(10c) was at the lower end of the 2–10% range observed by GLC, suggesting that some of it was a thermal product. (b) We are indebted to Mr. R. Zerfing for this experiment.

(17) Boiling points and melting points are uncorrected. Elemental analyses were performed under the direction of J. P. Gilbert of these laboratories. ^{1}H NMR spectra were obtained with Jeol (USA) C-60 HL and Hitachi Perkin-Elmer R-24 spectrometers. ^{13}C NMR spectra were obtained with a Varian CFT-20 spectrometer. All chemical shifts are referred to tetramethylsilane. Mass spectra were obtained courtesy of Messrs. J. Smith and H. Flynn, and Patricia Cala, using LKB 9000, Varian MAT-371, and Finnegan 3200 spectrometers. For brevity, only parts of some spectra are reported. GLC analyses were performed on a Hewlett Packard 5830A gas chromatograph using thermal conductivity detection. Three columns, 6 ft × 1/8 in. stainless steel, packed with 10% SP 2401, 10% SP 2340, and 10% OV-225, all on 80–100 mesh Supelcoport, were used with He as a carrier gas. The appropriate hydrocarbon was used as an internal standard in all chromatographies used for yield calculations. The "usual workup" involved washing organic solvent solutions with water, drying over magnesium sulfate, and evaporating to dryness in vacuo.

(18) H. Breederveld, *Recl. Trav. Chim. Pays-Bas*, **79**, 1197–1202 (1960).

Preparation of 6β-Imidopenicillinate 1(*S*)-Oxides

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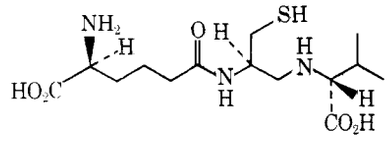
Examples of the as yet unknown 6β-imidopenicillinate 1(*S*)-oxides were prepared and the stereochemistry was proven unambiguously by x-ray diffraction. These substances were thermodynamically stable with respect to the corresponding 1(*R*)-oxides as shown by equilibration via thermal ring opening. The possible significance of these results with respect to the biogenetic relationships of penicillins and cephalosporins is discussed.

The biogenesis of the β-lactam antibiotics, penicillins and cephalosporins,[1] is now generally recognized to derive from Arnstein's tripeptide, L-α-aminoadipyl-L-cysteinyl-D-valine (**1**), since the bioconversion of this substance to penicillins has been reported.[2] The isolation of this substance from *Cephalosporium* sp. has also been reported.[3] The sequence of reactions involved in the conversion of **1** into penicillin N (**2**) and cephalosporin C (**3**) is still unknown; however, two suggestions have been made. Thus, in one case,[4] a priori formation of monocyclic species (**4**) is followed in a branched pathway by the formation of **2** and **3**.[5] An earlier alternative, suggested by Abraham,[6] is the bioconversion of **2** to **3**, but, until recently,[7] this scheme has had little support. The latter is attractive, since the in vitro ring expansion of penicillin sulfoxides to deacetoxycephalosporins is the basis of a commercial production of these compounds.[8] Thus, for example, refluxing methyl 6β-phenoxyacetamidopenicillinate 1(*S*)-oxide (**5**) in xylene with a trace of acid gives the deacetoxycephalosporin (**7**) by way of the sulfenic acid (**6**).[9]



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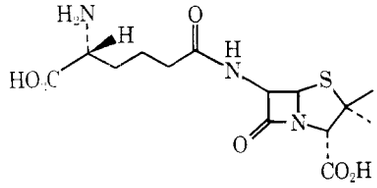

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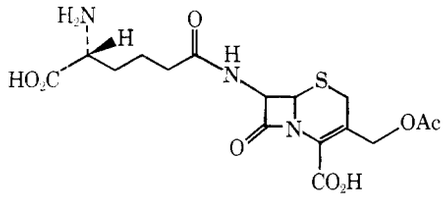

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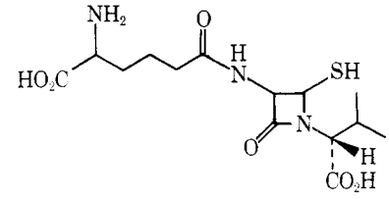

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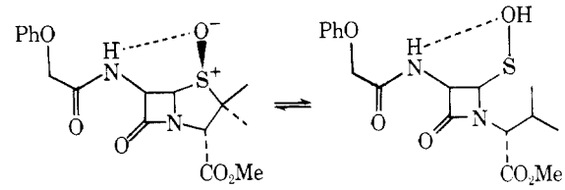
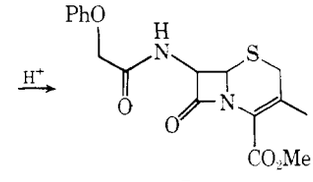


