Structural Studies on Penicillin Derivatives. I. The Configuration of Phenoxymethyl Penicillin Sulfoxide

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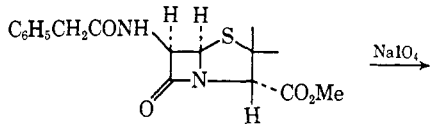
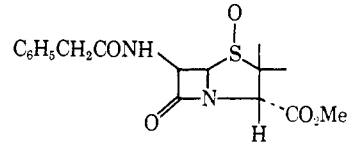
Abstract: From a study of nuclear Overhauser effects (NOE) in phenoxymethyl penicillin (III), phenoxymethyl penicillin sulfoxide (IV), and phenoxymethyl penicillin sulfone (V), it has been possible to assign the methyl signals in the nmr spectra of these compounds and to derive information regarding thiazolidine ring conformation in solution. Using the McConnell approach to chemical-shift calculations, aromatic solvent-induced shifts (ASIS), and hydrogen-bonding studies, the sulfoxide configuration of IV is indicated to be (*S*). The configuration of the sulfoxide IV is verified by an X-ray crystallographic investigation which also shows that basic conformational differences exist between III and IV. The molecular anisotropy of the sulfoxide bond is discussed in both qualitative and quantitative terms. A mechanistic rationale for the formation and existence of one isomer of IV is presented.

The first oxidation of a penicillin to its sulfoxide was reported by Sykes and Todd[1] who converted methyl benzylpenicillinate (I) to its sulfoxide (II) using sodium metaperiodate.



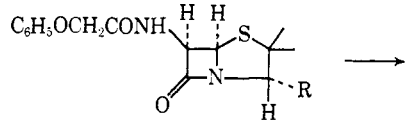
I



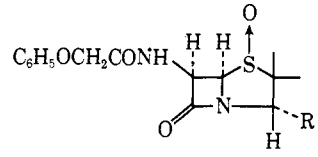
II

Several groups of workers[2-4] have since reported the oxidation of various penicillin derivatives to their corresponding sulfoxides.

Theoretically, two sulfoxide isomers could exist; however, no reference has been made to this possibility in the literature nor has there been any report of the oxidation of a penicillin giving rise to a diastereoisomeric mixture.



III



IV

From work in these laboratories in 1957, it was established[5] that the oxidation of phenoxymethyl penicillin (III, R = CO_2H) gave only one sulfoxide as determined by the usual physical chemical criteria. Moreover, extensive variations[6] of the oxidizing agent (hydrogen peroxide, *m*-chloroperbenzoic acid, sodium metaperiodate, and ozone) and solvent gave a single sulfoxide isomer.

The elegant work of Morin and coworkers[7] in converting methyl phenoxymethyl penicillinate sulfoxide into methyl phenoxymethyl desacetoxycephalosporinate prompted us to investigate the configuration of the penicillin sulfoxides as a first step in understanding the mechanistic pathway of the Morin rearrangement.

In spite of previous work which indicated that only one sulfoxide exists, we examined several modifications of the penicillin molecule and reaction conditions in attempts to obtain the other isomer. However, variations of substituents at position 6 ($C_6H_5CH_2CONH$–, MeCONH–, $C_6H_5OCH_2CONH$–) and position 3 (R = CO_2Me, $CO_2CH_2CCl_3$, CH_2OH, CONH, CONH-*t*-Bu) together with variations in the oxidation conditions gave in all cases only one sulfoxide isomer.

There are several known methods[8,9] for the inversion or racemization of a sulfoxide and application of these methods to methyl phenoxymethyl penicillinate sulfoxide (IV, R = CO_2Me) gave either recovered starting material (using trimethyloxonium fluoroborate) or rapid decomposition with no observable isomerization of the sulfoxide (using acetyl chloride).

We considered that the best approach to use initially in determining the sulfoxide configuration was that of nuclear magnetic resonance, a method used by Morin, *et al.*,[10] in arriving at the suggested configuration of IV as being IVa.

(1) P. Sykes and A. R. Todd, Committee on Penicillin Synthesis Reports 526, 677, "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, pp 156, 927, 946, 1008.

(2) A. W. Chou, N. M. Hall, and J. R. E. Hoover, *J. Org. Chem.*, **27**, 1381 (1962).

(3) E. Guddol, P. Morch, and L. Tybring, *Tetrahedron Letters*, **No. 9**, 381 (1962).

(4) J. M. Essery, K. Dabado, W. J. Gottstein, A. Hullstrand, and L. C. Cheney, *J. Org. Chem.*, **30**, 4388 (1965).

(5) E. Flynn, Eli Lilly and Company, private communication.

(6) R. B. Morin, Eli Lilly and Company, private communication.

(7) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **85**, 1896 (1963).

(8) C. Johnson and D. McCants, Jr., *ibid.*, **87**, 5404 (1965).

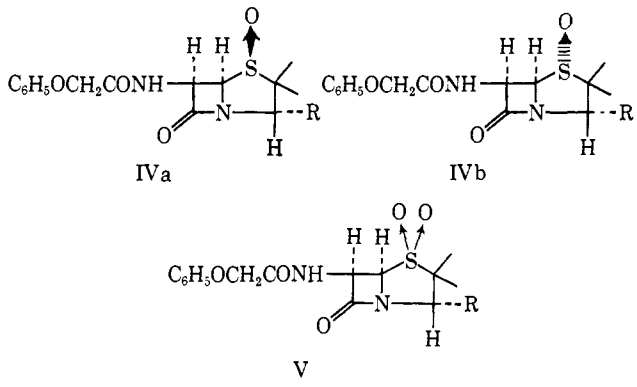
(9) (a) E. Jonsson, *Tetrahedron Letters*, 3675 (1967); (b) S. Oae and M. Kise, *Tetrahedron Letters*, 1409 (1967).

(10) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **91**, 1401 (1969).

