Supplementary Material Available: A tabulation of our and other workers' results on the thermal and photochemical isomerization of **2a** plus experimental details (and tabulation) of our attempts to prepare **2b** and **2c** (6 pages). Ordering information is given on any current masthead page.

Dehydrogenation of the Azetidinone Sulfenic Acid Generated from Penicillin Sulfoxide[1]

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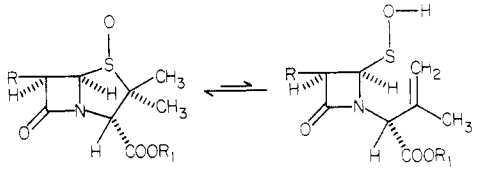
Received December 30, 1980

The beauty and unlimited opportunities of penicillin chemistry lie in the fact that many functional groups are brought into combination in a relatively small molecule. In addition, some of these groups can be transformed into new, reactive functionalities which give a special challenge to the chemistry of the penicillin molecule. A typical example of a transformation which creates a highly reactive functionality is the thermal equilibrium of penicillin sulfoxide **1** and the azetidinone sulfenic acid **2** (eq 1).



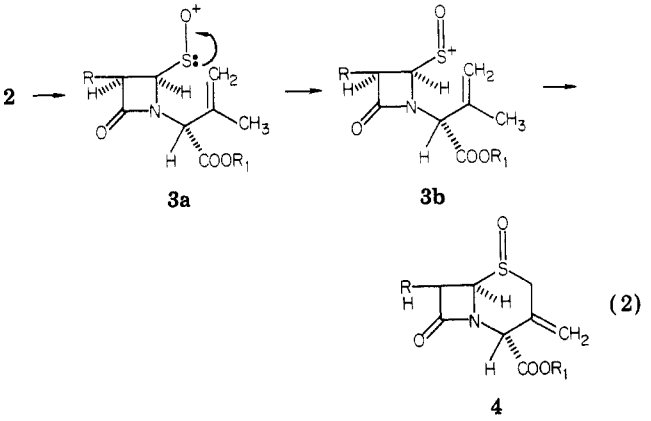
(1)

1 **2**

Although the sulfenic acid group in **2** consists of only three atoms, i.e., S, O, and H, many different and distinct reactions have been successfully performed on each of these atoms in spite of the fact that the S–O–H group is attached to the very sensitive four-membered azetidinone ring.[2] Our interest in finding a new way to form the sulfinium cation **3b**, which is a proposed intermediate in the preparation of 3-methylenecepham sulfoxide (**4**),[3] led us to study the dehydrogenation of the azetidinone sulfenic acid **2**, and our results are reported here.

We hoped that the hydrogen atom of the sulfenic acid group in **2** could be abstracted as the hydride ion H^-, forming the intermediate **3a** and that the resonance form **3b** might then ring close to the *exo*-methylene sulfoxide **4** (eq 2).

To test this idea the sulfenic acid **2**, prepared by thermolysis of penicillin sulfoxide **1**, was treated with *p*-benzoquinone or chloranil (1 equiv, refluxing toluene, 2 h). A mixture of five compounds was obtained which was separated by chromatography over silica gel. From the first fraction, the crystalline deacetoxycephem **9** (mp 189–190 °C), was isolated in 3.4% yield (Scheme I). The structure was established by comparison with an authentic sample. The second fraction provided a mixture of 2-(sulfinoxymethyl)penams **5** and **6** and the 3-sulfinoxycepham **7** (total yield 48.5%).



3a **3b**

(2)

4

By repeated chromatography these isomers were separated and isolated as colorless amorphous solids. From the third fraction was isolated the 3-sulfinoxycepham ester **8** in 13.3% yield.

Elemental analyses for **5–8** were correct for empirical formula $C_{46}H_{44}N_6O_{16}S_2$, consistent with the conclusion that these compounds are isomeric and also dimers of the original penicillin molecule. The dimeric nature of these compounds can be clearly seen by examination of the NMR spectra.