5 **6**



7

An immediate objection that could be raised to this hypothesis is that the relatively high temperatures (in the region of 100 °C) required to initiate the thermal ring opening (syn elimination) of **5** to **6** would hardly be available in vivo. An

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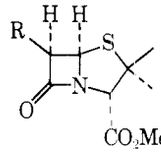
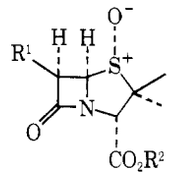
answer to this problem must be sought in the various factors which control the thermal stability of penicillin sulfoxides. Oxidation of methyl 6β-phenoxyacetamidopenicillinate (**8**) gives only the (*S*)-sulfoxide **5**, whereas the similar oxidation of methyl 6β-phthalimidopenicillinate (**9**) yields only the

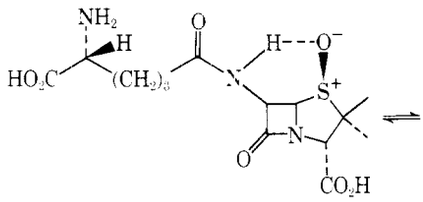




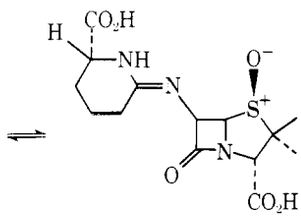
8, R = $NHCOCH_2OPh$ **10**
9, R = Phthalimido

(*R*)-sulfoxide **10** (R^1 = phthalimido, R^2 = methyl).[10] Presumably, the NH group of **8** directs the reagent to the β face, yielding the (*S*)-sulfoxide, whereas in **9**, with no such group, the sterically more accessible α face provides the epimeric (*R*)-oxide.[11] Thus, the more readily accessible (*S*)-sulfoxides, at least with 6β-amido substituents, cf. **2** and **3**, are the more sterically hindered; however, the demonstrated presence of the hydrogen bond between the sulfoxide and the amide side chain has been suggested[12] as stabilizing these species (**5**) toward the syn elimination to **6**.[13]

Consequently, we argued that if penicillin *N*-(*S*)-sulfoxide **11** were a biointermediate for deacetoxycephalosporin C (**13**),



11



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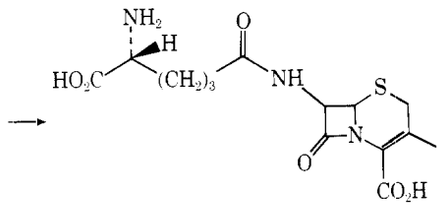
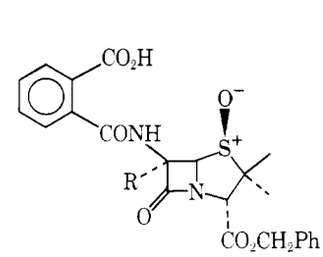
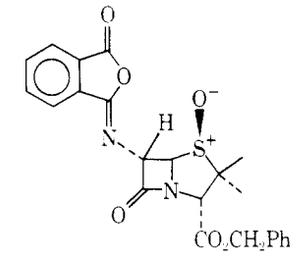


13

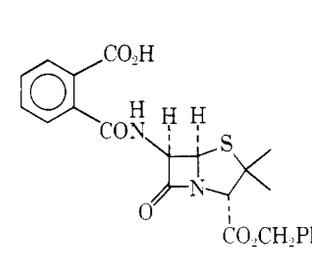
a suggestion which is in stereochemical accord with the derivation of both penicillins and cephalosporins from chiral methyl-labeled valine,[14] then some means must exist for "switching off" this stabilizing H bond. Such a mechanism could involve the α-aminoadipyl side chain, via cyclic amidine formation, as **12**,[15] in which the steric overcrowding of the sulfoxide might accelerate the ring-opening elimination sufficiently to allow its occurrence under physiological conditions. To test this hypothesis, it was necessary to prepare a penicillin (*S*)-oxide with a 6β side chain containing no NH group and to study the facility of ring opening. To date there is no report of such compounds.