Table I. Nuclear Overhauser Effects (NOE) in Phenoxymethyl Penicillin, Phenoxymethyl Penicillin Sulfoxide, and Phenoxymethyl Penicillin Sulfone Derivatives

Compound	Protons irradiated δ, ppm[a]	Proton obsd	Intensity increase, % (±3)[b] CCl_4	C_6D_6
Phenoxymethyl penicillin (III, R = COOMe)	Low-field methyl (1.54) [1.20]	H_3	21	22
		H_5	Nil	Nil
	High-field methyl (1.45) [1.18]	H_3	7	12
		H_5	Nil	Nil
Phenoxymethyl penicillin sulfoxide (IV, R = COOMe)	Low-field methyl (1.70) [1.25]	H_3	26	27
		H_5	Nil	Nil
	High-field methyl (1.18) [0.51]	H_3	Nil	Nil
		H_5	14	14
Phenoxylmethyl penicillin sulfone (V, R = $CO_2CH_2CCl_3$)	Low-field methyl (1.67) [1.21]	H_3	22	18
		H_5	Nil	Nil
	High-field methyl (1.47) [1.05]	H_3	Nil	Nil
		H_5	11	10

[a] Figures in parentheses and square brackets indicate resonance positions in CCl_4 and C_6D_6 solutions, respectively. [b] Given as the percentage increase in integrated intensity on irradiation. All NOE experiments were carried out on nitrogen-sparged solutions (sample concentrations were *ca.* 8% w/v) with TMS as internal field frequency lock in carbon tetrachloride and benzene (9% of solution) as internal field frequency lock in deuteriobenzene.



Nuclear Magnetic Resonance Studies

In order for nmr chemical-shift calculations and solvent-shift studies to be meaningful, chemical-shift assignments for the various protons must be unequivocal. These can be made for protons H_3, H_5, and H_6 from their splitting patterns (H_3 = singlet, H_5 = doublet, H_6 = quartet). However, as both the geminal methyl protons (2α-CH_3 and 2β-CH_3) appear as singlets, unequivocal assignment of these methyl protons to specific signals in their nmr spectra is not possible based on chemical shift information alone.

Previous X-ray studies[11] of several salts of benzyl penicillanic acid together with our X-ray investigation of IV established that the conformation of the thiazolidine ring, which as shown in Figure 1 may be a or b, is the former for the sulfide and the latter for the sulfoxide. However, since X-ray studies are carried out in the solid state, it remained to be proven that these were the conformations adopted in solution. Any attempt to treat the sulfoxide bond anisotropy in a quantitative manner makes it imperative to assess first any thiazolidine ring conformational changes between solutions of III, IV, and the corresponding sulfone (V).

Nuclear Overhauser Effects (NOE) in Penicillin Derivatives

In order to circumvent ambiguity in the chemical-shift assignment of the methyl protons and to obtain information regarding the conformational nature of the thiazolidine ring in solution in these systems, a study of *internal nuclear Overhauser effects*[12] (NOE) in some derivatives of III, IV, and V was undertaken. The results of this study are summarized in Table I.

From the NOE studies,[12] it has been possible to determine experimentally which protons in conformationally rigid systems are situated proximal to each other. As a result, this technique provides us with a method for ascertaining the relative spatial proximity of the different protons in the penicillin systems studied (III–V) and consequently allows a complete chemical-shift assignment of the methyl proton signals and an assessment of conformation differences between III, IV, and V in solution.

Conformation a necessitates that the 2β- and 2α-methyl groups lie close to H_3 (r = 2.1 and 2.5 Å, respectively)[13] whereas in conformation b only the 2β-methyl protons are situated proximal to H_3 (r = 2.1 Å). Thus the β-methyl protons in either conformation should contribute to the intramolecular relaxation of H_3 while, to a lesser degree, the α-methyl protons should relax H_3 in conformation a only. Additionally, in conformation b, proton H_5 should be relaxed by the 2α-methyl protons (r = 2.4 Å) whereas in conformation a, the distance between H_5 and the 2α-methyl protons is too

(11) D. Crowfoot, C. W. Bunn, B. W. Rodgers-Low, and A. Turner-Jones, "Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p 310.

(12) F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, **87**, 5250 (1965); R. H. Martin and J. C. Nouls, *Tetrahedron Letters*, 2727 (1968), and references cited therein.

(13) The values quoted here for r indicate the distance of closest approach made by the methyl protons and tertiary protons situated at C(3) and C(5) as measured from Dreiding models.

Table II. Proton Resonance Data[a] for the Various Phenoxymethyl Penicillin (III), Phenoxymethyl Penicillin Sulfoxide (IV), and Phenoxymethyl Penicillin Sulfone (V) Derivatives Studied[b]

