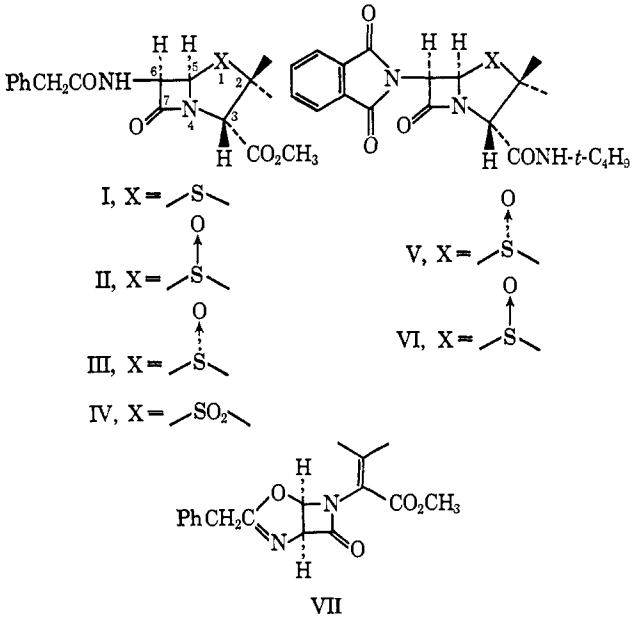
Table I. Proton Magnetic Resonance Values[a]

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.

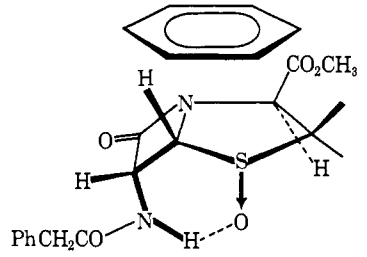


Figure 1. Solvation of sulfoxide II.

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.

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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).

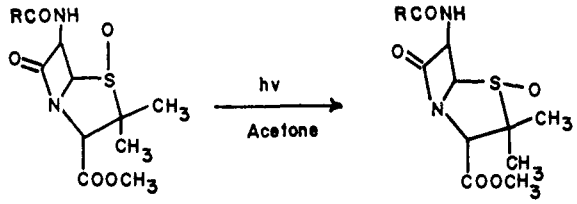
(2) R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *ibid.*, 91, 1408 (1969).

Table I. N–H Proton Shifts[a,b]

Compound	δ_{CDCl_3}	$\delta_{DMSO\text{-}d_6}$	Δ^c
Phenoxymethylpenicillin (**6**)	7.83	8.64	1.26
Phenoxymethylpenicillin (*S*)-sulfoxide (**2**)	8.27	8.27	0.00
Phenoxymethylpenicillin (*R*)-sulfoxide (**4**)	7.34	9.21	1.87
Phenoxymethylpenicillin sulfone (**8**)	8.14	8.39	0.25
Methylpenicillin (**5**)	6.35	8.64	2.29
Methylpenicillin (*S*)-sulfoxide (**1**)	7.03	7.81	0.78
Methylpenicillin (*R*)-sulfoxide (**3**)	6.65	9.00	2.35
Methylpenicillin sulfone (**7**)	6.84	8.48	1.64

[a] N–H shifts of the methyl esters reported in parts per million relative to TMS as internal standard. [b] Chemical shifts were recorded at 100 Hz in the frequency-sweep mode and were read directly from the frequency counter. Shift values reported are thus expected to be accurate to ±0.05 Hz. Sample concentrations were all less than approximately 5% w/v. [c] $\Delta = \delta_{CDCl_3} - \delta_{DMSO\text{-}d_6}$.

Because attempts to prepare the (*R*)-sulfoxides by oxidative methods or by chemical inversion of the (*S*)-sulfoxides using the trimethyloxonium fluoroborate method[3] were unsuccessful, our attention turned to the possibility of photochemically inverting the penicillin (*S*)-sulfoxides. We now wish to report the preparation of penicillin (*R*)-sulfoxides by a photochemical inversion of the *S* isomers together with a discussion of the conformation of the *R* isomers compared with other penicillin models.



