO·CH_2Ph) is heated in trifluoroacetic acid;[126] the anhydride (168; R^1 = O·$COCF_3$, R^2 = NH·CO·CH_2Ph) is the likely precursor of these products. Under similar conditions the phthalimido-derivative (7; R^1 = OMe, R^2 = phthalimido) affords the thiazolidine (173), as a mixture of diastereoisomers,[127] possibly by way of the thiazoline (171) and the anhydride (172; R = phthalimido).

In contrast with trifluoroacetic acid, acetic acid[128] reacts with the penicillanate (7; R^1 = OMe, R^2 = NH·CO·CH_2Ph) to give the thiazolidine (174), presumably by an intramolecular, acetyl-group transfer from the anhydride (168; R^1 = O·COMe, R^2 = NH·CO·CH_2Ph). A related reaction, affording the bicyclic derivative (175), occurs when the penam [118; R^1 = $CH(OMe_2)$, R^2 = NH·CO·CH_2·OPh] is treated with acetic acid.[78]

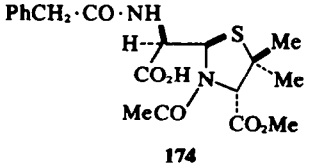
Oxidation of the penam [78; R = NH·CO·CH(Me)OPh] with mercury(II) acetate in hot benzene is reported to give the thiazolidinone-oxazolinone (177)—a substance with pronounced antibacterial activity.[66] The derivative (176) is claimed to be an intermediate in the reorganization; it can



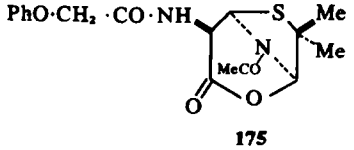
172



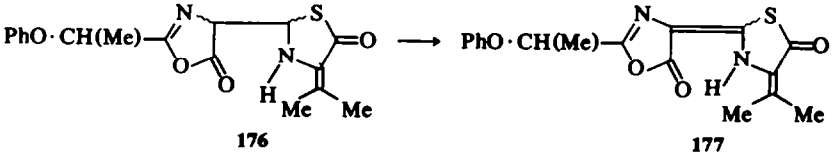
173



174



175



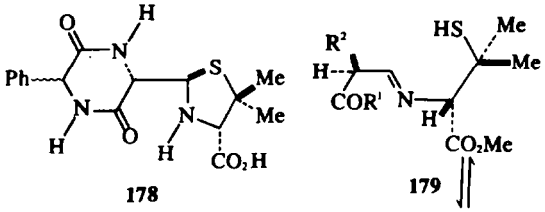
176 177

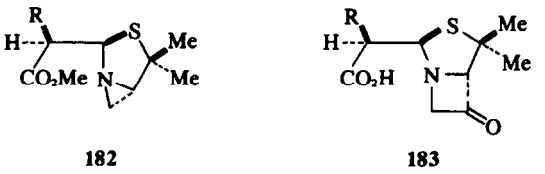
be prepared by treating the starting material with boron trifluoride and represents a rare example of an isolable thiazolidinyl-oxazolinone. However, the status of this work must be questioned since workers at Beecham Research Laboratories[129] were unable to confirm the formation of the derivative (177). Moreover, although they observed the production of an antibacterial substance, this material was also formed when mercury(II) acetate was heated in benzene!

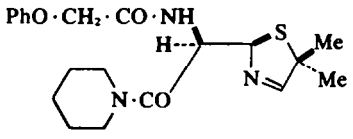
A further example involving an intramolecular cleavage of the β-lactam linkage is provided by the hydrolysis of the penicillanate [85; R^1 = OH, R^2 = NH·CO·CH(NH_2)Ph] to the thiazolidinyl-piperazine (178); the 6β-isomer [7; R^1 = OH, R^2 = NH·CO·CH(NH_2)Ph] does not undergo a comparable reaction, possibly because the *endo*-face of the β-lactam CO group is more hindered.[130]

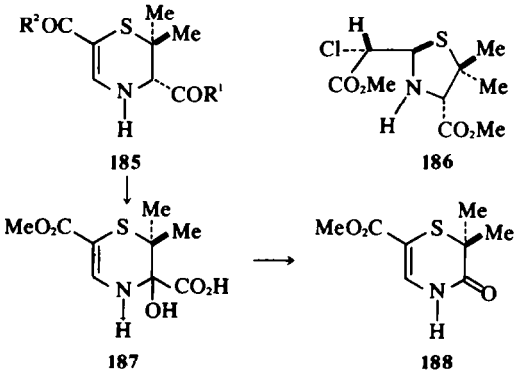
Although a thiazolidinylacetyl derivative (168), is often the initial product of the reaction of a penicillanate with a nucleophile, in many instances it readily undergoes further reactions. For example, under basic conditions it may isomerize to a mixture of the diastereoisomers (181), by way of the intermediates (179 and 180). An intramolecular trapping of the thiazolidinyl N atom is implicated in the reactions of the tosylate (117; R^1 = O·SO_2·C_6H_4·Me-*p*, R^2 = NH·CPh_3 or NH·CO·CH_2Ph) with basic methanol to give[76,77] the thiazolidine-aziridine (182; R = NH·CPh_3 or NH·CO·CH_2Ph), and of the diazo-ketone (7; R^1 = CHN_2, R^2 = NH·CO·CH_2·OPh) with hydrochloric acid to yield[56] the thiazolidine-azetidinone (183; R = NH·CO·CH_2·OPh). Irradiation of the diazo-ketone (7; R^1 = CHN_2, R^2 = phthalimido) in aqueous dioxan also induces[131] the formation of the thiazolidine-azetidinone (183; R = phthalimido). Treatment of the penam (118; R^1 = H, R^2 = NH·CO·CH_2·OPh) with piperidinium benzoate[78] affords the thiazolidine (184).