The structure of the azetidinone sulfinic acid portion of esters **5–8** was established by IR, NMR, and mass spectra. The IR spectra of these esters display an absorption band at 1780 cm^{-1}, indicating the presence of the azetidinone carbonyl. The NMR spectra show characteristic quartets and doublets for azetidinone portions with coupling constants J = 4.5 and 9.0 Hz. In addition, all these esters have a singlet at δ 1.9–2.0 for methyl protons and typical allylic signals between δ 5.0 and 5.3, which when the compound is treated with triethylamine for 10 min changed to two 3-proton singlets at δ 2.21 and 2.27 due to the presence of the isopropylidene group.[4] The major fragmentation peaks at m/e 451, 483, and 501 indicate the presence of the azetidinone sulfinate fragment and the penam and cepham moiety in these molecules.

Treatment of a mixture of **5–8** with methanesulfonic acid afforded after chromatography 3-methylenecepham sulfoxide **4**. This results provides chemical support for the sulfinic acid ester portion of compounds **5–8**.[3]

The structures of 3β-hydroxycephams and 2β-hydroxymethylpenams, fragments of esters **5–8**, were also ascertained by NMR spectra and chemical reactions. Thus the 3β-hydroxy-3-methylcepham fragment in **7** was easily recognized by the characteristic AB quartet at δ 2.85 and 3.48 (J = 15 Hz), the saturated methyl singlet at δ 1.4, and the H-4 singlet at δ 4.78. Similarly, the diastereoisomer **8** displays the AB quartet at δ 2.15 and 3.24 (J = 15 Hz), the methyl protons at δ 1.48, and the H-4 proton at δ 4.35.[5]

The isomeric 2α-oxymethylpenam part of **5** was deduced from the NMR spectrum in which the 2β-methyl protons show chemical shift at δ 1.31, the 2-methylene AB quartet at δ 3.75 and 3.89 (J = 11.0 Hz), and the H-3 singlet at δ 4.75. These signals for the methyl and methylene protons were shifted significantly upon oxidation of the penam sulfur to the corresponding sulfoxide. Thus in the sulfoxide the 2β-methyl group has an upfield chemical shift to δ 1.25 and the methylene protons a downfield shift to δ 4.48. Similar chemical shifts between the sulfide and

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(2) P. G. Sammes, *Chem. Rev.*, **76**, 113 (1976); R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Acc. Chem. Res.*, **6**, 32 (1973).
(3) S. Kukolja, S. R. Lammert, M. R. Gleissner, and A. I. Ellis, *J. Am. Chem. Soc.*, **98**, 5040 (1976); S. Kukolja in "Recent Advances in the Chemistry of β-Lactam Antibiotics", J. Elks, Ed., The Chemical Society, Burlington House, London, 1977, p 181.
(4) R. D. G. Cooper and F. L. Jose, *J. Am. Chem. Soc.*, **92**, 2575 (1970).
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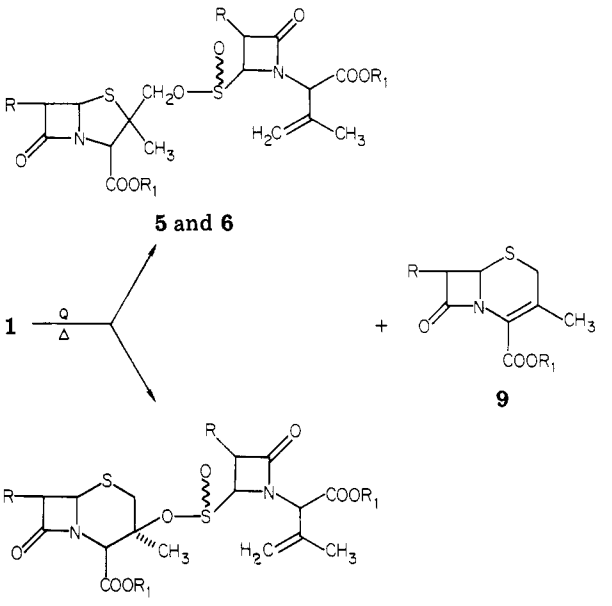
Scheme I[a]