Compd	Solvent	Resonance							
		H_3	H_5	H_6	2α-Me[c]	2β-Me[c]	CO_2CH_3	CH_2[d]	$CO_2CH_2CCl_3$
III, R = COOMe	CCl_4	4.36	5.53	5.62	1.45	1.54	3.73	4.48	
	$CDCl_3$	4.47	5.58	5.74	1.49	1.60	3.78	4.56	
	C_6D_6	4.39	5.11	5.54	1.13	1.20	3.15	4.07	
IV, R = COOMe	CCl_4	4.59	4.95	6.02	1.18	1.70	3.79	4.48	
	$CDCl_3$	4.69	5.03	6.10	1.23	1.73	3.82	4.54	
	C_6D_6	4.65	3.77	5.93	0.51	1.25	3.09	4.19 (15), 3.95 (15)	
III, R = CD_2OH	CCl_4	3.88	5.34	5.60	1.46	1.49		4.52	
	$CDCl_3$	3.94	5.38	5.68	1.49	1.49		4.56	
	C_6D_6	3.61	4.61	5.56	0.96	1.12		4.09	
IV, R = CD_2OH	CCl_4	4.07	4.86	5.95	1.27	1.59		4.49	
	$CDCl_3$	4.14	4.90	6.02	1.29	1.62		4.54	
	C_6D_6	3.91	3.63	5.96	0.49	1.13		4.20 (15), 3.97 (15)	
III, R = CONH-*t*-Bu	CCl_4	4.09	5.39	5.72	1.54	1.75		4.53	
	$CDCl_3$	4.09	5.39	5.82	1.54	1.75		4.53	
	C_6D_6	4.12			1.32	1.52		3.99	
IV, R = CONH-*t*-Bu	CCl_4	4.36	4.90	6.03	1.22	1.78		4.48	
	$CDCl_3$	4.48	4.98	6.14	1.26	1.81		4.55	
	C_6D_6	4.53	3.58	5.93	0.68	1.55		4.18 (15), 3.95 (15)	
III, R = $CO_2CH_2CCl_3$	CCl_4	4.49	5.58	5.68	1.56	1.60		4.48	4.82 (12), 4.67 (12)
	$CDCl_3$	4.60	5.62	5.77	1.59	1.66		4.56	4.86 (12), 4.71 (12)
	C_6D_6	4.45	5.11	5.53	1.20	1.22		4.06	4.35 (12), 4.14 (12)
IV, R = $CO_2CH_2CCl_3$	CCl_4	4.74	5.00	6.07	1.29	1.78		4.50	5.00 (12), 4.66 (12)
	$CDCl_3$	4.82	5.06	6.12	1.32	1.82		4.55	5.03 (12), 4.67 (12)
	C_6D_6	4.74	3.77	5.94	0.64	1.36		4.19 (15), 3.95 (15)	4.49 (12), 3.87 (12)
V, R = $CO_2CH_2CCl_3$	CCl_4	4.58	4.75	6.17	1.47	1.67		4.53	5.08 (12), 4.66 (12)
	$CDCl_3$	4.66	4.82	6.19	1.51	1.69		4.56	4.99 (12), 4.68 (12)
	C_6D_6	4.48	3.68	5.89	1.05	1.21		3.93	4.38 (12), 3.88 (12)

[a] In parts per million. Sample concentrations were *ca.* 2–3% w/v. At this concentration solute–solvent interactions are expected to be negligible. [b] *J* values in hertz in parentheses. [c] Methyl groups are correctly assigned based on results obtained from NOE studies on these systems. [d] CH_2 refers to the methylene protons in the phenoxymethyl penicillin side chain.

Table III. Chemical Shifts[a] Observed for the Different Protons in the Penicillin System upon Oxidation to the Corresponding Sulfoxide and Sulfone Derivatives

Example[b]	Solvent	Resonance[c]				
		H_3	H_5	H_6	2α-CH_3	2β-CH_3
$\Delta\delta_{III\rightarrow IV}$	CCl_4	−0.23	+0.58	−0.40	+0.27	−0.16
R = COOMe	$CDCl_3$	−0.22	+0.55	−0.36	+0.26	−0.13
$\Delta\delta_{III\rightarrow IV}$	CCl_4	−0.19	+0.48	−0.35	+0.19	−0.10
R = CD_2OH	$CDCl_3$	−0.20	+0.48	−0.34	+0.20	−0.13
$\Delta\delta_{III\rightarrow IV}$	CCl_4	−0.27	+0.49	−0.31	+0.32	−0.03
R = CONH-*t*-Bu	$CDCl_3$	−0.39	+0.41	−0.32	+0.32	−0.06
$\Delta\delta_{III\rightarrow IV}$	CCl_4	−0.25	+0.58	−0.39	+0.27	−0.18
R = $CO_2CH_2CCl_3$	$CDCl_3$	−0.22	+0.56	−0.35	+0.27	−0.16
$\Delta\delta_{III\rightarrow V}$	CCl_4	−0.09	+0.83	−0.49	+0.09	−0.07
R = $CO_2CH_2CCl_3$	$CDCl_3$	−0.06	+0.08	−0.42	+0.08	−0.03

[a] In parts per million. [b] $\Delta\delta_{III\rightarrow IV} = (\delta_{sulfide} - \delta_{sulfoxide})$, $\Delta\delta_{III\rightarrow V} = (\delta_{sulfide} - \delta_{sulfone})$. [c] Mean observed shift values (±0.05 ppm) in CCl_4 for case of III → IV: $H_3 = -0.23$, $H_5 = +0.53$, $H_6 = -0.35$, 2α-$CH_3 = +0.25$, and 2β-$CH_3 = -0.15$.

large for an expected relaxation of H_5 by the 2α-methyl group.

As the results in Table I indicate, irradiation of the high-field methyl peaks in the nmr spectra of III, IV (R = CO_2Me), and V (R = $CO_2CH_2CCl_3$) results in a 7–12% increase for H_3 in the sulfide (III), whereas in IV and V the increase in H_3 is negligible. For H_5 an increase in intensity is obtained only for IV and V (14 and 11%, respectively). Alternatively, saturation of the low-field methyl group increases the intensity of H_3 in all cases (21–22, 26–27, and 15–22% for III, IV, and V, respectively), no effect at all being observed with H_5.