1, R = CH_3
2, R = $C_6H_5OCH_2$

3, R = CH_3
4, R = $C_6H_5OCH_2$

Irradiation of methylpenicillin (*S*)-sulfoxide methyl ester (**1**) in acetone (Pyrex filter; He atmosphere; 450-W Hanovia medium-pressure Hg arc lamp) gives a single product which is separated from unreacted starting material as an amorphous glass by column chromatography on silica gel. The following is offered as evidence for the assignment to this product of the (*R*)-sulfoxide structure **3**: α_D +186° (1%, dioxane);[4] mol wt 288 and empirical formula $C_{11}H_{16}N_2O_5S$ confirmed by high-resolution mass spectrometry;[5] ir ($CHCl_3$) 1800 (β-lactam C=O), 1760, 1680, and 1050 cm^{-1} (sulfoxide); nmr ($CDCl_3$) δ 1.32 (s, 3, CH_3), 1.70 (s, 3, CH_3), 2.09 (s, 3, CH_3CONH), 3.83 (s, 3, $COOCH_3$), 4.38 (s, 1, H_3), 4.72 (d, 1, J = 4 Hz, H_5), and 5.51 (q, 1, J = 4 and 9 Hz, H_6). The presence of the β-lactam is thus confirmed by both ir and nmr spectral evidence. Additionally, the coupling constant of 4 Hz between H_5 and H_6 dictates the *cis* orientation of these protons since vicinal *trans*-β-lactam protons display a coupling of approximately 2 Hz.[6]

A chemical verification of the structure was obtained by oxidizing the *R* isomer **3** with *m*-chloroperbenzoic acid in refluxing $CHCl_3$ to a sulfone (**7**) which was identical with the sulfone obtained by similar oxidation of the (*S*)-sulfoxide **1**. Although refluxing benzene converts **3** to **1**, refluxing $CHCl_3$ did not effect the same conversion in the amount of time used in the oxidation.

Irradiation of phenoxymethylpenicillin (*S*)-sulfoxide methyl ester (**2**) in a similar manner to the above method gives the *R* isomer **4**: nmr ($CDCl_3$) δ 1.32 (s, 3, CH_3), 1.68 (s, 3, CH_3), 3.83 (s, 3, $COOCH_3$), 4.41 (s, 1, H_3), 4.58 (s, 2, CH_2), 4.78 (d, 1, J = 4 Hz, H_5), 5.55 (q, 1, J = 4 and 9 Hz, H_6), and 7.1 (m, 5, aromatic protons).

A strong intramolecular hydrogen bond between the amide proton and oxygen of the (*S*)-sulfoxide **2** was inferred from the results of an earlier pmr study[2] of the hydrogen-bonding properties of the amide proton of **2**. The observations which supported this conclusion were: (a) the resonance position of the amide proton of **2**, δ 8.27, arises at a considerably lower field value than the corresponding amide proton of the sulfide **6**, δ 7.83, and (b) the amide proton of **2** suffers no appreciable shift to lower field in DMSO-d_6 solution relative to $CDCl_3$ while the analogous amide proton of **6** is shifted to lower field by 1.26 ppm (see Table I).

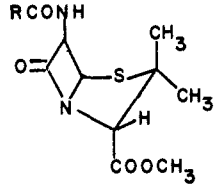
Extending these hydrogen-bonding studies to the (*R*)-sulfoxides **3** and **4**, we anticipated that the distance (approximately 3.4 Å as measured from Dreiding models) between amide proton and sulfoxide oxygen would be too great for the existence of an intramolecular hydrogen bond of more than nominal strength. This proved to be the case. The amide protons of the *R* isomers **3** and **4** resonate at higher field than the corresponding protons of the *S* isomers **1** and **2** and in addition suffer appreciable shifts to lower field in DMSO-d_6 solution relative to $CDCl_3$ (see Table I).