[a] R = $C_6H_5OCH_2CONH$; R_1 = $CH_2C_6H_4$-*p*-NO_2; Q = *p*-benzoquinone or chloranil. Compounds **5** and **7** are epimeric with **6** and **8** at the sulfinyl sulfur atom.

sulfoxide group in a penam system are well documented in the literature.[6] The diastereomeric penam **6** shows a chemical shift for the saturated methyl protons at δ 1.38, the AB quartet for the methylene hydrogens at δ 3.78 and 3.90 (J = 11.0 Hz), and the H-3 singlet at δ 4.91.

When **5**–**8** were refluxed in DMF for 45 min, deacetoxycephalosporin **9** was formed and isolated by chromtography. The conversion of methyl-substituted penicillins and 3-substituted cephams to 3-cephem **9** by heating in DMF has been reported earlier,[7] and these transformations firmly support the proposed structures for compounds **5**–**8**.

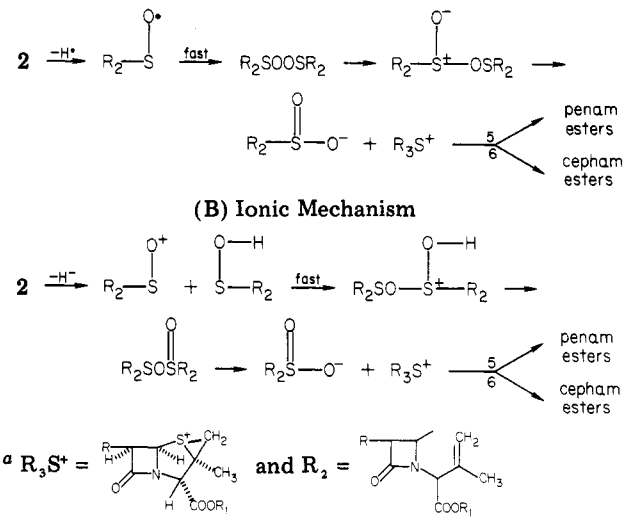
On the basis of the evidence presented, we believe that compounds **6** and **8** are epimeric with **5** and **7** at the sulfinyl sulfur atom.

Although our initial goal—the direct synthesis of *exo*-methylenecepham **4**—was not achieved, the formation of the sulfinate esters indicates that the anticipated dehydrogenation of the sulfenic acid **2** does take place. It is not clear whether the hydrogen atom is abstracted as a hydride ion (H^-, path B, Scheme II) or as a radical ($H\cdot$, path A), but the formation of both penam and cepham esters indicates that ion R_3S^+ is probably an intermediate at some point in the reaction pathway. The formation of R_3S^+ is conceivable as a result of the rearrangement of a dimerized intermediate. Whether the reaction path is initiated by a radical (path A) or ionic (path B) dehydrogenation has not been determined.

Experimental Section

Reaction of (Phenoxymethyl)pencillin Sulfoxide *p*-Nitrobenzyl Ester with *p*-Benzoquinone. In order to remove the moisture, 125 mL of toluene and 5.0 g (10 mmol) of 6-(phenoxyacetamido)penicillanate sulfoxide *p*-nitrobenzyl ester was refluxed for 15 min under a Dean-Stark adapter. After that, 1.1 g (10 mmol) of *p*-benzoquinone was added, and heating at reflux temperature was continued for 2 h. Solvent was removed, 10 mL

Scheme II[a]



[a] R_3S^+ = and R_2 =

of chloroform was added to the residue, and the insoluble black precipitate was filtered off. The filtrate was evaporated to dryness to a brown foam which was chromotographed over a column (200 g of silica gel, 4 × 90 cm). The column was developed with a 7:3 mixture of ethyl acetate–*n*-hexane, the eluant being collected in 18-mL fractions. The following fractions were collected.