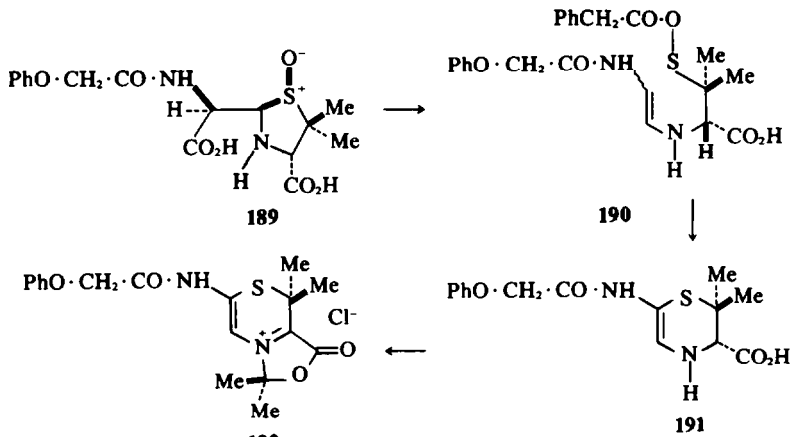
The dihydrothiazine (185; R^1 = OMe, R^2 = N_3) is pro-

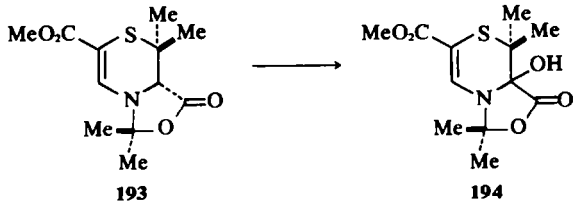












duced when the chloro-ester (**105**; $R^1 = H$, $R^2 = Cl$) is treated with sodium azide in NN-dimethylformamide.[132] It has been established in the corresponding reaction with methanolic sodium methoxide, which yields the dihydrothiazine (**185**; $R^1 = R^2 = OMe$), that the thiazolidinylacetate (**186**) is an intermediate. The ring expansion is probably initiated by a base-induced isomerization of the thiazolidinylacetate (**186**) to the thiol (**179**; $R^1 = OMe$, $R^2 = Cl$). The rearrangement is a general one for 6α-halopenicillanic acid derivatives and can be induced by several nucleophiles.[133,134]

The outcome of the reaction of the aminopenicillanate (**7**; $R^1 = OH$, $R^2 = NH_2$) with methanolic hydrochloric acid and sodium nitrite is critically dependent upon the water concentration.[135] In a 30% aqueous medium, 6α-chloropenicillanic acid is the predominant product, whereas, in the absence of water, a complex series of reactions ensue to give the dihydrothiazinone (**188**). Under non-aqueous conditions methanolysis of the starting material is faster than deamination, leading to the intermediate (**168**; $R^1 = OMe$, $R^2 = NH_2$). This species probably undergoes a deaminative ring enlargement to the dihydrothiazine (**185**; $R^1 = OH$, $R^2 = OMe$), which affords the product (**188**) by way of the hydroxy-acid (**187**).

The 1β-oxide (**23**; $R^1 = OH$, $R^2 = NH{\cdot}CO{\cdot}CH_2{\cdot}OPh$) undergoes a remarkable reorganization when treated with phenylacetyl chloride in acetone[136] to give the thiazinium chloride (**192**). Although the mechanism has not been elucidated, it seems likely that the reaction is initiated by a hydrolysis of the 4–7 bond to give the penicilloic acid (**189**). The dihydrothiazine (**191**), formed by way of the sulphenic anhydride (**190**), may also be a possible intermediate. Thus, work in the author's laboratory has established that the closely related dihydrothiazine (**185**; $R^1 = OH$, $R^2 = OMe$) is converted initially into the dihydrothiazine-oxazolidinone (**193**) in acetone containing toluene-*p*-sulphonic acid. Moreover, under the reaction conditions the derivative undergoes an oxidation[137] to the hydroxy-compound (**194**).

Self-condensation reactions of penicillanoyl derivatives are also documented.[138,139] For example, at pH 6–7 the potassium salt (**7**; $R^1 = OK$, $R^2 = NH_2$) affords the polymer (**195**; $n = 5$ or 6). A dimerization, yielding the bis(thiazolidinyl)-piperazine (**196**), results when the aminopenicillanate (**7**; $R^1 = O{\cdot}CH_2{\cdot}OMe$, $R^2 = NH_2$) is treated with acetic acid in dichloromethane.[140]

EPIMERIZATIONS

A penicillanoyl derivative contains acidic H atoms at positions 3 and 6. In the case of a penicillanoyl 1,1-dioxide, and possibly a penicillanoyl 1-oxide, the 5-H atom also possesses acidic character. Deprotonation-reprotonation processes may, therefore, result in a change of configuration at these sites.