The observed difference of 0.78 ppm in solvent-induced shifts between the amide proton of **1** and **2** is interpreted to indicate that the intramolecular hydrogen bond in **1** is partially disrupted by intermolecular hydrogen bonding to the solvent molecules. Thus, the strength of the intramolecular hydrogen bond formed in these systems is considered to be greater in **2** than in **1**.

Information regarding the conformation of the thiazolidine ring in the (*R*)-sulfoxides **3** and **4** is obtained from a study of internal nuclear Overhauser effects[7,8] (NOE) in these compounds. Irradiation at the low-field methyl signals in the nmr spectra of **3** and **4** results in integrated intensity increases of approximately 20 ± 3% for H_3 only while irradiation at the high-field

(3) C. R. Johnson, *J. Am. Chem. Soc.*, 85, 1020 (1963).
(4) Rotation of *S* isomer **1**: α_D +278° (1%, dioxane).
(5) Satisfactory analyses were obtained for all new compounds.
(6) I. McMillan and R. J. Stoodley, *Tetrahedron Letters*, 1205 (1966).
(7) F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, 87, 5250 (1965).
(8) R. H. Martin and J. C. Nouls, *Tetrahedron Letters*, 2727 (1968), and references cited therein.

methyl signals results in intensity increases of 13 ± 3% for H_5 only. These results require that H_3 be in spatial proximity to the low-field methyl group (which must therefore be assigned the β orientation) and that H_5 be in spatial proximity to the high-field methyl group (which must therefore be assigned the α orientation). Thus, the thiazolidine ring conformation of the (*R*)-sulfoxides is approximately the same as the conformation of the (*S*)-sulfoxides and considerably different from the conformations of the parent sulfides, **5** and **6**.



5, R = CH_3
6, R = $C_6H_5OCH_2$

The observed shift of 0.80 ppm to higher field for H_5 in going from either of the sulfides **5** or **6** to the corresponding (*R*)-sulfoxides **3** or **4** is unexpected in light of the present concepts of the screening environment associated with the sulfoxide bond.[2,9,10] Since H_5 in the *R* isomers is located in the deshielding region of the sulfoxide bond, a shift to lower field when compared with the same proton in the parent sulfide was expected. Perhaps differences in side-chain conformations originating from differences in intramolecular hydrogen bonding in the sulfoxide isomers play an important role in explaining this anomalous observation. However, lack of quantitative agreement obtained in a recent study[2] as well as qualitative and quantitative discrepancies observed for protons adjacent to the sulfoxide bond in a number of model *t*-butylthiane sulfoxides[11] and 1,4-oxathiane S-oxides[12] suggest that the presently accepted model for the screening environment associated with the sulfoxide bond may be more complicated than previously assumed, especially for protons adjacent to the sulfoxide bond.

(9) K. W. Buck, *et al.*, *Chem. Commun.*, 759 (1966).
(10) P. B. Sollman, R. Nagarajan, and R. M. Dodson, *ibid.*, 552 (1967).
(11) To be published.
(12) A. B. Foster, *et al.*, *Chem. Commun.*, 1086 (1968).

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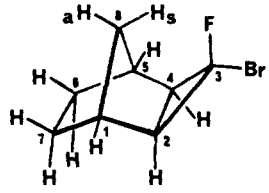
The Stereochemical Requirements for Proton–Fluorine Spin–Spin Coupling over Five Bonds[1]

Sir:

Numerous cases have been recorded of proton–fluorine spin–spin coupling over five bonds ($^5J_{HF}$). From examination of various fluoro steroids, Cross has formulated the geometric requirement for such coupling as the "converging vector rule."[2] From other examples, it is clear that the magnitude of the coupling is closely related to the internuclear distance between the coupled hydrogen and fluorine atoms.[3-5] Unfortunately, all these cases of $^5J_{HF}$ coupling deal exclusively with methyl protons.[6] Thus, the exact arrangement of the nuclei undergoing interaction is unknown as the particular proton or protons responsible cannot be specified. We now report results obtained from *syn*-3-fluoro-*anti*-3-bromo-*exo*-tricyclo[3.2.1.$0^{2,4}$]-octane (I) in which the spatial relation of the coupling