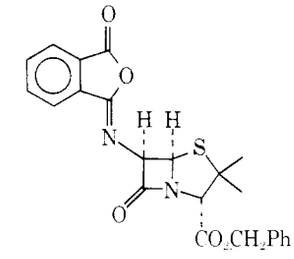
Condensation of benzyl 6β-aminopenicillinate 1(*S*)-oxide with phthalic anhydride cleanly afforded the phthalamic acid **14a** (R = H) which with DCC gave the 6α-isoimidopenicillin 1(*S*)-oxide (**15**) instead of the expected 6β-isoimide **16a** (R = H). Interestingly, a similar sequence conducted on the parent benzyl 6β-aminopenicillinate gave the 6β-isoimido product **18** via the phthalamic acid **17**. Clearly, the epimerization of





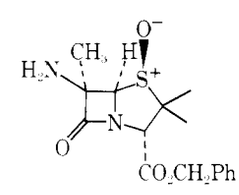
14a, R = H **15**
b, R = Me

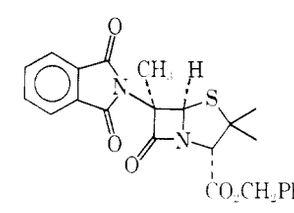




17 **18**

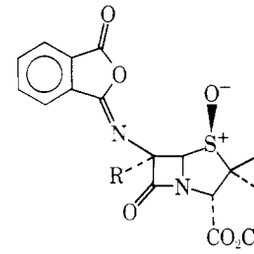
C-6 during dehydration of the phthalamic acid **14a** (R = H) is consequent on the presence of the 1(*S*)-oxide function in **14a** (R = H), although it is not clear whether this effect is steric or the result of an inductive acidification of the 6α-hydrogen.

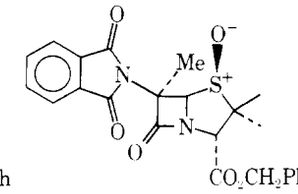




19 **22**

In order to avoid this unwanted epimerization, we replaced the 6α-hydrogen by a methyl group. Thus, the known benzyl 6β-amino-6α-methylpenicillinate[16] was oxidized to the (*S*)-sulfoxide **19** and converted sequentially to the phthalamic acid **14b** (R = Me) and the 6β-isoimide **16b** (R = Me). Unfortunately, the spectral properties of **16b** (R = Me) did not allow





16a, R = H **20**
b, R = Me

unambiguous assignment of sulfoxide stereochemistry, which was critical since if the proposed hypothesis of instability of such 6β-imido 1(*S*)-oxides were correct then thermal ring opening at the ambient temperature of the dehydration could possibly have inverted this sulfoxide stereochemistry. If this were true, it would require a sulfenic acid intermediate, cf. **6**, which should be detectable by its known chemistry. Consequently, the phthalamic acid **14b** (R = Me) was treated with DCC in the presence of excess norbornadiene, a reagent known to intercept sulfenic acids.[17] However, no adduct was found

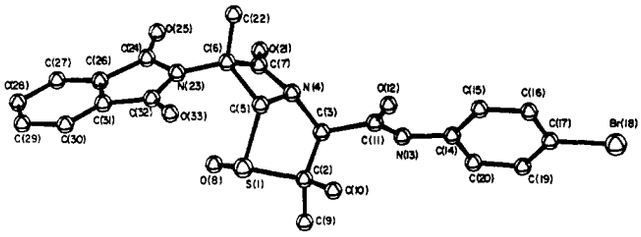
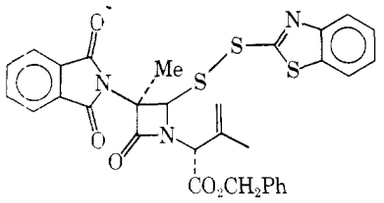


Figure 1. A computer-generated drawing of **23.**

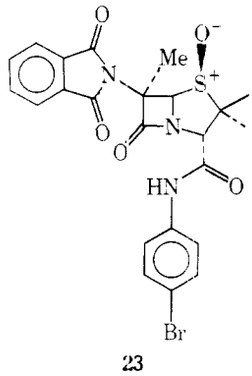
and, interestingly, the presence of diene effected a change in the mode of ring closure to the imide **20.** The origin of this effect is unknown. That the sulfoxide **20** is the thermodynamically more stable was shown by its reisolation, unchanged, after prolonged refluxing in toluene. Treatment of **20** with 2-mercaptobenzthiazole in refluxing benzene gave, via trapping of the sulfenic acid, the β-lactam **21.** Reduction



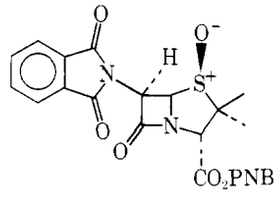
21

of **20** with phosphorus tribromide gave the corresponding sulfide **22** which was reoxidized with peracid to the same sulfoxide **20.** From this chemical evidence, one would infer that the configuration of the sulfoxide in **20** is *R* based on analogy with the known oxidation chemistry of 6β-phthalimidopenicillin esters.[18]