I (fractions 39–43) gave 394 mg of crystalline *p*-nitrobenzyl 7-(phenoxyacetamido)-3-methyl-3-cephem-4-carboxylate (**9**), mp 189-190 °C, which is identical (TLC, IR, NMR) with an authentic sample.

II (fractions 45–67) gave 1.98 g of a mixture of two isomeric penams and a cepham compound. These three components were separated by repeated chromatography as described below.

III (fractions 69–83) constituted 815 mg of a mixture of penam and cepham compounds.

IV (fractions 85–93) afforded 265 mg of pure cepham ester **7** as a colorless foam: NMR ($CDCl_3$) δ 1.4 (s, 3 H, CH_3), 1.91 (s, 3 H, CH_3), 2.85 and 3.48 (AB q, J = 15 Hz, 2H, C_2-H), 4.53 and 4.6 (2 s, both 2 H, $PhOCH_2$), 4.78 (s, 1 H, C_4-H), 5.25 (m, 5 H, C_6-H, vinyllic and allylic H's), 5.63 and 5.8 (2 dd, 2 H, C_7-H's), 6.9–7.7 (m, 12 aromatic and NH H's); IR ($CHCl_3$) 1780, 1742, 1690, 1682 cm^{-1}.

An 800-mg amount of fraction II was rechromatographed over a silica gel column (2.5 × 40 cm) which was prewashed with acetic acid. The column was developed with a 9:1 mixture of chloroform–ethyl acetate at the rate of 3 mL/min, and the following five fractions were collected.

A (fractions 18–25) yielded 120 mg of pure cepham ester **8** as a colorless foam: NMR ($CDCl_3$) δ 1.48 (s, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 2.15 and 3.24 (AB q, 2 H, J = 15 Hz, C_2-H), 4.35 (s, 1 H, C_4-H), 4.44 (s, 2 H, $PhOCH_2$), 4.70 (s, 2 H, $PhOCH_2$), 5.07, 5.25, and 5.32 (3 s, 3 vinyllic and allylic H's), 5.18 and 5.32 (2 d, J = 4.5 Hz, 2 H, (CH's), 5.87 and 6.1 (2 dd, J = 4.5 and 10 Hz, 2 H, C_7-H's), 7.2, (center of m for 12 aromatic and NH protons); IR ($CHCl_3$) 1774, 1740, 1690, 1672, 1519, 1343 cm^{-1}.

B (fractions 26–33) gave 134 mg of a mixture of cepham **8** and penam **5** esters.

C (fractions 35–45) yielded 266 mg of pure penam isomer **5** as a colorless amorphous solid: NMR ($CDCl_3$) δ 1.31 (s, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 3.75 and 3.89 (AB q, J = 11.0 Hz, 2 H, penam CH_2), 4.42 and 4.6 (AB q, J = 15 Hz, 2 H), 4.62 (s, 2 H, $PhOCH_2$), 4.75 (s, 1 H, C_3-H), 4.98–5.3 (m, 8 H, d for C_5-H, 2 CH_2 of pNB, 3 vinyllic and allylic H), 5.55 (d, J = 4.5 Hz, 1 H, C_5-H), 5.75 and 5.95 (2 dd, J = 4.5 and 9 Hz, 2 H, C_6-H's), 6.8–7.6 (m, 18 aromatic H), and 7.9 and 8.15 (2 d, J = 9.0 Hz, 2 NH); IR ($CHCl_3$) 1788, 1745, 1682, 1523, 1349 cm^{-1}.

D (fractions 47–53) yielded 105 mg of two penam isomers **5** and **6**.