I

fluorine and hydrogen atoms is precisely defined by the rigid framework of the molecule.[7]

At 94.1 MHz the ^{19}F resonance of I shows as a quintuplet at 146 ppm upfield from trichlorofluoromethane, thereby indicating that the fluorine atom couples to just four protons to about the same extent ($J_{FH} \sim 3.5$ Hz) (Figure 1). It can be reasonably assumed that two of these protons are the vicinal ones on C_2 and C_4.[8] An immediate clue to the identity of the other two is provided by the additional multiplicity displayed by the resonances of the *syn* and *anti* C_8 protons (Figure 2).[9] These additional splittings are unexpectedly large: 3.6 and 3.0 Hz for the *syn* and *anti* protons; moreover, they

(1) To be regarded as part XIX of a series entitled "The Stereochemistry of Bicyclo[3.2.1]octane." For part XVIII see C. W. Jefford and W. Wojnarowski, *Tetrahedron*, in press.

(2) A. D. Cross and P. W. Landis, *J. Amer. Chem. Soc.*, **86**, 4005 (1964); A. D. Cross, *ibid.*, **86**, 4011 (1964).
(3) D. R. Davis, R. P. Lutz, and J. D. Roberts, *ibid.*, **83**, 246 (1961); M. Takahashi, D. R. Davis, and J. D. Roberts, *ibid.*, **84**, 2935 (1962); D. F. Evans, S. L. Manatt, and D. D. Elleman, *ibid.*, **85**, 238 (1963); M. S. Newman, R. G. Mentzer, and G. Slomp, *ibid.*, **85**, 4018 (1963); A. Lewin, *ibid.*, **86**, 2303 (1964); J. Burdon, *Tetrahedron*, **21**, 1101 (1965); J. P. N. Brewer, H. Heaney, and B. A. Marples, *Chem. Commun.*, 27 (1967).
(4) P. C. Myrhe, J. W. Edmonds, and J. D. Kruger, *J. Amer. Chem. Soc.*, **88**, 2459 (1966).
(5) This statement is based on ref 4. However, the relationship is open to question when dissimilar systems are being compared as the effect of substituents on J_{HF} is unusually large and is not well understood (*cf.* ref 8).
(6) A solitary case dealing with methylene protons constitutes an apparent exception to both the converging vector and the proximity rules (A. B. Foster, R. Hems, L. D. Hall, and J. F. Manville, *Chem. Commun.*, 158 (1968).
(7) Compound I is a product obtained by the action of fluorobromocarbene on norbornene (C. W. Jefford and D. T. Hill, manuscript submitted for publication); proton nmr spectra of the *anti*-chloro analog of I (L. Ghosez, G. Slinckx, M. Glineur, P. Hoet, and P. Laroche, *Tetrahedron Lett.*, 2773 (1967)) were examined and found to be in agreement.
(8) The present value of $^3J_{HF}$ is small compared with that reported for the structurally similar 1-chloro-1-fluoro-2,2-diphenylcyclopropane ($^3J_{HF}$ = 6.3 Hz: K. L. Williamson, Y.-F. Li, F. H. Hall, and S. Swager, *J. Amer. Chem. Soc.*, **88**, 5678 (1966)) and *exo*-7-bromo-*endo*-7-fluoronorcarane ($^3J_{HF}$ = 13.0 Hz; T. Ando, F. Namigata, H. Yamanaka, and W. Funasaka, *ibid.*, **89**, 5719 (1967)). However, $^3J_{HF}$ is notoriously sensitive to substituents (C. W. Jefford, D. T. Hill, and K. C. Ramey, paper submitted for publication).
(9) It will be seen from Figure 2 that only a portion of the AB pattern for the *syn* C_8 is observable as the upfield branch is obscured by overlap with other resonances. Nevertheless the assignment is assured by a knowledge of the shielding experienced in the *exo*-tricyclo[3.2.1.$0^{2,4}$]-octane skeleton (C. W. Jefford and R. T. Medary, *Tetrahedron*, **23**, 4123 (1967)).