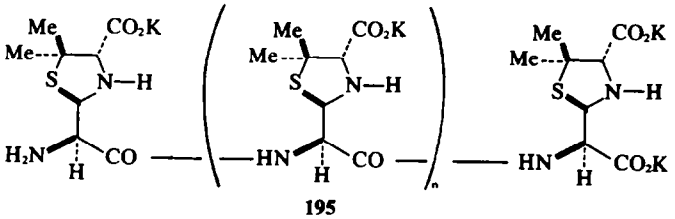
Although there is forceful evidence (pp. 10–13) that the 3-H atom can be removed under basic conditions, the derived anion undergoes β-elimination more rapidly than reprotonation. There is no indication that the 5-H atom of a penicillanoyl 1-oxide or 1,1-dioxide is sufficiently acidic to be removed. As already discussed (pp. 16–17) deprotonation-reprotonation may occur at position 6, resulting in an epimerization at this centre.

Epimerization at position 6

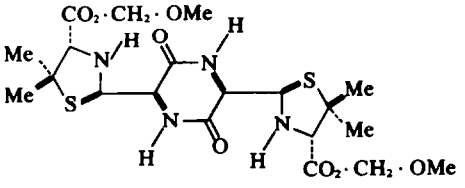
The first indication that a penicillanoyl derivative could undergo a change in configuration at position 6 was provided by Wolfe and Lee,[141] who isolated the 6α-phthalimidopenicillanate (**85**; $R^1 = OMe$, R^2 = phthalimido) from the reaction of the 6β-derivative (**7**; $R^1 = OMe$, R^2 = phthalimido) with sodium hydride in tetrahydrofuran, potassium t-butoxide in t-butyl alcohol or triethylamine in dichloromethane. It was subsequently shown,[96,99] with the tertiary amine as the base, that the epimerization was accompanied by the formation of the thiazepinone (**146**; $R^1 = CO_2Me$, R^2 = phthalimido)—both products were derived under kinetically controlled conditions. However, in the presence of a strong base, epimerization was the exclusive reaction.[104]

Thermodynamic aspects. In the epimerization of the methoxymethyl ester (**7**;$R^1 = O{\cdot}CH_2{\cdot}OMe$, R^2 = phthalimido), which was induced by 1,5-diazabicyclo[4.3.0]non-5-ene, it was established that the 6α-isomer (**85**; $R^1 = O{\cdot}CH_2{\cdot}OMe$, R^2 = phthalimido) comprised greater than 99% of the equilibrium mixture.[104] It is now clear that when a bulky group, such as phthalimido,[55,104,141] 2,2-dimethyl-5-oxo-3-phenylimidazolidin-1-yl,[142,143] or trialkylammonium,[143,144] is present at the 6-position, there is an overwhelming preference for the 6α-isomer. The higher free energy of the 6β-isomer is ascribed to a compressional interaction between the 6-substituent and the 2β-Me group.

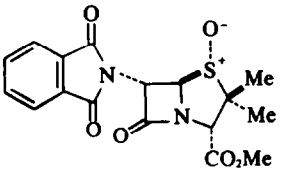
A reduction in the steric requirement of the 6-substituent is expected to increase the equilibrium



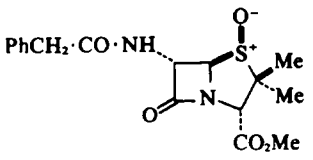
195



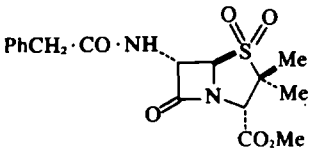
196



197



198



199

concentration of the 6β-isomer. This expectation has been realized in the case of aldiminopenicillanates (e.g. 7; $R^1 = O{\cdot}CH_2{\cdot}OMe$, $R^2 = N{:}CH{\cdot}C_6H_4{\cdot}NO_2\text{-}p$),[104,145] imino-ethers [e.g. 7; $R^1 = O{\cdot}CH_2Ph$, $R^2 = N{:}C(O{\cdot}SiMe_3)CH_2{\cdot}OPh$],[106,107] imino-chlorides [e.g. 7; $R^1 = O{\cdot}CH_2{\cdot}O{\cdot}COBu^t$, $R^2 = N{:}C(Cl)CH_2Ph$],[146] imino-alkoxides [e.g. 7; $R^1 = OMe$, $R^2 = N{:}C(OLi)CH_2{\cdot}OPh$][147] and isocyanopenicillanates (e.g. 7; $R^1 = OMe$, $R^2 = N^+{:}C^-$)[57]—as much as 47% of the 6β-isomer can be present at equilibrium.

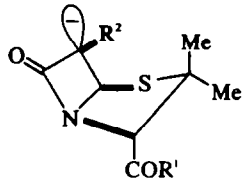
A similar trend is observed with penicillanoyl 1-oxides and 1,1-dioxides. Thus, in the presence of triethylamine the 6β-derivative (23; $R^1 = OMe$, R^2 = phthalimido) is converted[148] into the 6α-isomer (197; $R^1 = OMe$, R^2 = phthalimido). 6β-Acetamido-derivatives (e.g. 23; $R^1 = OMe$, $R^2 = NH{\cdot}CO{\cdot}CH_2Ph$) equilibrate with the 6α-isomers (e.g. 198) in the presence of diethylamine[80] or NO-bis(trimethylsilyl)acetamide and 1,5-diazabicyclo-[4.3.0]non-5-ene.[15,35,149] Equilibration of penicillanoyl 1,1-dioxides can be effected with 1,5-diazabicyclo[4.3.0]non-5-ene;[150] the 6α-acetamido-derivative (e.g. 199) comprises *ca.* 60% of the equilibrium mixture.