E (fractions 55–80) gave 101 mg of the second penam isomer **6** as a colorless solid: NMR ($CDCl_3$) δ 1.38 (s, 3 H, CH_3), 1.87 (s, 3 H, CH_3), 3.78 and 3.90 (AB q, J = 11.0 Hz, 2 H, penam CH_2), 4.46 and 4.5 (2 s, both 2 H, 2 $PhOcH_2$), 4.63 (s, 1 H, C_3-H), 4.9–5.3

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(m, 9 H, 2 C_5-H), 4.9–5.3 (m, 9 H, 2 C_5-H, 2 CH_2 of pNB, 3 vinyllic and allyllic H), 5.68 (m, 2 H, 2 dd of C_6-H's), 6.9–7.6 (m, 18 aromatic H and 2 NH); IR ($CHCl_3$) 1785, 1742, 1692, 1680 cm^{-1}.

Anal. Calcd for $C_{46}H_{44}N_6O_{16}S_2$: C, 55.19; H, 4.43; N, 8.46; O, 25.57; S, 6.41. Found: C, 54.92; H, 4.67; N, 8.64; O, 25.82; S, 6.19.

Preparation of *p*-Nitrobenzyl 7-(Phenoxyacetamido)-3-methyl-3-cepham-4-carboxylate (9). A 260-mg sample of fraction II was refluxed in 3 mL of dimethylformamide for 45 min, and while the solution was hot, about half of the solvent was evaporated under reduced pressure. The remaining half was dissolved in 20 mL of ethyl acetate and washed with 1 N HCl (3 × 10 mL), a saturated solution of sodium bicarbonate, and brine. After being dried the solvent was evaporated, and the residue was chromatographed on a preparative silica gel plate by using a 7:3 mixture of ethyl acetate–hexane. The major component was extracted with acetone and the NMR of the isolated material was consistent with that of the title compound.

A similar reaction was repeated with cephams **7** and **8**, and the title compound was isolated by preparative thin-layer chromatography.

Preparation of *p*-Nitrobenzyl 1-Oxo-7-(phenoxyacetamido)-3-methylenecepham-4-carboxylate (4). A 815-mg sample of fraction III (containing 1:1 mixture of penam **5** and cepham **7**) was stirred in 4.8 mL of methanesulfonic acid for 35 min at room temperature. A solution was slowly poured onto 7.5 g of $NaHCO_3$ in 75 mL of water and 50 mL of ethyl acetate. The organic layer was separated, washed with brine, and dried and the solvent evaporated. The residue was dissolved in 2.0 mL of ethyl acetate, and the title compound crystallized out after scratching and keeping the solution in a refrigerator overnight. The isolated product is identical (NMR, IR, TLC) with an authentic sample.[3]

Oxidation of the Penam Sulfur in 5 to the Sulfoxide. A mixture of 636 mg of the penam **5** and 200 mg of *m*-chloroperbenzoic acid in 20 mL of dichloromethane was kept at room temperature for 45 min. The solution was washed with an aqueous solution of sodium bisulfite and brine. After the mixture was dried over $MgSO_4$, the solvent was evaporated to give 530 mg of the crude product which was purified by chromatography over silica gel (ethyl acetate–hexane, 7:3). Fractions 14–24 contained 170 mg of the pure penam sulfoxide isolated as a colorless foam: NMR ($CDCl_3$) δ 1.25 (s, 3 H, CH_3), 1.96 (s, 3 H, CH_3), 4.48 (s, 2 H, CH_2O), 4.52 (s, 4 H, $PhOCH_2$), 4.59 (s, 1 H, C_3-H), 4.85 (d, J = 4.5 Hz, 1 H, C_5-H), 5.02–5.5 (m, d, C_5-H, 2 CH_2 of pNB, 3 allyllic H), 5.98–6.17 (2 dd, J = 4.5 and 9 Hz, 2 H, C_6-H's), 6.8–7.52 (m, 18 aromatic H), 8.13–8.23 (2 d, J = 9.0 Hz, 2 NH); IR ($CHCl_3$) 1790, 1745, 1695, cm^{-1}.

