the aldehydes 8 and 9 identified by their nmr spectra: aldehyde 8, 1.00 (s, 9 H, t-butyl), 1.01 (d, $J_{CH_{1,H}} =$ 6.8 cps, 3 H, methyl), 2.08 ppm (q, $J_{H,CH_{2}} =$ 6.8 cps, 1 H, methine); aldehyde 9, 1.00 (s, 9 H, t-butyl), 1.00 (methyl), 9.68 ppm ($W_{h/2} =$ 1.1 cps, 1 H, CHO). The ratio of 8:9 for each epoxide was determined from the relative integral of the 2.08- and 9.68-ppm nmr signals. For epoxide 3 the ratio of deuteride: hydride migration, *i.e.*, 9:8, was 1:0.89 (standard deviation 0.03), while for epoxide 4 it was 1:2.65 (standard deviation 0.08).

These results reveal a marked preference for the migration of the group (hydrogen or deuterium) cis to the methyl group in epoxides 3 and 4. This stereoselectivity may be rationalized in terms of Scheme I. Slow C-O bond heterolysis in 10 gives the discrete carbonium ion 11. The direction of rotation about the central C-C bond is controlled by the larger nonbonded interaction between the *t*-butyl and solvated OBF_3 groups and gives conformer 12 in which H_b is favorably oriented for migration. Competing with the H_b migration process is the establishment of conformational equilibrium (K = 1) between 12 and 13.⁹ In conformer 13 H_a is now in the favored migration orientation. The origin of the stereoselectivity of the rearrangement lies in the relative magnitude of the rate constants, k and k_{H_a} (or k_{H_b}), which may if they are comparable¹⁰ lead to a concentration bias, relative to 13, in favor of conformer 12. This conformer (12) can undergo H_b migration (rate constant k_{H_b}) or conformationally equilibrate (rate constant k).

On the basis of this mechanistic model¹¹ and substituting the results from the rearrangement of epoxides 3 and 4, the relative values of the rate constants for deuteride ($k_{\rm D} = 1.0$) and hydride ($k_{\rm H} = 1.71$) migration and the 12 \rightarrow 13 conformational change (k = 1.84) were evaluated using the expressions

$$9/8 = 1/0.89 = (k_D/k_H)[1 + (k_H/k)]$$

8/9 = 2.65 = $k_H/k_D[1 + k_D/k]$

The formation of dioxolane 7 by reaction¹² of the aldehydes 8 and 9 with epoxides 3 or 4 introduces a correction due to the secondary isotope effect (A) for that reaction. The magnitude of this secondary isotope effect is not known, but the relative values of k, $k_{\rm H}$, and $k_{\rm D}$ have been evaluated (Table I) for reasonable values of A. For the epoxide 14, the data

(9) While conformations i and ii could also lead to H_a and H_b migration, respectively, they may be neglected since their populations would be small as a result of the near-eclipsing of the *t*-butyl and OBF_a^- groups.



(10) Such comparability of rates has been noted earlier in other carbonium ion studies: C. J. Collins, W. A. Bonner, and C. T. Lester, J. Amer. Chem. Soc., 81, 466 (1959); C. J. Collins and B. N. Benjamin, *ibid.*, 85, 2519 (1963).

(11) The possibility of the reversible collapse of conformer 12 to epoxide 10, via 11, and the analogous collapse of conformer 13 to the epimeric epoxide does not invalidate the results derived using this simplified model.

(12) B. N. Blackett, J. M. Coxon, M. P. Hartshorn, A. J. Lewis, G. R. Little, and G. J. Wright, *Tetrahedron*, in press.

Table I. Effect of the Magnitude of the Secondary Isotope Effect (A)

A	k_{D}	$k_{\rm H}$	k	Stereo- selectivity
1.00	1.00	1.71	1.84	1.93
1.05	1.00	1.64	1.83	1.90
1.10	1.00	1.57	1.81	1.87
1.15	1.00	1.51	1.80	1.84
1.20	1.00	1.46	1.80	1.81

allow the estimation of a preference for the migration of that hydrogen atom cis to the methyl group in the range 1.81-1.93:1.

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Structural Studies on Penicillin Derivatives. IV. A Novel Rearrangement of Penicillin V Sulfoxide

Sir:

The penicillin sulfoxides, which were first prepared¹ over 20 years ago, have far greater β -lactam stability than the corresponding sulfides; indeed, Morin and coworkers² have shown that it is possible to achieve considerable modification of the thiazolidine ring without concomitant rupture of the β -lactam. They proposed that a sulfenic acid (2b) was the intermediate in their transformations of 1b to the β -lactam containing products.