Kinetic aspects. Wolfe and Lee[141] noted that the conversion of the 6β-phthalimido-derivative (7; $R^1 = OMe$, R^2 = phthalimido) into the 6α-isomer (85; $R^1 = OMe$, R^2 = phthalimido) with potassium t-butoxide in 2-methylpropan-2-[$^2H_1$]ol was accompanied by deuterium exchange at position 6, although when the reaction was interrupted the recovered starting material contained no isotope. Under similar conditions it was claimed that the 6α-isomer incorporated no deuterium.

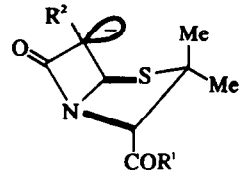
Clayton *et al.*[143] investigated the epimerization of the penicillanate (7; $R^1 = OH$, R^2 = 2,2-dimethyl-5-oxo-3-phenylimidazolidin-1-yl) in alkaline deuterium oxide. The formation of the 6α-isomer (85; $R^1 = OH$, R^2 = 2,2-dimethyl-5-oxo-3-phenylimidazolidin-1-yl), which was essentially complete, was accompanied by isotope incorporation at position 6. However, the 6α-isomer was observed to exchange deuterium at a rate which was not markedly slower than the original epimerization; a kinetic preference for *endo*-protonation was again observed.

With 1,5-diazabicyclo[4.3.0]non-5-ene in pyridine containing deuterium oxide, the 6α-derivative (150; $R^1 = H$, R^2 = phthalimido) underwent deuterium exchange at position 6 approximately 14-times slower than the 6β-isomer (150; R^1 = phthalimido, $R^2 = H$) epimerized.[101]

The foregoing results indicate that the large energy difference which separates the 6α- and 6β-isomers also separates the respective transition states involving the proton transfers. The ground-state energy difference is attributable to a steric interaction in the 6β-isomer involving the bulky 6-substituent and the 2β-Me group. A similar effect is probably responsible for the transition-state energy difference, suggesting that the carbanions (200; $R^1 = OMe$, R^2 = phthalimido) and (201; $R^1 = OMe$, R^2 = phthalimido) are approximate models for these transition states.[101,105]



200



201

Firestone *et al.*[151] have shown that the imines (7, $R^1 = O{\cdot}CH_2Ph$, $R^2 = N{:}CH{\cdot}C_6H_4{\cdot}NO_2\text{-}p$) and (85; $R^1 = O{\cdot}CH_2Ph$, $R^2 = N{:}CH{\cdot}C_6H_4{\cdot}NO_2\text{-}p$), when treated with phenyl-lithium in tetrahydrofuran at −78°, are converted into the carbanions (200; $R^1 = O{\cdot}CH_2Ph$, $R^2 = N{:}CH{\cdot}C_6H_4{\cdot}NO_2\text{-}p$) and (201; $R^1 = O{\cdot}CH_2Ph$, $R^2 = N{:}CH{\cdot}C_6H_4{\cdot}NO_2\text{-}p$). These species are configurationally stable since they afford the parent imine when quenched with acetic acid. However, if NN-dimethylformamide is added, prior to the quenching, a 2:1 mixture of the 6β-derivative (7; $R^1 = O{\cdot}CH_2Ph$, $R^2 = N{:}CH{\cdot}C_6H_4{\cdot}NO_2\text{-}p$), and the 6α-isomer (85; $R^1 = O{\cdot}CH_2Ph$, $R^2 = N{:}CH{\cdot}C_6H_4{\cdot}NO_2\text{-}p$) is obtained—at equilibrium the 6α-epimer predominates. An identical mixture is produced starting with either the 6β-derivative or the 6α-isomer. Evidently, NN-dimethylformamide causes the equilibration of the carbanions, which show a kinetic preference for *exo*-protonation. This procedure enables 6α-aldiminopenicillanates to be converted into the thermodynamically less stable 6β-isomers—a result of considerable practical significance in the synthesis of cephalosporins and their analogues.[152–155]

Although beyond the scope of this review, the carbanions derived from aldiminopenicillanates have been trapped with a wide range of electrophilic C sources,[144,156–162] with electrophilic halogen[163] and with S electrophiles.[164–165] There is a strong preference for the electrophile to enter the 6α-site.

In the presence of weak bases, 6β-phthalimidopenicillanates (e.g. 7; $R^1 = OMe$, R^2 = phthalimido) are converted[98,99,101,102] into mixtures of the 6α-isomers (e.g. 85; $R^1 = OMe$, R^2 = phthalimido) and the thiazepinones (e.g. 146; $R^1 = CO_2Me$, R^2 = phthalimido), probably by a common rate-determining process. The azetinones (e.g. 147; $R^1 = CO_2Me$, R^2 = phthalimido) are

implicated (pp. 16–17) as intermediates in the formation of the thiazepinones, and it has been suggested that these species represent the common intermediates.[99] Although they fulfil the requirement of possessing trigonal geometry at position 6 (p. 17), there are objections to invoking them as the precursors of the 6α-epimers. Thus, the configuration at position 5 of the epimer has been shown to be identical with that of its precursor.[145] Consequently, if the azetinone intervenes, its chiral centre must direct the protonation to exclusively regenerate the original configuration at position 5. A study of the reaction of the homopenicillanate (**150**: R^1 = phthalimido, R^2 = H) with tertiary amines has shown that the formation of the thiazepinone (**146**; $R^1 = CH_2{\cdot}CO_2Me$, R^2 = phthalimido) increases, at the expense of the epimer (**150**; R^1 = H, R^2 = phthalimido), as the strength of the base decreases.[101] It has been suggested that these results are consistent with the rate-determining formation of an enol-like intermediate, which undergoes competitive protonation to give the 6α-epimer and β-elimination to give the azetinone.[101,105]