From the above experimental observations, the following conclusions are drawn concerning III, IV, and V. (1) The 2β-methyl protons may be assigned to the low-field methyl signals in the nmr spectra of derivatives of III, IV, and V (in both CCl_4 and C_6D_6 solutions) since, because of proximity, only 2β-CH_3 protons are capable of relaxing H_3. The high-field methyl signals may consequently be assigned to the 2α-methyl protons. It is noted that no crossover of the methyl signals occurs in these compounds when comparing the nmr spectra taken in carbon tetrachloride with those taken in deuteriobenzene solutions. (2) There exist in solution definite differences between the conformation of the thiazolidine ring in the sulfide (III), sulfoxide (IV), and sulfone (V). This conclusion is established by the observation that, upon irradiation of the 2α-methyl protons, the H_5 signal is enhanced in the sulfoxide (IV) and sulfone (V) but not in the sulfide (III). Only in conformation b can H_5 be relaxed by the 2α-

Table IV. McConnell Calculations for Screening Effect of S→O Bond in Both the (*R*)- and (*S*)-Sulfoxides (IVa and IVb)

Calculations for case of	Proton	θ, deg	R, Å[a]	GF[b]	$\Delta\delta^{-19.2}{}_{calcd}$	$\Delta\delta^{-32.2}{}_{calcd}$	$\Delta\delta_{obsd}$[c]
Sulfide (III)	H_3	20	2.8	+0.01484	−0.28	−0.47	−0.23
β-Sulfoxide (IVa)	H_5	38	3.0	−0.01065	+0.21	+0.35	+0.53
	H_6	80	3.8	+0.00553	−0.11	−0.18	−0.35
	2α-CH_3	28	3.7	−0.00881	+0.17	+0.29	+0.25
	2β-CH_3	80	3.0	+0.01018	−0.20	−0.33	−0.15
Sulfide (III)	H_3	20	3.7	−0.01085	+0.21	+0.35	−0.23
α-Sulfoxide (IVb)	H_5	78	2.6	+0.01651	−0.32	−0.54	+0.53
	H_6	58	4.0	+0.00820	−0.02	−0.03	−0.35
	2α-CH_3	87	3.0	+0.01224	−0.23	−0.39	+0.25
	2β-CH_3	58	3.2	+0.00160	−0.03	−0.05	−0.15

[a] Measurements of θ and R were made on Dreiding models. Each value represents the mean of three measurements on two different models. Values of θ and R were reproducible to ±2° and ±0.1 Å, respectively. [b] GF represents the geometric factor of eq 1, *i.e.*, $GF = (1 - 3\cos^2\theta)/3R^3$. [c] $\Delta\delta_{obsd}$ are the mean shift values (±0.05 ppm) observed (see Table III).

methyl protons; and thus, in solution, the sulfide (III) and sulfoxide (IV) apparently adopt the same conformations as those which exist in the crystal. Also, the sulfone (V) in solution has the same conformation as the sulfoxide (IV). Based on the results obtained from NOE studies of the penicillin derivatives studied (III–V), complete and unambiguous assignments of all relevant protons have been made for a variety of phenoxymethyl penicillin derivatives and are recorded in Table II. From Table II is derived Table III, which summarizes the changes in chemical shifts experienced by the different protons in the phenoxymethyl penicillin nucleus upon oxidation to the sulfoxide (δ(sulfide) − δ(sulfoxide)) and sulfone (δ(sulfide) − δ(sulfone)).

Chemical-Shift Calculations

Previous nmr studies[14–16] of both an empirical and theoretical nature on a variety of different molecular systems containing the sulfoxide bond have led earlier groups to propose that, qualitatively at least, the screening environment around the S→O bond approximates that of the acetylenic triple bond.

Indeed it now appears to be quite firmly established that the sulfur–oxygen bond in sulfoxides is a p^2–pd hybrid double bond, and Burg[17] considers that because of d,p-π overlap the S→O bond is "electronically a triple bond with bond order not less than two." If this is the case, the electronic distribution about an axis through the sulfur and oxygen atoms of the S→O bond must be symmetric or very nearly so.

For bonds which possess axial symmetry, the well-known and extensively invoked McConnell point dipole approximation[18] (see eq 1 below) is an extremely useful expression relating the sign and magnitude of nuclear screening on a given proton to its spatial position relative to the anisotropic function under consideration

$$\sigma = \Delta\chi\frac{(1 - 3\cos^2\theta)}{3R^3} \qquad (1)$$

where R = distance between the proton under study and the electrical center of gravity of the anisotropic bond,[19] θ = the angle between the direction R and the symmetry axis of the anisotropic bond, and $\Delta\chi$ = a constant (anisotropy) characteristic of the bond under consideration.[20]

Consequently, this approach to the calculation of chemical-shift values offers considerable promise as a means of differentiating between the two isomeric sulfoxides (IVa and IVb) and therefore of determining the configuration of the S→O bond in the oxidation product IV. Using eq 1 and the appropriate parameters measured directly from Dreiding models, chemical shift values were calculated for protons H_3, H_5, H_6, 2α-CH_3, and 2β-CH_3 for the two possible stereoisomers IVa and IVb in the change III → IVa and III → IVb (Table IV) and were compared with the mean observed chemical-shift values (see Table III) for these same protons ($\Delta\delta^{obsd} = \delta^{obsd}{}_{sulfide} - \delta^{obsd}{}_{sulfoxide}$). Inspection of the results listed in Table IV indicates that excellent qualitative agreement is attained between observed and calculated shift values for the (*S*)-sulfoxide (IVa) only (*i.e.*, all shifts agree in sign), while similar agreement for the (*R*)-sulfoxide (IVb) is not apparent. Although these conclusions are not unequivocal, the calculated values for the *S* stereoisomer (IVa) are in better agreement (qualitative) with the observed shift values, and thus the S→O bond in the peracid oxida-

(14) K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Quadir, and J. M. Webber, *Chem. Commun.*, 759 (1966); A. B. Foster, J. M. Duxbury, T. D. Inch, and J. M. Webber, *ibid.*, 881 (1966).

(15) P. C. Lauterbur, J. G. Prichard, and R. L. Vollmer, *J. Chem. Soc.*, 5307 (1963).

(16) P. B. Sollman, R. Nagarajan, and R. M. Dodson, *Chem. Commun.*, 552 (1967).

(17) A. B. Burg in "Organic Sulphur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, London, 1961, p 36.

(18) H. M. McConnell, *J. Chem. Phys.*, 37, 226 (1957).