Removal of the benzyl ester of **20** by catalytic hydrogenolysis gave the derived acid, which with *p*-bromoaniline gave the amide **23** via the mixed anhydride synthesis. The structure



23



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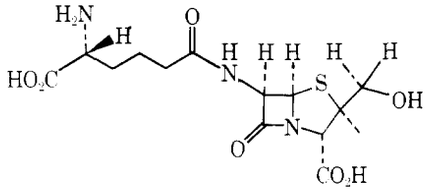
and configuration of **23** was determined by an x-ray diffraction analysis, proving the sulfoxide to be in the *S* configuration. Figure 1 is a perspective drawing of the final x-ray model of **23.** All bond distances and angles agree well with generally accepted values and no abnormally short intermolecular contacts were observed save one intermolecular NH···O–S distance of 2.87 Å. Thus, **23** and therefore **20** and **16b** (R = Me) are first examples of 6β-imidopenicillin (*S*)-sulfoxides. They are also the more stable of the epimers at sulfur as shown by the equilibration experiments.

In the course of some other work, it was found that prolonged refluxing of *p*-nitrobenzyl 6β-phthalimidopenicillinate 1(*R*)-oxide (**10,** R^1 = phthalimido, R^2 = *p*-nitrobenzyl) in toluene gave a highly insoluble substance (90%) which proved to be the corresponding 1(*S*)-oxide **24,** whose NMR spectrum showed the presence of two cis-oriented protons at C-5 and C-6. This supports the idea that the 6β-imidopenicillinate 1(*S*)-oxides are the more stable isomers both in the 6α-methyl and the 6α-hydrogen series. The same order of stability apparently is also true in the 6α-imidopenicillinates as was shown in the work of Spry,[19] who demonstrated that the equilibrium between the (*R*)- and (*S*)-sulfoxides of methyl 6-epiphthalimidopenicillinate favors the (*S*)-sulfoxide. An extrapolation of this finding is that the order of stability of the sulfoxides, 1(*S*) > 1(*R*), is not the result of steric factors, since particularly with a 6β-imido function of the 1(*S*) series is far more hindered, nor is it the result of hydrogen bonding since these species contain no such H bond.

With respect to our original hypothesis concerning the possible in vivo conversion of **11** to **13** via **12,** it is evident from the results presented above that a 1(*S*)-oxide such as **12** is not, at least on chemical grounds, a likely, labile, intermediate in this hypothetical transformation. In view of the known facility[20] of conversion of β-chloromethylpenams into cephems, it therefore seems reasonable to consider the β-hydroxymethylpenicillin N (**25**) as an alternative chemically reasonable precursor to deacetoxycephalosporin C in vivo.[21]



25

Experimental Section

General Procedures. Melting points were taken on a Thomas-Hoover capillary melting point apparatus or on a Kofler Micro Hot Stage block and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer Model 700 infrared spectrophotometer and were calibrated against polystyrene. Nuclear magnetic resonance spectra were obtained on a Varian Associates T-60 or a Perkin-Elmer R-20B or R-22 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane with the notations giving the multiplicity of the signal, the coupling constant if applicable, and the number of protons. Spin multiplicity is given by s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E spectrometer.

Silica gel for column chromatography was Merck silica gel 60, no. 7734. Analytical thin-layer chromatography was performed on Baker-flex silica gel IB-F or Merck precoated silica gel TLC plates 60F-254. Preparative thin-layer separations were carried out on Merck silica gel GF 254 (type 60), no. 7730, on 200 × 200 × 1.25 mm layers.

Benzyl 6β-(*o*-Carboxybenzamido)penam-3α-carboxylate 1β-Oxide (14a). To a solution of benzyl 6β-aminopenam-3α-carboxylate 1β-oxide (223 mg, 0.69 mmol) in dichloromethane (4 mL) was added a solution of phthalic anhydride (103 mg, 0.69 mmol) in tetrahydrofuran (4 mL). After stirring for 2 h, the solution was concentrated in vacuo leaving **14a** in quantitative yield (320 mg) as a white foam: NMR ($CDCl_3$) δ 1.08 (s, 3 H), 1.56 (s, 3 H), 4.67 (s, 1 H), 5.21 (s, 2 H), 5.33 (d, J = 4 Hz, 1 H), 6.23 (dd, J = 4, 10 Hz, 1 H), 7.40 (s, 5 H), 7.40–8.05 (m, 5 H), 10.38 (br s, 1 H); IR ($CDCl_3$) 3450–2950, 1780, 1740, 1720 (br) cm^{-1}.