CONCLUSION

The chemistry of penicillanic acids is unrivalled as a source of diverse molecular rearrangements. This behaviour can be attributed, in large measure, to the presence of the fused thiazolidine–azetidinone ring system. The majority of the bonds of this bicyclic backbone are potentially activated for cleavage and, in many cases, the activation energies for different bond ruptures are similar. In consequence, small changes in structure or in experimental conditions can dramatically influence the outcome of a reaction. After more than three decades of experience, chemists are beginning to understand the poise of these delicate molecules, which have been described[166] as "diabolic concatenations of reactive groupings". The ingenuity which is being displayed in effecting their structural modification in a prescribed manner is a tribute to contemporary organic chemistry.

REFERENCES

[1]*Cephalosporins and Penicillins: Chemistry and Biology* (Edited by E. H. Flynn). Academic Press, New York (1972).
[2]R. J. Stoodley, *Progr. Org. Chem.* **8**, 102 (1973).
[3]J. H. C. Nayler, *Adv. Drug. Res.* **7**, 1 (1973).
[4]D. N. McGregor, *Fortschr. Chem. org. Naturstoffe* **XXXI**, 1 (1974).
[5]W. A. Spitzer, T. Goodson Jr., M. A. Chaney and N. D. Jones, *Tetrahedron Letters* 4311 (1974).
[6]M. Yoshimoto, S. Ishihara, E. Nakayama, E. Shoji, H. Kuwano and N. Soma, *Ibid.* 4387 (1972).
[7]M. Numata, Y. Imashiro, I. Minamida and M. Yamaoka, *Ibid.* 5097 (1927).
[8]D. H. R. Barton, F. Comer and P. G. Sammes, *J. Am. Chem. Soc.* **91**, 1529 (1969).
[9]R. A. Archer and P. V. DeMarco, *Ibid.* **91**, 1530 (1969).
[10]D. O. Spry, *Ibid.* **92**, 5006 (1970).
[11]R. D. G. Cooper, *Ibid.* **92**, 5010 (1970).
[12]D. H. R. Barton, F. Comer, D. G. T. Greig, G. Lucente, P. G. Sammes and W. G. E. Underwood, *Chem. Comm.* 1059 (1970).
[13]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, *Ibid.* 1683 (1970).
[14]D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt and W. G. E. Underwood, *J. Chem. Soc.* (C), 3540 (1971).
[15]A. J. Vlietinck, E. Roets, H. Vanderhaeghe and S. Toppet, *J. Org. Chem.* **39**, 441 (1974).
[16]D. O. Spry, unpublished results (1970) quoted in Ref. 1, p. 214.
[17]R. D. G. Cooper, P. V. DeMarco, J. C. Cheng and N. D. Jones, *J. Am. Chem. Soc.* **91**, 1408 (1969).
[18]T. S. Chou, J. R. Burgtorf, A. L. Ellis, S. R. Lammert and S. P. Kukolja, *Ibid.* **96**, 1609 (1974).
[19]C. A. Kingsbury and D. J. Cram, *Ibid.* **82**, 1810 (1960).
[20]R. D. Allan, D. H. R. Barton, M. Girijavallabhan and P. G. Sammes, *J.C.S. Perkin I* 1456 (1974).
[21]I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, G. H. Hewitt, B. E. Looker, A. Mowatt, C. A. Robson and W. G. Underwood, *Ibid.* 1187 (1973).
[22]D. H. R. Barton, I. H. Coates, P. G. Sammes and C. M. Cooper, *Ibid.* 1459 (1974).
[23]S. Terao, T. Matsuo, S. Tsushima, N. Matsumoto, T. Miyawaki and M. Miyamoto, *J.C.S. Chem. Comm.* 1304 (1972).
[24]R. D. G. Cooper and F. L. José, unpublished results (1970) quoted in Ref. 1, pp. 240–241.
[25]R. D. G. Cooper and F. J. José, unpublished results (1970) quoted in Ref. 1 pp. 239–240.
[26]T. S. Chou, *Tetrahedron Letters* 725 (1974).
[27]G. A. Koppel and S. Kukolja, *J. C. S. Chem. Comm.* 57 (1975).
[28]S. Kukolja and S. R. Lammert, *Angew. Chem. Internat. Edn.* **12**, 67 (1973).
[29]R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon and S. L. Andrews, *J. Am. Chem. Soc.* **85**, 1896 (1963); *Ibid.* **91**, 1401 (1969).
[30]R. D. G. Cooper, L. D. Hatfield and D. O. Spry, unpublished results (1970) quoted in Ref. 1, p. 216.
[31]D. O. Spry, *J.C.S. Chem. Comm.* 259 (1973).
[32]J. P. Clayton, J. H. C. Nayler, M. J. Pearson and R. Southgate, *J.C.S. Perkin I* **22** (1974).
[33]L. D. Hatfield, J. W. Fisher, F. L. José, W. L. Garbrecht and R. D. G. Cooper, unpublished results quoted in Ref. 42, p. 37.
[34]T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi and T. Oku, *Tetrahedron Letters* 3001 (1973).
[35]G. E. Gutowski, *Ibid.* 1779 (1970).
[36]G. E. Gutowski, B. J. Foster, C. J. Daniels and J. W. Fisher, *Ibid.* 3433 (1971).
[37]W. J. Gottstein, P. F. Misco and L. C. Cheney, *J. Org. Chem.* **37**, 2765 (1972).
[38]D. H. R. Barton, M. Girijavallabhan and P. G. Sammes, *J. C. S. Perkin I* 929 (1972).
[39]J. E. Baldwin, F. J. Urban, R. D. G. Cooper and F. L. José, *J. Am. Chem. Soc.* **95**, 2401 (1973).
[40]R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen and G. W. Huffman, *J. Org. Chem.* **36**, 1259 (1971).
[41]S. Kukolja and S. R. Lammert, *J. Am. Chem. Soc.* **94**, 7169 (1972).
[42]R. D. G. Cooper, L. D. Hatfield and D. O. Spry, *Accounts Chem. Res.* **6**, 32 (1973).
[43]F. Johnson, *Chem. Rev.* **68**, 375 (1968).
[44]I. Ager, D. H. R. Barton, G. Lucente and P. G. Sammes, *J. C. S. Chem. Comm.* 601 (1972).
[45]D. H. R. Barton, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, B. E. Looker and W. G. E. Underwood, *Chem. Comm.* 1137 (1971).
[46]R. D. Allan, D. H. R. Barton, M. Girijavallabhan, P. G. Sammes and M. V. Taylor, *J. C. S. Perkin I* 1182 (1973).
[47]R. D. G. Cooper and F. L. José, *J. Am. Chem. Soc.* **92**, 2575 (1970).
[48]R. D. G. Cooper and F. L. José, *Ibid.* **94**, 1021 (1972).
[49]R. D. G. Cooper and F. L. José, unpublished results (1970) quoted in Ref. 1, p. 201.
[50]L. D. Hatfield, J. Fisher, F. L. José and R. D. G. Cooper, *Tetrahedron Letters* 4897 (1970).
[51]R. B. Morin, T. McGrath and R. Shuman, unpublished results (1970) quoted in Ref. 1, p. 190 and pp. 222–223.
[52]T. J. Wallace, J. E. Hofmann and A. Schriesheim, *J. Am. Chem. Soc.* **85**, 2739 (1963).
[53]S. Wolfe, J. C. Godfrey, C. T. Holdrege and Y. G. Perron, *Ibid.* **85**, 643 (1963); *Can. J. Chem.* **46**, 2549 (1968).
[54]S. Wolfe, *Ibid.* **45**, 459 (1967).
[55]B. G. Ramsay and R. J. Stoodley, *Chem. Comm.* 1517 (1970); *J. Chem. Soc.* (C) 3859 (1971).

