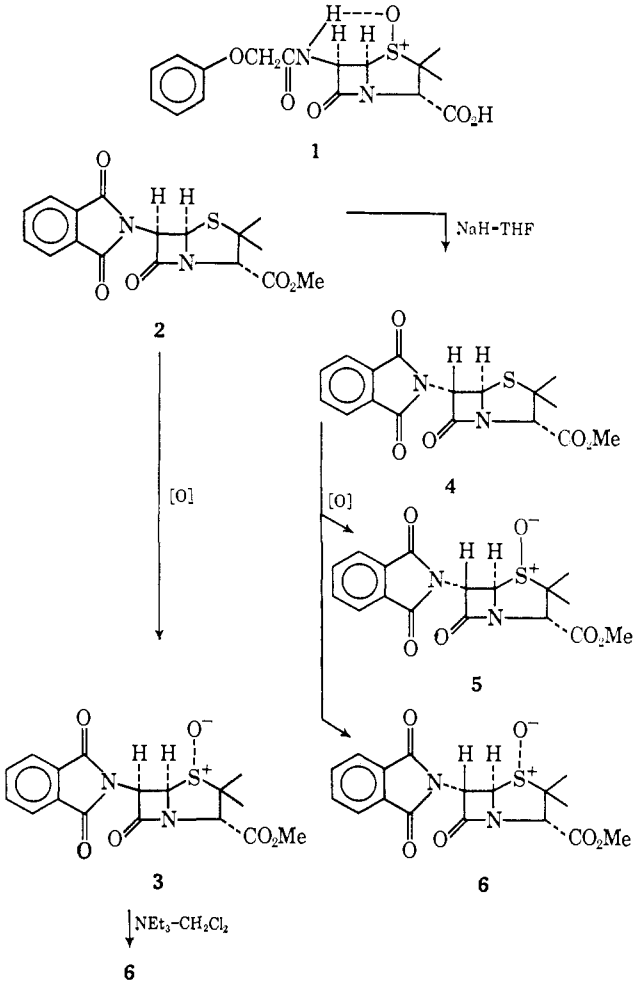
Communications to the Editor

Structural Studies on Penicillin Derivatives. II. The Configuration of Phthalimidopenicillin and Epiphthalimidopenicillin Sulfoxides

Sir:

We have previously reported the sulfoxide configuration in phenoxymethylpenicillin sulfoxide (**1**) to be *S*.[1]



We proposed that the *S* configuration, although more sterically hindered, was the result of the directing influence of the 6β-amido proton, either through hydrogen bonding with the oxidants (reagent approach control) or through thermodynamic control in which the *S* configuration is stabilized by an internal 6β-amido proton–sulfoxide hydrogen bond. In the absence of the 6β-amido proton, steric control should be the major directing influence in the oxidation.

Oxidation of methyl phthalimidopenicillinate (**2**) using *m*-chloroperbenzoic acid in chloroform gave as the major product the crystalline sulfoxide **3**, mp 134°, $[\alpha]D$ +70° (dioxane). The nmr values of **3** are shown in Table I. Assignments for the 2α-methyl signal (1.33 ppm) and the H_5 signal (4.86 ppm; doublet) in **3** were based on the observation of an internal nuclear Overhauser effect between these two signals (*ca.* 9%).[2] A similar effect was also observed between H_3 (4.61 ppm) and the 2β-methyl group (1.83 ppm) (18%) but not between H_3 and the 2α-methyl group. Sulfide **2** gave positive effects between H_3 (4.68 ppm) and the 2α- and 2β-methyl groups (1.51 ppm, 14%, and 1.82 ppm, 26%, respectively). Thus parallel conformational differences exist between **2** and **3**, as has been previously reported for phenoxymethylpenicillin and its sulfoxide **1**.

Table I. Solvent Shifts for 6β-Phthalimidopenicillins[a]

	H_3	H_5[b]	H_6[b]	2β-Me	2α-Me
2, $CDCl_3$	4.68	5.60	5.68	1.82	1.51
C_6D_6	4.72	5.29	5.30	1.67	1.25
Δ_2 ($\delta_{CDCl_3} - \delta_{C_6D_6}$)[c]	−0.04	+0.31	+0.38	+0.15	+0.26
3, $CDCl_3$	4.61	4.86	5.89	1.83	1.33
C_6D_6	4.57	4.36	5.29	1.46	1.17
Δ_3 ($\delta_{CDCl_3} - \delta_{C_6D_6}$)[c]	+0.04	+0.50	+0.60	+0.37	+0.16
$\Delta_3 - \Delta_2$[c]	+0.08	+0.19	+0.22	+0.22	−0.10

[a] In parts per million in 1% solutions (infinite dilution) using TMS as internal reference, measured on a Varian HA-100. [b] Doublet, J = 4.5 Hz. [c] Positive values represent shielding and negative values deshielding.