Benzyl 6α-Isophthalimidopenam-3α-carboxylate 1β-Oxide (15). To a solution of DCC (143 mg, 0.69 mmol) in tetrahydrofuran (4 mL) was added a solution of **14a** (320 mg, 0.69 mmol) in tetrahydrofuran (3 mL), and the resulting solution was stirred at room temperature for 18 h and then concentrated to dryness in vacuo. Ethyl acetate (5 mL) was added to the residue and the suspended solid removed by filtration. The filtrate was concentrated in vacuo and the residue was purified by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as eluant; R_f 0.4), affording **15** in 67% yield (210 mg) as a yellow syrup: NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.71 (s, 3 H), 4.55 (s, 1 H), 5.05 (d, J = 1 Hz, 1 H), 5.15 (d, J = 1 Hz, 2 H), 5.25 (d, J = 1 Hz, 1 H), 7.22 (s, 5 H), 7.45–7.92 (m, 4 H); IR ($CHCl_3$) 1810, 1780, 1740, 1710 1695 cm^{-1}.

Benzyl 6β-(*o*-Carboxybenzamido)penam-3α-carboxylate (17). To a solution of 6-APA benzyl ester (61 mg, 0.2 mmol) in tetrahy-

drofuran (2 mL) was added a solution of phthalic anhydride (30 mg, 0.2 mmol) in tetrahydrofuran (2 mL). After stirring for 105 min, the solution was concentrated in vacuo, leaving **17** in quantitative yield (90 mg) as a white foam: NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.60 (s, 3 H), 4.43 (s, 1 H), 5.20 (s, 2 H), 5.5–5.92 (m, 2 H), 7.00 (d, J = 8 Hz, 1 H), 7.35 (s, 5 H), 7.40–8.00 (m, 4 H), 8.77 (br s, 1 H); IR ($CHCl_3$) 3500–2950, 1780, 1740, 1700 cm^{-1}.

Benzyl 6β-Isophthalimidopenam-3α-carboxylate (18). To a solution of DCC (41 mg, 0.2 mmol) in tetrahydrofuran (5 mL) was added a solution of **17** (90 mg, 0.2 mmol), and the resulting mixture was stirred at room temperature for 18 h and then concentrated in vacuo. Ethyl acetate (5 mL) was added and the suspended solid was removed by filtration. The filtrate was concentrated to dryness in vacuo, leaving a syrup. Purification by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as eluant; R_f 0.5) afforded **18** in 84% yield (73 mg) as a yellow syrup: NMR ($CDCl_3$) δ 1.45 (s, 3 H), 1.67 (s, 3 H), 4.53 (s, 1 H), 5.23 (s, 2 H), 5.60, 5.73 (AB q, J_{AB} = 4 Hz, 2 H), 7.40 (s, 5 H), 7.65–8.05 (m, 4 H); IR ($CHCl_3$) 1805, 1780, 1735, 1700 cm^{-1}.

Benzyl 6β-Amino-6α-methylpenam-3α-carboxylate 1β-Oxide (19). Benzyl 6β-amino-6α-methylpenicillinate (106 mg, 0.32 mmol) was dissolved in dichloromethane (4 mL) and cooled to −15 °C. A solution of *m*-chloroperbenzoic acid (56 mg, 0.32 mmol) in dichloromethane (2 mL) was added dropwise, and the resulting solution was stirred in the cold for 90 min and at room temperature for 40 min. The mixture was concentrated in vacuo and the residue was redissolved in ethyl acetate. This solution was washed with saturated sodium bicarbonate and brine and was dried ($MgSO_4$) and concentrated in vacuo, leaving **19** in 94% yield (95 mg) as a white foam: NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.70 (s, 3 H), 1.75 (s, 3 H), 2.50 (br s, 2 H), 4.55 (s, 2 H, H-3 and H-5), 5.10 (d, J = 2 Hz, 2 H), 7.3 (s, 5 H); IR ($CHCl_3$) 3500, 3410, 1780, 1740 cm^{-1}.

Benzyl 6β-(*o*-Carboxybenzamido)-6α-methylpenam-3α-carboxylate 1β-Oxide (14b). **19** (108 mg, 0.32 mmol) was dissolved in dichloromethane (2 mL) and to this solution was added a solution of phthalic anhydride (48 mg, 0.32 mmol) in tetrahydrofuran (2 mL). The resulting solution was stirred at room temperature for 2 h and then concentrated in vacuo, leaving **14b** in quantitative yield (155 mg) as a pale-yellow foam: NMR ($CDCl_3$) δ 1.15 (s, 3 H), 1.65 (s, 3 H), 1.95 (s, 3 H), 4.50 (s, 1 H), 4.85 (s, 1 H), 5.20 (d, J = 2 Hz, 2 H), 7.20 (s, 5 H), 7.20–8.00 (m, 4 H), 9.00 (br s, 1 H); IR ($CHCl_3$) 3500–2900, 1780, 1735, 1700 cm^{-1}.