[56]B. G. Ramsay and R. J. Stoodley, *Ibid.* 3864 (1971).
[57]P. H. Bentley and J. P. Clayton, *J. C. S. Chem. Comm.* 278 (1974).
[58]J. P. Clayton, *J. Chem. Soc.* (C), 2123 (1969).
[59]J. P. Clayton, J. H. C. Nayler, R. Southgate and P. Tolliday, *Chem. Comm.* 590 (1970).
[60]E. G. Brain, I. McMillan, J. H. C. Nayler, R. Southgate and P. Tolliday, *J. C. S. Perkin I* 562 (1975).
[61]J. H. C. Nayler, M. J. Pearson and R. Southgate, *J. C. S. Chem. Comm.* 57 (1973).
[62]R. Southgate, unpublished results (1970) personal communication.
[63]S. Kukolja, R. D. G. Cooper and R. B. Morin, *Tetrahedron Letters* 3381 (1969).
[64]H. Bundgaard and H. R. Angelo, *Ibid.* 3001 (1974).
[65]C. J. Veal and D. W. Young, *J. C. S. Chem. Comm.* 266 (1974).
[66]S. Wolfe, C. Ferrari and W. S. Lee, *Tetrahedron Letters* 3385 (1969).
[67]N. S. Watson and R. J. Stoodley, unpublished results (1973).
[68]M. D. Bachi and O. Goldberg, *J. C. S. Perkin I* 1184 (1974).
[69]T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguti and T. Oku, *Ger. Offen.* 2,358,178 (1974); *Chem. Abst.* 49674 (1974).
[70]S. Wolfe, R. N. Bassett, S. M. Caldwell and F. I. Wasson, *J. Am. Chem. Soc.* 91, 7205 (1969).
[71]R. Thomas, *J. C. S. Chem. Comm.* 478 (1972).
[72]J. E. Baldwin and J. Kitchin, unpublished results (1974) personal communication.
[73]T. S. Chou, personal communication (1975).
[74]R. Lattrell, *Liebigs Ann. Chem.* 1361 (1974).
[75]C. A. Grob, *Angew. Chem. Internat. Edn.* 8, 535 (1969).
[76]M. R. Bell and R. Oesterlin, *Tetrahedron Letters* 4975 (1968).
[77]M. R. Bell, S. D. Clemans and R. Oesterlin, *J. Med. Chem.* 13, 389 (1970).
[78]K. Heusler, *Helv. Chim. Acta* 55, 388 (1972).
[79]J. C. Sheehan and K. G. Brandt, *J. Am. Chem. Soc.* 87, 5468 (1965).
[80]D. H. R. Barton, I. H. Coates and P. G. Sammes, *J. C. S. Perkin I* 599 (1973).
[81]K. Ninomiya, T. Shioiri and S. Yamada, *Tetrahedron* 30, 2151 (1974).
[82]J. C. Sheehan and C. A. Panetta, *J. Org. Chem.* 38, 940 (1973).
[83]J. C. Sheehan, H. C. Dalzell, J. M. Greenwood and D. R. Ponzi, *Ibid.* 39, 277 (1974).
[84]R. J. Stoodley and N. R. Whitehouse, unpublished results (1971).
[85]J. C. Sheehan and J. U. Piper, *J. Org. Chem.* 38, 3492 (1973).
[86]B. Fechtig, H. Bickel and K. Heusler, *Helv. Chim. Acta* 55, 417 (1972).
[87]S. Kukolja, *J. Am. Chem. Soc.* 93, 6267 (1971).
[88]S. Kukolja and S. R. Lammert, *Croat. Chim. Acta* 44, 299 (1972).
[89]S. Kukolja and S. R. Lammert, *Ibid.* 44, 423 (1972).
[90]M. M. Campbell, G. Johnson, A. F. Cameron and I. R. Cameron, *J. C. S. Chem. Comm.* 868 (1974); *J. C. S. Perkin I* 1208 (1975).
[91]J. C. Sheehan, *Molecular Modification in Drug Design Adv. Chem. Series No. 45*, p. 15. American Chemical Society, Washington (1964).
[92]E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson and R. Southgate, *J. C. S. Chem. Comm.* 229 (1972).
[93]S. Wolfe, W. S. Lee, G. Kannengiesser and J.-B. Ducep, *Can. J. Chem.* 50, 2894 (1972).
[94]S. Wolfe, S.-L. Lee, J.-B. Ducep, G. Kannengiesser and W. S. Lee, *Ibid.* 53, 497 (1975).
[95]R. J. Stoodley and N. R. Whitehouse, *J. C. S. Chem. Comm.* 477 (1973); *J. C. S. Perkin I* 181 (1974).
[96]R. J. Stoodley and N. R. Whitehouse, *Ibid.* 32 (1973).
[97]R. J. Stoodley and N. S. Watson, *Ibid.* 883 (1975).
[98]O. K. J. Kovacs, B. Ekström and B. Sjöberg, *Tetrahedron Letters* 1863 (1969); *Acta Chem. Scand.* 27, 677 (1973).
[99]S. Wolfe, W. S. Lee and R. Misra, *Chem. Comm.* 1067 (1970).
[100]J. R. Jackson and R. J. Stoodley, unpublished results (1971).
[101]B. G. Ramsay and R. J. Stoodley, *Chem. Comm.* 450 (1971).
[102]J. R. Jackson and R. J. Stoodley, *Ibid.* 14 (1970); *J. C. S. Perkin I* 1063 (1972).