Aromatic solvent induced shifts ($\delta_{CDCl_3} - \delta_{C_6D_6}$) can be a useful method in deriving stereochemistry.[1,3] In the presence of a polar functional group, *e.g.*, a sulfoxide, the aromatic solvent associates with the positive end of the solute dipole, and for phenoxymethylpenicillin sulfoxide (β-sulfoxide) this gives large shielding effects for H_5 and the 2α-methyl protons.[1] Although consideration of Table I would indicate that **3** does not have the *S* configuration (β-sulfoxide) and thus is the α-sulfoxide, the results do not allow a definitive assignment of the stereochemistry.[4]

Compound **2** was isomerized by sodium hydride–tetrahydrofuran into the 6α derivative **4**, mp 179–180°, $[\alpha]D$ +215° (dioxane).[5] Oxidation of **4** using *m*-chloroperbenzoic acid in chloroform gave two sulfoxides (ratio 4:1), separable by silica gel chromatography (gradient elution, benzene → benzene–ethyl acetate, 3:1) into the less polar **5**,[6] mp 173°, $[\alpha]D$ +288° (dioxane), and **6**, mp 134°, $[\alpha]D$ +54° (dioxane). Compound **6** could also be prepared by the epimerization of **3** (triethylamine in methylene chloride).

The nmr solvent shift data for **5** and **6** (see Table II) allow a more definitive assignment of their stereo-

(1) R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Am. Chem. Soc.*, **91**, 1408 (1969).

(2) For a detailed discussion of the application of internal nuclear Overhauser effect to the complete assignment of the nmr spectrum and to the assessment of conformational changes in the penicillin molecule, see ref 1.

(3) T. Ledaal, *Tetrahedron Letters*, 1683 (1968).

(4) Presumably, due to steric interactions with the bulky phthalimido group, the solvent molecules are not allowed to complex in a simple manner with the positive end of the sulfoxide dipole, *i.e.*, from the β face of the molecule.

(5) S. Wolfe and W. S. Lee, *Chem. Commun.*, 242 (1968).

(6) All new compounds gave satisfactory microanalytical data.

chemistry than was possible for **3**.[7] In **5**, H_5 and the 2α-methyl group are shielded, whereas in **6**, H_3, H_6, and the 2β-methyl group are shielded.[8] Therefore, **5** is assigned the 6α-β-sulfoxide stereochemistry, and **6**, the 6α-α-sulfoxide stereochemistry. By derivation, **3** is the α-sulfoxide, and the mechanism of oxidation of **2** and **4** proceeds by steric control of stereochemistry.

Table II

	H_3[a]	H_5[b]	H_6[b]	2β-Me	2α-Me
4, $CDCl_3$	4.63	5.57	5.39	1.49	1.66
C_6D_6	4.50	5.54	5.48	1.21	1.14
Δ_4 ($\delta_{CDCl_3} - \delta_{C_6D_6}$)	+0.13	+0.03	−0.09	+0.28	+0.52
5, $CDCl_3$	4.58	5.35	5.79	1.73	1.29
C_6D_6	4.58	4.66	6.13	1.35	0.73
Δ_5 ($\delta_{CDCl_3} - \delta_{C_6D_6}$)	0.00	+0.69	−0.34	+0.38	+0.56
$\Delta_5 - \Delta_4$	−0.13	+0.66	−0.25	+0.10	+0.04
6, $CDCl_3$	4.60	5.16	5.65	1.51	1.46
C_6D_6	4.27	5.23	5.60	1.15	0.77
Δ_6 ($\delta_{CDCl_3} - \delta_{C_6D_6}$)	+0.33	−0.07	+0.05	+0.42	+0.69
$\Delta_6 - \Delta_4$	+0.20	−0.10	+0.14	+0.14	+0.17

[a] The assignments were made using internal Overhauser effects and replacement of H_6 in **4** by deuterium. [b] Doublet, J = 2.1 Hz.

The chemical shift differences associated with the processes **2** → **3**, **4** → **5**, and **4** → **6** (see Table III) do not agree with the values predicted, assuming the sulfoxide bond anisotropy is solely acetylenic in character.[1,9]

Table III. Chemical Shift Values (in ppm)

	H_3	H_5	H_6	2β-Me	2α-Me
Sulfide **2** → sulfoxide **3** ($CDCl_3$)	+0.07	+0.74	−0.21	−0.01	+0.18
Sulfide **4** → sulfoxide **5** ($CDCl_3$)	+0.05	+0.22	−0.40	−0.24	+0.37
Sulfide **4** → sulfoxide **6** ($CDCl_3$)	+0.03	+0.41	−0.26	−0.02	+0.20

These anomalies, the shielding of H_5 and the 2α-methyl group in **3** and **6**, can be explained if it is assumed that any groups which are α-antiaxial to the lone-pair electrons of the sulfoxide group come under shielding influence. This "lone-pair effect" has been previously noted in the piperidine and thiane 1-oxide molecules.[10]

Similar conclusions on the configuration of the phenylmethylpenicillin sulfoxides and phthalimidopenicillin sulfoxides have been reached independently by Barton, Comer, and Sammes.[11]

(7) In the 6α series the phthalimido group no longer presents a large steric hindrance to the formation of expected solute–solvent collision complexes.