Benzyl 6β-Isophthalimido-6α-methylpenam-3α-carboxylate 1β-Oxide (16b). **14b** (155 mg, 0.32 mmol) was dissolved in tetrahydrofuran (12 mL) and added dropwise to a stirring solution of DCC (67 mg, 0.32 mmol) in tetrahydrofuran (20 mL), and the resulting mixture was stirred at room temperature for 18 h and then concentrated in vacuo to dryness. To the residue was added ethyl acetate (5 mL) and a suspended solid was removed by filtration. The filtrate was concentrated in vacuo. Purification of the residue by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as the eluant; R_f 0.2) afforded **16b** in 48% yield (72 mg) as a pale-yellow foam: NMR ($CDCl_3$) δ 1.20 (s, 3 H), 1.65 (s, 3 H), 2.00 (s, 3 H), 4.60 (s, 3 H), 5.00 (s, 1 H), 5.20 (d, J = 2 Hz, 2 H), 7.20 (s, 5 H), 7.40–8.00 (m, 4 H); IR ($CHCl_3$) 1790 (br), 1740 cm^{-1}.

Benzyl 6β-Phthalimido-6α-methylpenam-3α-carboxylate 1β-Oxide (20) from 14b. **14b** (63 mg, 0.13 mmol) was dissolved in tetrahydrofuran (4 mL) and was added dropwise to a stirring solution containing DCC (27 mg, 0.13 mmol) and norbornadiene (240 μL, 2.6 mmol) in tetrahydrofuran (7 mL). The resulting solution was stirred for 15 h and then concentrated in vacuo. To the residue was added ethyl acetate (5 mL), and the suspended solid was removed by filtration. The filtrate was concentrated in vacuo and the residue was purified by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as the eluant; R_f 0.3) affording **20** in 86% yield (52 mg) as a white amorphous solid: mp 180–183 °C (dec); NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.65 (s, 3 H), 2.10 (s, 3 H), 4.70 (s, 1 H), 5.00 (s, 1 H), 5.30 (d, J = 2 Hz, 2 H), 7.40 (s, 5 H), 7.60–7.90 (m, 4 H); IR ($CHCl_3$) 1790, 1735 (br) cm^{-1}.

(3*R*,4*R*)-1-[(1*R*)-Benzoxycarbonyl-2-methyl-2-propenyl]-3-phthalimido-3-methyl-4-(benzthiazole-2-dithio)-2-azetidinone (21). A solution of **20** (46 mg, 0.1 mmol) and 2-mercaptobenzthiazole (17 mg, 0.1 mmol) in dry benzene (4 mL) was refluxed under nitrogen for 3 h and then concentrated in vacuo. Preparative TLC on silica gel (2:1 benzene–ethyl acetate as the eluant; R_f 0.6) afforded **21** in 60% yield (37 mg) as a clear, colorless syrup: NMR ($CDCl_3$) δ 2.15 (s, 3 H), 2.25 (s, 3 H), 5.05 (s, 1 H), 5.25 (br d, 4 H, $-OCH_2Ph$ and $C{=}CH_2$), 5.50 (s, 1 H), 7.30 (s, 5 H), 7.30–8.00 (m, 8 H); IR ($CHCl_3$) 1770, 1735, (br) cm^{-1}. The starting sulfoxide was also isolated in 30% yield (14 mg).

Benzyl 6β-Phthalimido-6α-methylpenam-3α-carboxylate (22). The sulfoxide **20** (40 mg, 0.086 mmol) was dissolved in dry DMF (1 mL) and cooled under N_2 to −5 °C. Phosphorus tribromide (40 μL, 5 equiv) was added, and the resulting solution was stirred in the cold for 10 min and then poured into saturated sodium bicarbonate (10 mL). This was extracted with ethyl acetate, and the organic phase was washed with 1 N HCl and saline and dried ($MgSO_4$). Concentration in vacuo left a syrup (43 mg). Purification by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as the eluant; R_f 0.5) afforded **22** in 65% yield (25 mg) as a clear, colorless syrup: NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.47 (s, 3 H), 1.95 (s, 3 H), 4.53 (s, 1 H), 5.13 (s, 2 H), 5.50 (s, 1 H), 7.30 (s, 5 H), 7.68 (m, 4 H).