(19) The electrical center of gravity of the S→O bond is assumed to be the midpoint of the bond. Earlier workers [J. G. Pritchard and P. C. Lauterbur, *J. Chem. Soc.*, 2105 (1961)] had reached this conclusion because the nonbonding and valence electrons about sulfur should contribute approximately the same amount to the coordinate susceptibilities as those electrons about oxygen.

(20) Since to our knowledge no reliable values for the S→O bond anisotropy have yet been published, the values used in this work are those reported earlier for the acetylenic bond [S. Castellano and J. Lorenc, *J. Phys. Chem.*, **69**, 3552 (1965); J. A. Pople, *J. Chem. Phys.*, 37, 53 (1962)], *i.e.*, −19.2 and −32.2 × 10^{-30} cm^3 $molecule^{-1}$. This approach is expected to be valid since, if the S→O bond possesses axial symmetry, the sign of the shielding at any given point in space around this bond will be the same as that for the C≡C bond. A correct value for the magnitude of $\Delta\chi$ is not absolutely critical for these calculations since only qualitative agreement is necessary to be indicative of the sulfoxide isomer obtained during oxidation.

Table V. Benzene-Induced Solvent Shifts [$\Delta = \delta(CCl_4)$ or $\delta(CDCl_3) - \delta(C_6D_6)$] for the Different Protons in the Phenoxymethyl Penicillin Derivatives Studied

Compd	Δ, ppm[a]	Resonance[b] H_3	H_5	H_6	2α-CH_3	2β-CH_3	CO_2CH_3
III	Δ^1	−0.03	+0.42	+0.08	+0.32	+0.34	+0.58
R = COOMe	Δ^2	+0.08	+0.47	+0.20	+0.36	+0.40	+0.63
IV	Δ^1	−0.06	+1.18	+0.09	+0.67	+0.45	+0.70
R = COOMe	Δ^2	+0.04	+1.26	+0.17	+0.72	+0.48	+0.73
V	Δ^1	+0.10	+1.07	+0.28	+0.42	+0.46	
R = $CO_2CH_2CCl_3$	Δ^2	+0.18	+1.14	+0.30	+0.46	+0.48	
III	Δ^1	+0.27	+0.73	+0.04	+0.50	+0.37	
R = CD_2OH	Δ^2	+0.33	+0.77	+0.12	+0.53	+0.37	
IV	Δ^1	+0.16	+1.23	−0.01	+0.78	+0.46	
R = CD_2OH	Δ^2	+0.23	+1.27	+0.06	+0.08	+0.49	
III	Δ^1	−0.03			+0.22	+0.23	
R = CONH-*t*-Bu	Δ^2	−0.03			+0.22	+0.23	
IV	Δ^2	−0.17	+1.32	+0.10	+0.54	+0.23	
R = CONH-*t*-Bu	Δ^2	−0.05	+1.40	+0.21	+0.58	+0.26	
III	Δ^1	+0.04	+0.47	+0.15	+0.36	+0.38	
R = $CO_2CH_2CCl_3$	Δ^2	+0.15	+0.51	+0.24	+0.39	+0.44	
IV	Δ^1	0.00	+1.23	+0.13	+0.65	+0.42	
R = $CO_2CH_2CCl_3$	Δ^2	+0.08	+1.29	+0.18	+0.68	+0.46	

[a] $\Delta^1 = \delta(CCl_4) - \delta(C_6D_6)$, $\Delta^2 = \delta(CDCl_3) - \delta(C_6D_6)$. [b] For III (R = CONH-*t*-Bu), data unobtainable due to insolubility.

tion product of phenoxymethyl penicillin is strongly indicated to have the *S* configuration (IVa).

The absence of conformational parity[21] within the compounds whose shifts are compared, the questionable assumption of sulfoxide bond axial symmetry, and the little understood screening effect of the sulfur lone-pair electrons are possible contributing factors to this lack of a quantitative agreement.

Solvent-Shift Studies

Aromatic solvent-induced shifts (ASIS)[22] provide further confirmatory evidence in support of the *S* configuration for the S→O bond in IV. Since it has been experimentally well established that aromatic systems like benzene are capable of coordinating at electron-deficient sites (provided by polar functions) within a solute molecule,[23] solute protons situated in the vicinity of a polar functional group should experience large screening effects as a result of the large anisotropy in the magnetic susceptibility of the associated aromatic system.[24]

Thus, as the sign of nuclear screening experienced by solute protons is dependent upon the relative orientation of both solute and solvent molecules in the associated complex, it was possible, if the geometry of the complex could be inferred or deduced, to determine the orientation of the functional group in question from the sign of the shifts observed for the solute protons.

Recently, Ledall[25] proposed that the geometry of benzene–solute collision complexes involving solutes containing any polar functional group can be rationalized in terms of one common model. The model presumes that the dipole axis of the polar functional group in the solute molecule is located along the sixfold axis of symmetry of the benzene system with the positive end of polar function nearest, and the negative end farthest away from it. The nature of this association is conveniently illustrated for the dimethyl sulfoxide–benzene collision complex (see Figure 2, a), the proposed geometry of which explains the observed solvent-shift value observed for the methyl protons in dimethyl sulfoxide (values in parentheses in parts per million (ppm)).

Assuming that collision complexes of similar geometry are formed between solvent benzene molecules

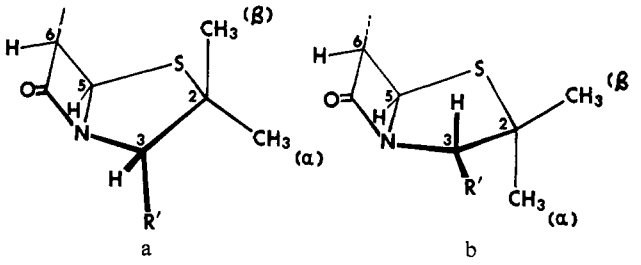


Figure 1. Possible thiazolidine ring conformations.