[103]B. G. Ramsay and R. J. Stoodley, unpublished results (1970).
[104]J. R. Jackson and R. J. Stoodley, *Chem. Comm.* 647 (1971).
[105]Ref. 2, pp. 120–122.
[106]A. Vlietinck, E. Roets, P. Claes and H. Vanderhaeghe, *Tetrahedron Letters* 285 (1972).
[107]A. Vlietinck, E. Roets, P. Claes, G. Janssen and H. Vanderhaeghe, *J. C. S. Perkin I* 937 (1973).
[108]J. P. Clayton, R. Southgate, B. G. Ramsay and R. J. Stoodley, *J. Chem. Soc.* (C) 2089 (1970).
[109]J. C. Sheehan and Y. S. Lo, *J. Org. Chem.* 38, 3227 (1973).
[110]D. Law and R. J. Stoodley, unpublished results (1972).
[111]*The Chemistry of Penicillin* (Edited by H. T. Clarke, J. R. Johnson and R. Robinson). Princeton University Press, New Jersey (1949).
[112]M. A. Schwartz, *J. Pharm. Sci.* 54, 472 (1965).
[113]H. Bundgaard, *Ibid.* 60, 1273 (1971).
[114]T. Yamana, A. Tsuji and Y. Mizukami, *Chem. Pharm. Bull. Japan* 22, 1186 (1974).
[115]Ref. 111, Chap. XXIV.
[116]D. A. Johnson and C. A. Panetta, *J. Org. Chem.* 29, 1826 (1964).
[117]B. B. Levine, *Arch. Biochem. Biophys.* 93, 50 (1961).
[118]J. L. Longridge and D. Timms, *J. Chem. Soc.* (B), 852 (1971).
[119]F. P. Doyle, J. H. C. Nayler, H. Smith and E. R. Stove, *Nature* 191, 1091 (1961).
[120]A. Ballio, E. B. Chain, F. D. Di Accadia, M. Mauri, K. Rauer, M. J. Schlesinger and S. Schlesinger, *Ibid.* 191, 909 (1961).
[121]F. R. Batchelor, D. Gazzard and J. H. C. Nayler, *Ibid.* 191, 910 (1961).
[122]D. A. Johnson and G. A. Hardcastle Jr., *J. Am. Chem. Soc.* 83, 3534 (1961).
[123]R. J. Stoodley, unpublished results (1975).
[124]Ref. 111, pp. 158–161.
[125]A. B. A. Jansen and R. Robinson, *Monatsch. Chem.* 98, 1017 (1967).
[126]M. R. Bell, J. A. Carlson and R. Oesterlin, *J. Am. Chem. Soc.* 92, 2177 (1970); *J. Org. Chem.* 37, 2733 (1972).
[127]S. Kukolja, *J. Am. Chem. Soc.* 94, 7590 (1972).
[128]Ref. 111, p. 229.
[129]M. J. Pearson and R. Southgate, unpublished results (1970) quoted in Ref. 3, pp. 74–45.
[130]E. E. Roets, A. J. Vlietinck, G. A. Janssen and H. Vanderhaeghe, *J. C. S. Chem. Comm.* 483 (1973).
[131]B. G. Ramsay and R. J. Stoodley, *J. Chem. Soc.* (C), 1319 (1969).
[132]I. McMillan and R. J. Stoodley, *Tetrahedron Letters* 1205 (1966); *J. Chem. Soc.* (C), 2534 (1968).
[133]J. Kitchin and R. J. Stoodley, *J. Am. Chem. Soc.* 95, 3439 (1973); *J. C. S. Perkin I* 2460 (1973).
[134]N. Maggi and G. Cignarella, *Chem. Ind. (Milan)* 52, 164 (1970).
[135]R. J. Stoodley, *Tetrahedron Letters* 941 (1967); *J. Chem. Soc.* (C), 2891 (1968).
[136]R. Thomas and D. J. Williams, *J. C. S. Chem. Comm.* 226 (1973).
[137]R. J. Stoodley, unpublished results (1966).
[138]N. H. Grant, D. E. Clark and H. E. Album, *J. Am. Chem. Soc.* 84, 876 (1962).
[139]H. Smith and A. C. Marshall, *Nature* 232, 45 (1971).
[140]R. J. Stoodley, unpublished results (1964).
[141]S. Wolfe and W. S. Lee, *Chem. Comm.* 242 (1968).
[142]D. A. Johnson, D. Mania, C. A. Panetta and H. H. Silvestri, *Tetrahedron Letters* 1903 (1968).
[143]J. P. Clayton, J. H. C. Nayler, R. Southgate and E. R. Stove, *Chem. Comm.* 129 (1969).
[144]C. V. Kaiser, C. W. Ashbrook and J. E. Baldwin, *J. Am. Chem. Soc.* 93, 2342 (1971).
[145]J. R. Jackson and R. J. Stoodley, *J. C. S. Perkin I* 895 (1972).
[146]R. D. Carroll, E. S. Hamanaka, D. K. Pirie and W. M. Welch, *Tetrahedron Letters* 1515 (1974).
[147]G. A. Koppel, *Ibid.* 4233 (1973).
[148]R. D. G. Cooper, P. V. DeMarco and D. O. Spry, *J. Am. Chem. Soc.* 91, 1528 (1969).
[149]P. Claes, A. Vlietinck, E. Roets, H. Vanderhaeghe and S. Toppet, *J. C. S. Perkin I* 932 (1973).
[150]D. F. Corbett and R. J. Stoodley, unpublished results (1971).
[151]R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe and B. G. Christensen, *J. Org. Chem.* 39, 437 (1974).