Anal. Calcd for $C_{46}H_{44}N_6O_{17}S_2$: C, 54.33; H, 4.36; N, 8.26; S, 6.31; O, 26.74. Found: C, 54.08; H, 4.56; N, 8.08; S, 6.07; O, 27.00.

Acknowledgment. We are grateful to Dr. G. M. Maciak and associates for miroanalyses, J. L. Occolowitz for mass spectra, and T. K. Elzey for NMR measurements.

Registry No. 1, 29707-62-8; 2, 76665-50-4; 4, 61375-82-4; 5, 76739-44-1; 5 *S*-oxide, 76665-51-5; 6, 76665-52-6; 7, 76665-53-7; 8, 76738-30-2; 9, 28974-31-4.

o-Phenylenediamine from Sulfur, Ammonia, and Cyclohexane†

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Received December 24, 1980

Nazady[1] reported the synthesis of aniline from sulfur, ammonia, and cyclohexane in modest yield. During our investigation of this reaction, we discovered that a second nitrogen-containing product is produced under his conditions, *o*-phenylenediamine (OPD), the subject of this note.

Table I. *o*-Phenylenediamine Synthesis[a]

sulfur, mg	cyclohexane, μL	PhH, mL	NH_3, g	$PhNH_2$, mg	OPD, mg
100	200	2.5	0.5	25	3
100	200	2.5	1.0	10	11
400	800	1.5	1.0	76	18
400	800	1.5	2.0	109	109
400	1500	1.0	2.0	86	95
400	1500	0	2.0	83	95
800	2500	0	2.0	145	103
500	2500	0	1.0	94	29

[a] 1 h, 330 °C.

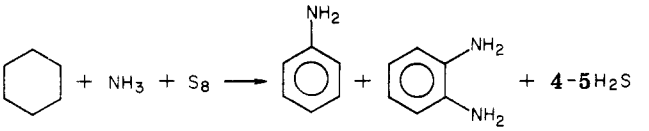
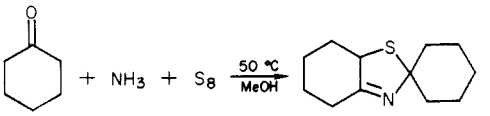


Table I gives the yield of aniline and OPD from the three ingredients at various reactant concentrations. In previous work[1] benzene was used as solvent; we find that it is merely an unnecessary diluent and reactor productivity is increased by replacing the benzene with additional cyclohexane. OPD is favored by high ammonia pressures and is less sensitive to other variables. GC analyses revealed that the regioselectivity to OPD was greater than 99%. Aniline is not the precursor of OPD not only because its amination is significantly slower than the formation of OPD under these conditions but also because *m*-phenylenediamine, the thermodynamically most stable isomer, is the major isomer produced, rather than the observed OPD from cyclohexane. Very little benzene is produced; excess cyclohexane is recovered unchanged.

The ortho selectivity has precedent in reactions of sulfur and amines with substituted organic compounds under milder conditions. Cyclohexanone reacts with sulfur and ammonia at 50 °C to give the spiro compound **2** in high yield.[2] Acetophenones react with sulfur and primary amines[3] to give hexathiocanes **3**. In both these examples



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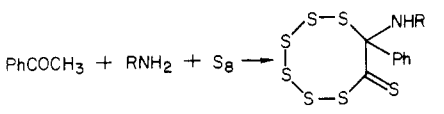

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replacement of the carbonyl oxygen by a nitrogen substitutent is accompanied by sulfur functionalization of the adjacent carbon.

Methylcyclohexane gives a mixture of products including a methyl-OPD, but also containing toluidines (*o*:*m*:*p* = 5:83:13) and an aminobenzonitrile.

These reactions may proceed via alternating dehydrogenations by sulfur and nucleophilic attacks by ammonia. The isomer distribution of the toluidines suggests that at

† Contribution no. 2864.

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