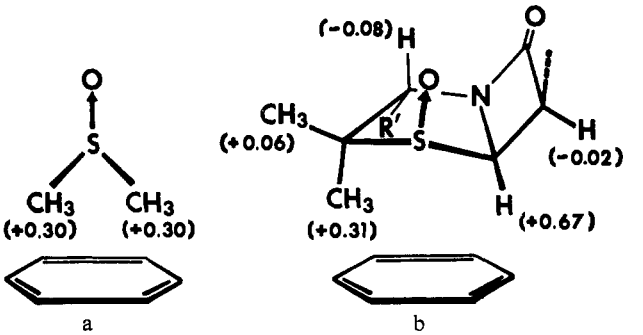


Figure 2. Proposed geometries of benzene–solute collision complexes of dimethyl sulfoxide (a), and phenoxymethyl penicillin-(*S*)-sulfoxide (b).

(21) J. W. ApSimon, W. G. Craig, P. V. DeMarco, D. W. Mathieson, and W. B. Whalley, *Tetrahedron*, 23, 2375 (1967).

(22) P. Lazlo in "Progress in Nuclear Magnetic Spectroscopy," Vol. 3, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, Ltd., London, 1967, p 348.

(23) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 7; J. Ronayne and D. H. Williams, *J. Chem. Soc., B*, 540 (1967), and references cited therein.

(24) J. A. Pople, *J. Chem. Phys.*, 24, 1111 (1956); J. A. Pople, W. G. Shneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp 180–183.

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

Table VI. Benzene-Induced Solvent-Shift Values [$\dot{\Delta}$ = Δ(sulfoxide) − Δ(sulfide)] for the Protons in the Phenoxymethyl Penicillin System Resulting from Solute–Solvent Association of Benzene with the S→O Bond

Case of	$\dot{\Delta}$, ppm[a]	Resonance: H_3	H_5	H_6	2α-CH_3	2β-CH_3	CO_2CH_3
III → IV	$\dot{\Delta}^1$	−0.03	+0.76	+0.01	+0.35	+0.11	+0.12
R = COOMe	$\dot{\Delta}^2$	−0.04	+0.79	−0.03	+0.36	+0.08	+0.10
III → IV	$\dot{\Delta}^1$	−0.11	+0.50	−0.05	+0.28	+0.09	
R = CD_2OH	$\dot{\Delta}^2$	−0.10	+0.50	−0.06	+0.27	+0.12	
III → IV	$\dot{\Delta}^2$	−0.14			+0.32	+0.00	
R = CONH-*t*-Bu	$\dot{\Delta}^2$	−0.02			+0.36	+0.03	
III → IV	$\dot{\Delta}^1$	−0.04	+0.76	−0.02	+0.29	+0.04	
R = $CO_2CH_2CCl_3$	$\dot{\Delta}^2$	−0.07	+0.78	−0.06	+0.29	+0.02	
III → V	$\dot{\Delta}^1$	+0.06	+0.60	+0.13	+0.06	+0.08	
R = $CO_2CH_2CCl_3$	$\dot{\Delta}^2$	+0.03	+0.63	+0.06	+0.07	+0.04	

[a] $\dot{\Delta}^1 = \Delta^1$(sulfoxide) − Δ^1(sulfide) and $\dot{\Delta}^2 = \Delta^2$(sulfoxide) − Δ^2(sulfide). Δ^1 and Δ^2 are defined in footnote *a*, Table V.

and the S→O bond in the penicillin system, then the geometry of the association differs in the two isomeric penicillin sulfoxides (IVa and IVb). For the (*S*)-sulfoxide (IVa), benzene association should take place from the α side of the solute molecule, *i.e.*, from the positively polarized end of the S→O bond (see Figure 2, b). The geometry of this complex together with the anisotropy associated with aromatic systems necessitates that the 2α-methyl and H_5 protons be strongly shielded while the remaining protons in the solute molecule (H_3, H_6, and 2β-CH_3) be only marginally affected.

Alternatively for the (*R*)-sulfoxide (IVb) the direction of benzene complexation with solute should be from the β face of the solute molecule; consequently it is anticipated that the 2β-methyl and H_3 protons will experience strong shielding effects in benzene solution (relative to CCl_4). For large solute molecules with more than one polar site, such as the penicillin systems here studied, several sites for coordination to solvent molecules are possible. Thus, benzene solvent-shift values (Δ values) recorded in Table V are the summation of solvent-shift contributions resulting from coordination of solvent molecules at each polar site within the solute molecule. Consequently, benzene-induced solvent-shift values for the different protons, resulting from coordination of benzene with the S→O bond only, may be better approximated by subtracting the various Δ values recorded (Table V) for the sulfoxide (IV) from the Δ values recorded in this same table for the corresponding sulfide (III). Since both sulfoxide (IV) and sulfide (III) possess the same polar functional groups, with the exception of the S→O bond in the former, the net shifts which result from this subtraction should be the solvent-shift values (Δ values) which reflect complexation of benzene to the S→O bond. Table VI summarizes the results of these calculations for protons in the different penicillin systems studied.

The results in Table VI indicate that the 2α-methyl protons and H_5 are strongly shielded (mean shifts are *ca.* +0.31 and +0.67 ppm, respectively) while H_3, H_6, and the 2β-methyl protons are only marginally affected (−0.08, −0.02, and +0.06 ppm, respectively). Only association b in Figure 2 is compatible with these observations, therefore these results are interpreted to indicate that the configuration of S→O in phenoxymethyl penicillin sulfoxide (IV) has the *S* configuration.