[152]N. G. Steinberg, R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Letters* 3567 (1974).
[153]R. A. Firestone, N. S. Maciejewicz and B. G. Christensen, *J. Org. Chem.* **39**, 3384 (1974).
[154]L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.* **96**, 5782 (1974).
[155]R. N. Guthikonda, L. D. Cama and B. G. Christensen, *Ibid.* **96**, 7584 (1974).
[156]R. Reiner and P. Zeller, *Helv. Chim. Acta* **51**, 1905 (1968).
[157]E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini and J. Z. Gougoutas, *J. Am. Chem. Soc.* **93**, 4324 (1971).
[158]E. H. W. Böhme, H. E. Applegate, J. B. Ewing, P. T. Funke, M. S. Puar and J. E. Dolfini, *J. Org. Chem.* **38**, 230 (1973).
[159]R. A. Firestone, N. Schelechow, D. B. R. Johnson and B. G. Christensen, *Tetrahedron Letters* 375 (1972).
[160]D. B. R. Johnson, S. M. Schmitt, R. A. Firestone and B. G. Christensen, *Ibid.* 4417 (1972).
[161]R. A. Firestone, N. Schelechow and B. G. Christensen, *J. C. S. Chem. Comm.* 1106 (1972).
[162]G. H. Rasmusson, G. F. Reynolds and G. E. Arth, *Tetrahedron Letters* 145 (1973).
[163]L. D. Cama and B. G. Christensen, *Ibid.* 3505 (1973).
[164]W. A. Slusarchyk, H. E. Applegate, P. Funke, W. Koster, M. S. Puar, M. Young and J. E. Dolfini, *J. Org. Chem.* **38**, 943 (1973).
[165]T. Jen, J. Frazee and J. R. Hoover, *Ibid.* **38**, 2857 (1973).
[166]R. B. Woodward, *Perspectives in Organic Chemistry* (Edited by A. R. Todd), p. 160. Interscience, New York (1956).