(8) The solvent and anisotropy shifts for the β- and α-sulfoxides agree with the values obtained previously for the phenoxymethylpenicillin sulfoxides (ref 1 and R. A. Archer and P. V. DeMarco, *J. Am. Chem. Soc.*, **91**, 1530 (1969).

(9) K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *Chem. Commun.*, 759 (1966); P. C. Lauterbur, J. G. Pritchard, and R. L. Vollmer, *J. Chem. Soc.*, 5307 (1963); P. B. Sollman, R. Nagarajan, and R. M. Dodson, *Chem. Commun.*, 552 (1967).

(10) J. B. Lambert and R. G. Keske, *J. Am. Chem. Soc.*, **88**, 620 (1966); J. B. Lambert and R. G. Keske, *J. Org. Chem.*, **31**, 3429 (1966).

(11) D. H. R. Barton, F. Comer, and P. G. Sammes, *J. Am. Chem. Soc.*, **91**, 1529 (1969). We thank these authors for their information.

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Stereoisomerism of Penicillin Sulfoxides

Sir:

Penicillins have long been known to form a single sulfoxide derivative[1] although two isomers are, of course, possible.[2] We have now found that oxidation of methyl 6β-phenylacetamidopenicillanate (I) by iodobenzene dichloride in aqueous pyridine[3] gives rise to two sulfoxides in an approximately 1:1 ratio. The less polar isomer was the normal crystalline sulfoxide II,[1] mp 128°, $[\alpha]_D$ +262° (*c* 1.1, dioxane), while the more polar sulfoxide (III) could only be obtained as an amorphous solid,[4] $[\alpha]_D$ +153° (*c* 1.6, dioxane). On heating the latter compound (III) in benzene it is converted into the crystalline isomer **II**. These compounds showed the pmr signals presented in Table I. The occurrence of a *syn*-axial effect[5] should result in deshielding of the protons at positions 3 and 6 in the penicillin nucleus, both protons being in similar geometrical relationship to the sulfur atom (see molecular models). Such an effect is observed for II but not for III and, therefore, one can assign II as the *S* isomer.[6] The vicinal proton at position 5 shows an upfield shift in both sulfoxides as well as in sulfone IV. The large upfield shift in sulfoxide III is possible due to the shielding caused by the *trans*-oriented lone pair on the sulfur atom; Lambert and Keske have reported a similar effect in thiane 1-oxide.[7] One of the geminal methyl groups in both sulfoxides is also deshielded by the *syn*-axial effect.

Solvent-induced chemical shifts were also valid in assignment of stereochemistry. According to Ledaal[8] one would predict a large upfield shift for the proton at position 5 in II on changing from deuteriochloroform to deuteriobenzene, since a collision complex with benzene molecules can form from the required less hindered side (see Figure 1); however, in III approach of solvent molecules would be from the other, less accessible side of the penicillin molecule. These results are summarized in Table II.

The preferential formation of the *S*-sulfoxide II by most oxidizing agents, including sodium metaperiodate, hydrogen peroxide, peracids, and even ozone, which tends to oxidize normal sulfides by steric approach control,[9] suggests that a powerful directing influence

(1) H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., "The Chemistry of Penicillin," University Press, Princeton, N. J., 1949, p 156.

(2) For examples see D. Barnard, L. . Bateman, and J. I. Cunneen, "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press Inc., New York, N. Y., 1961, p 229.

(3) G. Barbieri, M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc., C*, 659 (1968).

(4) All new compounds gave satisfactory analytical values.

(5) A. B. Foster, J. M. Duxbury, T. D. Inch, and J. M. Webber, *Chem. Commun.*, 881 (1967); K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *ibid.*, 759 (1966); R. Nagarajan, B. H. Choller, and R. M. Dodson, *ibid.*, 550 (1967); P. B. Sollman, R. Nagarajan, and R. M. Dodson, *ibid.*, 552 (1967).

(6) Similar results, as well as an X-ray determination on the normal *S*-sulfoxide of 6β-phenoxyacetamidopenicillanic acid, have been independently observed by R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Am. Chem. Soc.*, **91**, 1408 (1969). We thank Dr. Cooper for this information.

(7) J. R. Lambert and R. G. Keske, *ibid.*, **88**, 620 (1966); *J. Org. Chem.*, **31**, 3429 (1966).

(8) T. Ledaal, *Tetrahedron Letters*, 1683, (1968).

(9) C. R. Johnson and D. McCants, Jr., *J. Am. Chem. Soc.*, 87, 1109 (1965).