Hydrogen-Bonding Studies

The use of DMSO as a solvent for studying the nmr spectra of compounds containing hydroxyl groups has been well established.[26] The formation of hydrogen bonds has been shown generally to cause a downfield shift[27] of the resonance signal of the proton involved. As can be seen from Table VII, the –NH proton of III

Table VII. Proton Resonance Data[a] for the Amido Proton of III and IV

Compound	Solvent	–NH[b]	Downfield shift
III, R = CO_2Me	$CDCl_3$	7.42	
III, R = CO_2Me	DMSO (d_6)	8.63	1.21
IV, R = CO_2Me	$CDCl_3$	8.25	
IV, R = CO_2Me	DMSO (d_6)	8.25	...

[a] In parts per million. Positions given were measured using 5% solutions (w/v) after it had been ascertained that there was no concentration dependence. [b] –NH proton positions were given as the midpoint of the doublet.

(R = CO_2Me) is shifted downfield by 1.21 ppm in DMSO with respect to deuteriochloroform. This effect is due to solute–solvent hydrogen bonding in the DMSO solution, *i.e.*, the formation of a –NH···OS bond.

The –NH proton of the sulfoxide IV, while shifted downfield with respect to that of III when both were measured in deuteriochloroform, experienced no downfield shift on changing solvent to DMSO.

The downfield shift of the –NH proton of IV with respect to that of III in deuteriochloroform may be caused by intramolecular hydrogen bonding or by an anisotropic deshielding. However, the lack of shift in the spectrum of IV on changing solvent to DMSO must mean that the –NH proton is already intramolecularly hydrogen bonded to the sulfoxide bond and would not now be expected to be influenced by introduction of an external hydrogen bonding agent, *viz.* DMSO. This is only possible if IV has the *S* configuration.

X-Ray Crystallographic Study

The crystal structure work on phenoxymethyl peni-

(26) C. P. Rader, *J. Am. Chem. Soc.*, **88**, 1713 (1966), and references cited therein.
(27) J. N. Shoolery and M. T. Rogers, *ibid.*, **80**, 5121 (1958).

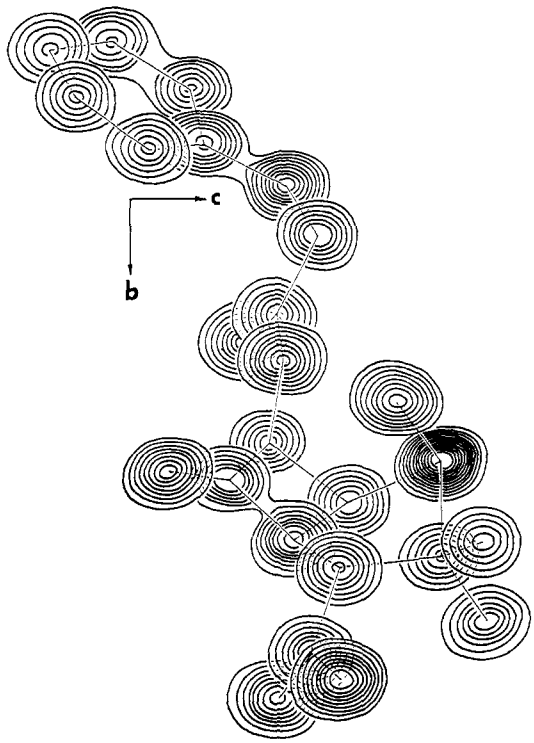


Figure 3. Composite three-dimensional electron density map, as viewed down the a axis. Contours are drawn at 2, 3, 4, . . . e Å^{-3} for all atoms except sulfur, where contours are at 2, 4, 6, . . . e Å^{-3}. The methanol molecule is not shown.

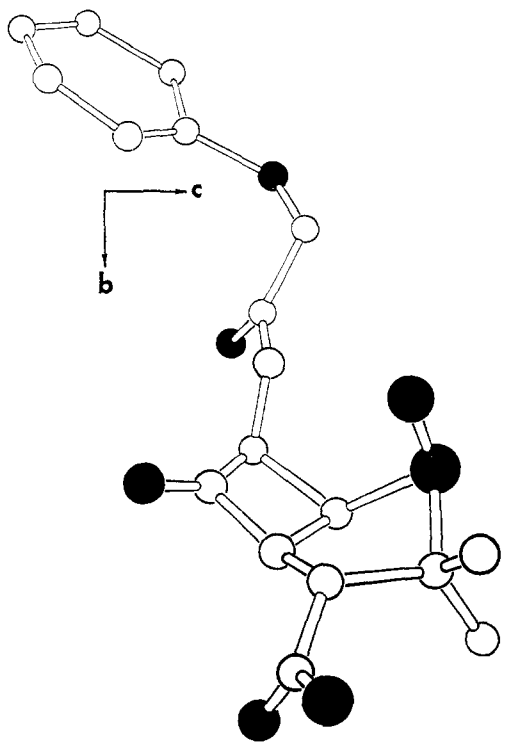


Figure 4. Skeletal conformation of molecule as viewed down a axis.

cillin sulfoxide (IV, R = CO_2H) confirmed the configuration proposed from nmr studies. Several modifications of the free acid crystallized from ethanol, methanol, and dimethyl sulfoxide have been investigated. Preparations crystallized from these three solvents have all been shown to incorporate a single molecule of solvent per molecule of phenoxymethyl penicillin sulfoxide. Crystals of the free acid from methanol were chosen for study and have been shown to belong to the noncentric orthorhombic space group $P2_12_12_1$, with the unit cell dimensions a = 16.747, b = 7.921, and c = 14.067 Å. The observed flotation density was 1.416 g/cm^3. With four molecules in the unit cell, the calculated molecular weight was 398.1. The molecular weight for $C_{16}H_{18}O_6N_2S \cdot CH_3OH$ was 398.4.

The intensities of approximately 2000 independent reflections were measured. The crystal appeared to be exceptionally stable to X-rays as there was no appreciable loss of intensity after irradiation for more than 10 days. Examination of a three-dimensional Patterson function calculated from the corrected intensity data gave a position for the sulfur atom, this position being confirmed by a structure factor calculation. The positions of the remaining 26 atoms, excluding hydrogens, were found by repeated calculation of three-dimensional electron density maps. The structure has been partially refined by least squares to an R factor of 20% for all the observed reflections.