Benzyl 6β-Phthalimido-6α-methylpenam-3α-carboxylate 1β-Oxide (20) from Oxidation of 22. To a −15 °C solution of **22** (22 mg, 0.049 mmol) in dichloromethane (1 mL) was added a solution of *m*-chloroperbenzoic acid (8 mg, 0.049 mmol) in dichloromethane (2 mL). The resulting solution was stirred in the cold for 1 h and then at room temperature for 45 min. The solution was washed with saturated sodium bicarbonate and saline and then was dried ($MgSO_4$) and concentrated in vacuo, leaving a foam. Purification by preparative TLC on silica gel (using 1:1 benzene–ethyl acetate as the eluant; R_f 0.3) afforded the sulfoxide **20** in 67% yield (15 mg) as a foam. NMR and IR spectra were identical to those for **20** obtained from the phthalamic acid **14b.**

6β-Phthalimido-6α-methylpenam-3α-*p*-bromocarboxanilide 1β-Oxide (23). To a solution of **20** (255 mg, 0.546 mmol) in glacial acetic acid (10 mL) and chloroform (10 mL) was added 255 mg of palladium on charcoal. This mixture was shaken mechanically under 1 atm of H_2 at room temperature for 4 h and then filtered. Chloroform was removed from the filtrate in vacuo and the remaining acetic acid solution was freeze-dried, leaving the acid as a white solid.

To a solution of the acid (75 mg, 0.199 mmol) in dry THF (6 mL) was added triethylamine (28 μL, 0.199 mmol) and the resulting solution was cooled to −5 °C. Ethyl chloroformate (16 μL, 0.199 mmol) was added dropwise to the stirring cold solution, and the resulting mixture was stirred in the cold for 15 min and then for 20 min while warming to room temperature. The turbid solution was recooled to 0 °C and *p*-bromoaniline (34 mg, 0.199 mmol) in THF (0.5 mL) was added dropwise. The reaction was stirred at room temperature for 85 min and then was concentrated in vacuo, leaving a foam. A chloroform solution of this product was washed with water, saturated sodium bicarbonate, and brine, dried ($MgSO_4$), and concentrated in vacuo to dryness. Preparative thin-layer chromatography on silica gel (1:1 benzene–ethyl acetate as eluant) afforded **23** as an amorphous solid (76 mg, 72%): NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.55 (s, 3 H), 2.13 (s, 3 H), 4.50 (s, 1 H), 5.05 (s, 1 H), 7.40 and 7.62 (AB q, J_{AB} = 7 Hz, 4 H), 7.75 (m, 4 H); IR ($CHCl_3$) 3400, 1805, 1715 cm^{-1}. Crystals for x-ray were obtained (mp 210–212 °C) (corrected) from acetone–petroleum ether by the "vapor diffusion" method.

X-Ray Analysis of 6β-Phthalimido-6α-methylpenam-3α-*p*-bromocarboxanilide 1β-Oxide (23). The crystals of **23** belonged to the unambiguously determined space group $P_c2_12_12_1$. Accurate lattice dimensions were obtained from a least-squares fit of 15 2θ values between 35.0° and 45.0°. The cell constants are a = 9.342 (4), b = 13.750 (7), and c = 18.635 Å. A calculated (Z = 4) and observed density of 1.46 g/cm^3 indicated one molecule of composition $C_{23}H_{20}O_5N_3SBr$ per asymmetric unit. All unique diffraction maxima with $2\theta \leq 114.1°$ were recorded in the θ scan mode using a computer-controlled four-circle diffractometer and graphite monochromated Cu Kα x-rays (1.54178 Å). Of the 1855 reflections surveyed, 1628 (88%) were judged observed [$I \geq 3\sigma(I)$] after correction for Lorentz polarization and background effects.

A sharpened three-dimensional Patterson[22] was readily deconvoluted to yield the bromine and sulfur position. A subsequent Fo synthesis revealed the rest of the nonhydrogen atoms. Full-matrix, least-squares refinements with anisotropic temperature factors for all nonhydrogen atoms have converged to a standard crystallographic residual of 0.050 for the observed reflections. Additional crystallographic details such as the positional and thermal parameters, bond distances and angles, and observed and calculated structure factors are presented in Tables I–IV (Supplementary Material).