In connection with our investigation into chemistry involving this proposed intermediate, we caused the penicillin sulfoxide ester (1a) to react with trimethyl phosphite in refluxing benzene and obtained, after 30 hr, a crystalline, less polar compound, 3, mp 138°, $[\alpha] D - 105^{\circ}$ (CHCl₃), in high yield (>80%). Highresolution mass spectrometry and elemental analysis³ indicated a molecular formula of C₁₈H₁₇Cl₃N₂O₄S, which represents a loss of the elements H₂O₂ from the starting sulfoxide. The ir spectrum had maxima at ν_{max} (CHCl₃) 1770 and 1745 cm⁻¹, and showed no absorption attributable to the amido side chain, *e.g.*, 3350 (NH), 1700 (amide I), and 1550 cm⁻¹ (amide II).

Compound 3, on treatment with triethylamine in methylene chloride, gave an isomer 4, mp 70°, $[\alpha]D$

 ^{(1) (}a) P. Sykes and A. R. Todd, "Committee on Penicillin Synthesis," Reports 526, 677; (b) "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) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino,

 ⁽²⁾ R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino,
W. B. Scanlon, and S. L. Andrews, J. Amer. Chem. Soc., 85, 1896
(1963); 91, 1401 (1969).

⁽³⁾ Satisfactory microanalytical data were obtained for all new compounds.





+16° (CHCl₃), ν_{max} (CHCl₃) 1770 and 1730 cm⁻¹

The nmr spectrum of 3 showed signals at δ 1.80 (3 H' broad singlet) and 5.10 (2 H, doublet) which on conversion to 4 changed to two three-proton singlets at δ 1.83 and 2.30. From the changes in nmr and ir spectra, this isomerism can be explained by the process⁴



The presence of this isopropylidene group is substantiated by isolation of dimethylpyruvic acid from vigorous base treatment of 4. The sustained presence of the β -lactam can be inferred from the existence of an AB quartet (J = 4 Hz) at δ 6.02 and 5.89 in 3 and δ^5 6.05 in 4. An additional smaller coupling of the lower field half of the AB quartet is associated with the methylene protons of the phenoxyacetamido side chain.⁶

From this evidence, we propose structures 3 and 4.⁷ Additional proof for the proposed structures is provided by the mass spectral fragmentation pattern, as

(4) N. J. Leonard and G. E. Wilson, J. Amer. Chem. Soc., 86, 5307 (1964).

(5) This resonance in 4 showed up as a two-proton singlet in deuteriochloroform or deuteriobenzene; however, use of trifluoroacetic acid-*d* gave the AB quartet (J = 4 Hz). The magnitude of the vicinal coupling constant (4 Hz) also showed the *cis* relationship of the two β -lactam protons.

(6) This long-range coupling is homoally lic through a C=N bond.

(7) An oxygen analog (i) of our proposed structure has been previously reported by Sheehan⁸ and Barton.⁹



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

(9) D. H. R. Barton, F. Comer, and P. G. Sammes, J. Amer. Chem. Soc., 91, 1529 (1969).

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shown in Figure 1 for 3, the major peak being fragmentation across the β -lactam, resulting in a thiazole (m/e191). Similar fragmentation can also be accomplished thermally by distilling 3 or 4 under vacuum when 2phenoxymethyl thiazole¹⁰ can be isolated.

The predominant reaction of 3 or 4 with strong acid or base is a cleavage of the C₅-N bond to give the 2,5disubstituted thiazoles (5a and 6a). Thiazole 6b has also been prepared in an independent manner¹¹ from phenoxyacetamidopenicillin.

The route of formation of 3 may be considered as an initial opening of sulfoxide 2a to the sulfenic acid 3a through a reversible, thermal, six-electron electrocyclic rearrangement.¹² The sulfenic acid is then reduced by



trimethyl phosphite to the thiol which undergoes a condensation with the amido side chain to give the thiazoline ring.



Further studies are in progress to obtain further evidence of the proposed mechanism.

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(10) Identified by comparison with 2-phenoxymethylthiazole prepared by an independent synthesis. Ir of the crude distillate showed a large absorption attributable to an isocyanate; however, this fragment has not yet been isolated.

(11) S. Kukolja, R. D. G. Cooper, and R. B. Morin, Tetrahedron Lett., 3381 (1969).

(12) Direct evidence for this concept will be presented in a forthcoming publication, J. Amer. Chem. Soc., in press.

> R. D. G. Cooper, F. L. José The Lilly Research Laboratories, Eli Lilly and Company Indianapolis, Indiana 46206 Received January 28, 1970