The composite three-dimensional electron-density map shown in Figure 3 is based on this partially refined structure. The conformation of the sulfoxide and of the thiazolidine ring substituents is shown clearly in Figure 4. As may be seen the methyl groups adjacent to the sulfoxide are α-axial and β-equatorial, while the carboxyl group is α-equatorial. The conformation of the thiazolidine ring is different from that found by Crowfoot, *et al.*,[11] in the crystal structures of the sodium and potassium benzylpenicillins. In their work the methyl groups appeared to be α-equatorial and β-axial and the carboxyl α-axial. Full details of the crystal structure will be published elsewhere.

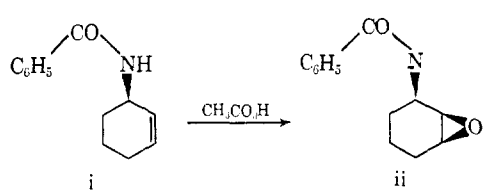
Discussion

It has been proposed[28] that the mechanism of oxidation of a sulfide to sulfoxide by peracid proceeds by a nucleophilic attack of the sulfur atom on the peracid. Therefore, from considerations of steric hindrance, the *S* configuration would seem to be the least likely product.

The investigations of Henbest and coworkers[29] have shown that the stereochemistry of epoxidation is influenced by the presence of hydrogen-bonding func-

(28) (a) C. G. Overberger and R. W. Cummins, *J. Am. Chem. Soc.*, 75, 4250 (1953); (b) S. A. Khan, M. Ashraf, and A. B. Chugtai, *Sci. Res.* (Dacca, Pakistan), 4, 135 (1967).

(29) (a) H. B. Henbest, Tilden Lecture of the Chemical Society, London, 1962, and references cited therein; (b) Winstein and coworkers [L. Goodman, S. Winstein, and R. Boscheen, *J. Am. Chem. Soc.*, **80**, 4312 (1958)] have reported the epoxidation of 3-benzamidocyclohexene (i) with peracetic acid to give the *cis*-epoxide (ii) due to the directing effect of the benzamido group.



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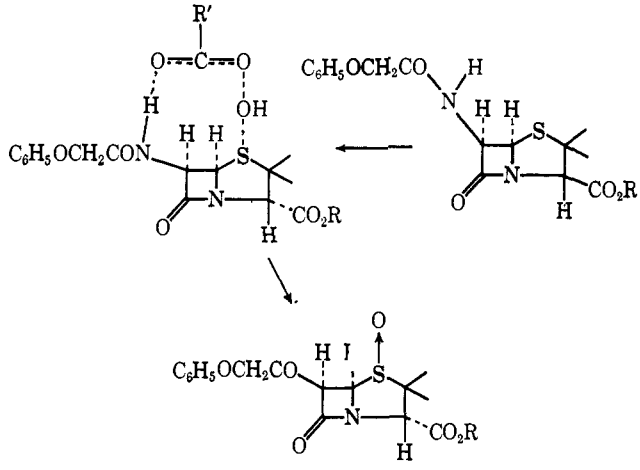

Figure 5.

tions, *e.g.*, hydroxyl, in positions close to the reaction site. He postulates that in nonpolar solvents oxidation occurs by a nucleophilic attack of the double bond on the peracid hydrogen bonded to the hydroxyl group. Application of the argument of "reagent approach control" to the oxidation of III → IV would require that the peracid be initially hydrogen bonded to the amido proton (see Figure 5). Theoretically, it would still be possible for either of the sulfur lone pairs of electrons to attack the hydroxyl oxygen of the peracid. However, inspection of the nonbonded interactions for both transition states indicates that the product with the *S* configuration (the stereochemistry *cis* to the amide side chain) represents a transition state with a lower energy barrier.

An alternative explanation is that no matter which isomer is initially formed, under the reaction conditions employed isomer equilibration may occur so that the final product is governed by thermodynamic factors, *i.e.*, the intramolecular hydrogen bond formed between the amido proton and the sulfoxide oxygen atom (a bond already shown to exist by nmr studies). This hydrogen bond can also be used to explain the inability to isomerize phenoxymethyl penicillin sulfoxide (IV, R = CO_2Me) to the *R* isomer and also the conformational differences found to exist between III and IV.

We have conducted nmr studies on the major sulfoxide formed by the peracid oxidation of a cephalosporin ester and have found that this also has the *S* configuration, presumably due to the same mechanistic reasons as discussed above.

A detailed discussion of the cephalosporin sulfoxide configuration will be published at a later date.

Experimental Section

Nmr spectra were recorded using a Varian HA-100 spectrometer in the frequency sweep mode. Sample concentrations were all less than *ca.* 5% w/v, and chemical shifts were measured by slowly sweeping (sweep time = 1000 sec) the recorder pen to the center of each resonance peak and observing difference 1 (*i.e.*, difference between the manual and sweep oscillator frequencies), on the frequency counter. Shift values measured in this manner were reproducible to ±0.01 Hz and are expected to be accurate to ±0.05 Hz. In the NOE studies the sweep width used was dependent on the difference in chemical shift between the group irradiated and the group observed. The irradiating audio oscillator was a Hewlett-Packard 200 ABR, and power requirements for NOE studies were determined by slowly increasing the output in 10-mV increments until signal increase was noted. Each peak indicating increases in signal height was integrated approximately five times with and without optimum power.

X-Ray diffraction intensities were measured with a Picker four-circle automated diffractometer using copper radiation and a scintillation detector. All calculations were carried out on an IBM 360-30 computer.

Acknowledgments. We wish to thank Dr. David Duchamp of the Upjohn Co., Kalamazoo, Mich., for making available to us some of the crystallographic computer programs used in this study.