***p*-Nitrobenzyl 6β-Phthalimidopenicillinate 1(*S*)-Oxide (24).** Toluene (50 mL) was dried by binary distillation for 2 h. Heat was removed temporarily and *p*-nitrobenzyl 6β-phthalimidopenicillinate 1(*R*)-oxide (**10**, R^1 = phthalimido; R^2 = *p*-nitrobenzyl), 2.0 g (5 mM), was added. The solution was refluxed for 6 h, during which time a crystalline and highly insoluble solid was formed. It was filtered and rinsed with acetone and vacuum dried to give the 1 (*S*)-oxide **24,** mp 204 °C (dec), in 90% yield. Proton NMR (100 MHz, Me_2SO-d_6) δ 1.20 (s, 3 H), 1.51 (s, 3 H), 4.63 (s, 1 H), 5.41 (s, 2 H), 5.68 (AB q, 2 H, J = 4.5 and 8.0 Hz), 7.72 (d, 2 H, J = 9.5 Hz), 8.27 (d, 2 H, J = 9.5 Hz) and

7.88 (ms, 4 H); IR (mull) 1790, 1780, 1720, 1515, 1460, 1380, 1345, 1270 cm^{-1}; ^{13}C NMR (Me_2SO-d_6, ref Me_4Si) δ 17.8, 19.0 (2-CH_3), 72.1 (C-2), 65.9 (C-3), 72.7 (C-5), 56.1 (C-6).[23]

In the combined solution of the toluene filtrate and acetone rinse, a 2–3% solid was recovered, which was identical to an authentic sample of the *p*-nitrobenzyl ester of 3-hydroxyl-3-methyl-7β-phthalimidocephalosporin.

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Registry No.—**10** (R^1 = phthalimido; R^2 = *p*-nitrobenzyl, 35160-70-4; **14a,** 65102-78-5; **14b,** 65102-79-6; **15,** 65102-80-9; **16b,** 65102-81-0; **17,** 65102-82-1; **18,** 65102-83-2; **19,** 65102-84-3; **20,** 65102-85-4; **21,** 65102-86-5; **22,** 65102-87-6; **23,** 65102-88-7; **24,** 65165-49-3; benzyl 6β-aminopenam-3α-carboxylate β-oxide, 65165-50-6; phthalic anhydride, 85-44-9; benzyl 6β-aminopenam-3α-carboxylate, 3956-31-8; benzyl 6β-amino-6α-methylpenicillinate, 36273-78-6; 2-mercaptobenzthiazole, 149-30-4.

Supplementary Material Available. Tables of atomic coordinates, temperature factors, bond angles, and bond distances (3 pages). Ordering information is given on any current masthead page.

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Haloaziridines. 2. Synthesis and Pyrolysis of Some *gem*-Dichloroaziridines[1,2]

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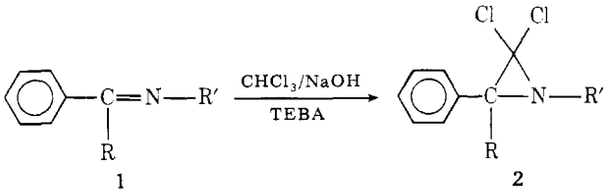
An improved synthesis of *gem*-dichloroaziridines from imines and dichlorocarbene is reported using chloroform, sodium hydroxide, and triethylbenzylammonium chloride to generate the dichlorocarbene. The preparation of some *gem*-dichloroaziridines from phenyl(trihalomethyl)mercury reagents is reported and the previous reports are examined. The *gem*-dichloroaziridines prepared under these latter conditions are subject to a phenylmercuric halide catalyzed ring-opening reaction. A pyrolysis study delineated the factors controlling the ring-opening reaction and demonstrated the synthetic utility of this reaction.

The preparation of *gem*-dichloroaziridines has been accomplished by the addition of dichlorocarbene to the carbon–nitrogen double bond of an imine. The dichlorocarbene in this reaction has been generated from the reaction of chloroform, hexachloroacetone, or ethyl trichloroacetate with the appropriate base.[4] Recently, Seyferth has reported the preparation of 1,3-diphenyl-2,2-dichloroaziridine in low yield using $PhHgCBrCl_2$ to generate the dichlorocarbene.[5] Makosza has reported the generation of dichlorocarbene from chloroform and aqueous sodium hydroxide using a phase-transfer agent.[6] These phase-transfer catalyzed two-phase reactions have been used in a variety of reactions in addition to generating dichlorocarbene. The chemistry of these types of reactions has been recently reviewed.[7]

Phase-Transfer Preparations. We have examined the preparation of *gem*-dichloroaziridines from imines (1) using



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aqueous sodium hydroxide, chloroform, and triethylbenzylammonium chloride (TEBA) as the phase-transfer agent. The isolated yields for this catalytic method are contrasted to the best yield obtained from the other reported methods

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