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).

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(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.

R. D. G. Cooper, Paul V. DeMarco, Douglas O. Spry
The Lilly Research Laboratories
Eli Lilly and Company Indianapolis, Indiana
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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).

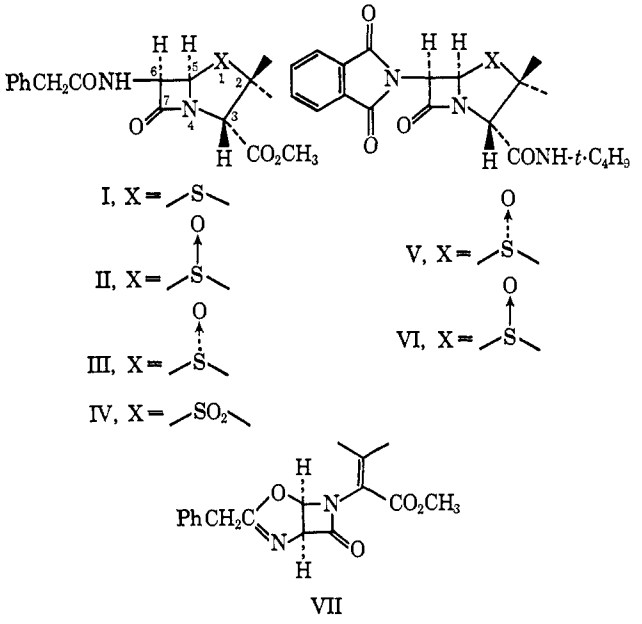
(8) T. Ledaal, *Tetrahedron Letters*, 1683, (1968).

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

Table I. Proton Magnetic Resonance Values[a]

Group	I	II	III	IV	II-I[b]	III-I
2-CH_3	8.55	8.83	8.76	8.68	+0.28	+0.21
2-CH_3	8.55	8.35	8.41	8.50	−0.21	−0.14
H-3	5.61	5.43	5.67	5.62	−0.18	+0.06
H-5	4.47 d (4 Hz)	5.08 d (4 Hz)	5.38 (4 Hz)	5.34 d (4 Hz)	+0.61	+0.91
H-6	4.39 dd (4, 11 Hz)	4.05 dd (4, 10 Hz)	4.79 dd (4, 7 Hz)	3.9 dd (4, 11 Hz)	−0.24	+0.40
NH	3.7 b	2.94 d (10 Hz)	3.18 d (7 Hz)	3.15 d (11 Hz)		
CH_2	6.30	6.47	6.46	6.46		
Ph	2.69 b	2.76 b	2.76 b	2.77[b]		
CH_3O	6.26	6.26	6.27	6.27		

[a] As τ values, in $CDCl_3$ with tetramethylsilane as internal reference, measured on a Varian HA-100 instrument as 10% w/v solutions; d, doublet; b, broad signal. [b] Positive values indicate upfield shifts, negative values downfield shifts relative to the starting sulfide.



must be present in the penicillin molecule. Models show that the 6β-amide proton could hydrogen bond with oxidants, thus directing their approach.[10] For 6β-phthalimidopenicillanate as its *t*-butylamide,[11] in which there is no 6β-amide proton, oxidation with *m*-chloroperbenzoic acid gave, directly, the sulfoxide V as an amorphous solid, $[\alpha]D$ +107° (*c* 1.3, dioxane), and none of the isomeric sulfoxide VI. Again pmr solvent shifts were valuable in assignment of stereochemistry.

The mechanism of the oxidation of I with iodobenzene dichloride must proceed by a two-step reaction in which the intermediate, either a complex or a sulfonium chloride, is capable of being hydrogen bonded by the amide side chain. Hydrolysis then proceeds with inversion about sulfur[12] to give, besides the normal sulfoxide (II), the new isomer (III). More direct participation of the side chain, such as formation of a N-chloramide, cannot be ruled out; one of the minor side products in the oxidation was the oxazoline VII, mp 127°, which is also formed by treatment of I with *t*-butyl hypochlorite and triethylamine.[13]

(10) H. B. Henbest, *Proc. Chem. Soc.* (London), 159 (1963); L. Goodman, S. Winstein and R. Boschan, *J. Am. Chem. Soc.*, 80, 4312 (1958).

(11) A complication with certain oxidants was the isomerization of the 6β-phthalimido group; *cf.* S. Wolfe and W. S. Lee, *Chem. Commun.*, 242 (1968).

(12) *Cf.* T. Higuchi, I. H. Pitman, and K. H. Gensch, *J. Am. Chem. Soc.*, 88, 5676 (1966); C. R. Johnson, *ibid.*, 85, 1020 (1963).

Table II. Solvent Shifts in Isomeric Sulfoxides[a]

Group	II	III
2-CH_3	+0.64	+0.09
2-CH_3	+0.41	+0.24
H-3	−0.07	−0.05
H-5	+0.99	+0.34
H-6	+0.04	+0.88

[a] Positive values indicate upfield shifts, negative values downfield shifts; *i.e.*, values as $\tau_{C_6D_6} - \tau_{CDCl_3}$. The values were calculated from chemical shifts, extrapolated to infinite dilution, measured on a Varian HA-100 instrument.

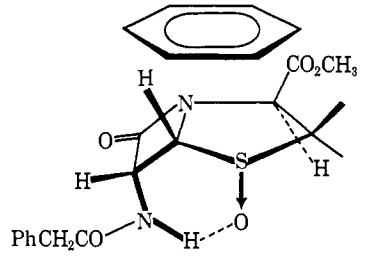


Figure 1. Solvation of sulfoxide II.

Acknowledgment. We thank Glaxo Research, Greenford, England, for a supply of penicillin G used in this work.

(13) J. C. Sheehan, "Molecular Modification in Drug Design," Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, p 15.

(14) Postdoctoral Fellow of the National Research Council of Canada.

D. H. R. Barton, F. Comer,[14] P. G. Sammes
Department of Chemistry, Imperial College
London, S.W.7, England
Received October 7, 1968

Photochemical Preparation and Conformational Analysis by Proton Magnetic Resonance of Penicillin (*R*)-Sulfoxides[1]

Sir:

Oxidation of penicillins by a variety of methods leads to a single sulfoxide which in the case of phenoxymethylpenicillin has been unequivocally established to have the *S* configuration by X-ray crystallography.[2]

(1) Photochemistry of Sulfoxides. II. For paper I, see R. A. Archer and B. S. Kitchell, *J. Am. Chem. Soc.*, 88, 3462 (1966).

(2) R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *ibid.*, 91, 1408 (1969).