of KCl the first-order rate constant for disappearance of **1b** decreases from an initial high value to a much lower value as the reaction proceeds (Table I). If the concentration of KCl is increased, the initial value of k_ψ/a_H increases, the final k_ψ/a_H decreases, and the concentration of **1b** remaining in solution when the lower final rate constant is attained decreases. This behavior is consistent with a mechanism in which Cl^- traps an intermediate to form **2d** which can reclose reversibly to **1b** and which hydrolyzes to the final product, **2b**, more slowly than does **1b** itself.

On a preparative scale, the unsubstituted analog, **2e**, of **2d** can be prepared as its HCl salt in 96% yield by reaction of **1a** with anhydrous HCl in ether;[15] addition of an ethanolic solution of **2e**·HCl to an equal volume of 5% Na_2CO_3 solution at 0°, followed by dilution with H_2O and extraction with CH_2Cl_2, leads to isolation of **1a** in quantitative yield. A solution of **2e**·HCl in water is stable for several hours; addition of an aliquot of such a solution to buffers of pH 7.7, 9.1, or 12 produces an increase in uv absorption to a value consistent with the ϵ of **1a**, followed by a decrease in OD at a rate equal to that observed for the hydrolysis of **1a** at the same pH. The reclosure rate is too rapid to be followed by a mechanical recorder ($t_{1/2} < 1$ sec).

Studies directed toward elucidation of the mechanisms of cleavage of 1-azabicyclobutanes are being continued.

Acknowledgment. Financial support from the National Science Foundation (GP-7488) and from the donors of the Petroleum Research Fund, administered by the American Chemical Society (3032-A1), is gratefully acknowledged.

(15) *Cf.* ref 5. Satisfactory analytical and spectral data have been obtained for 2e·HCl.

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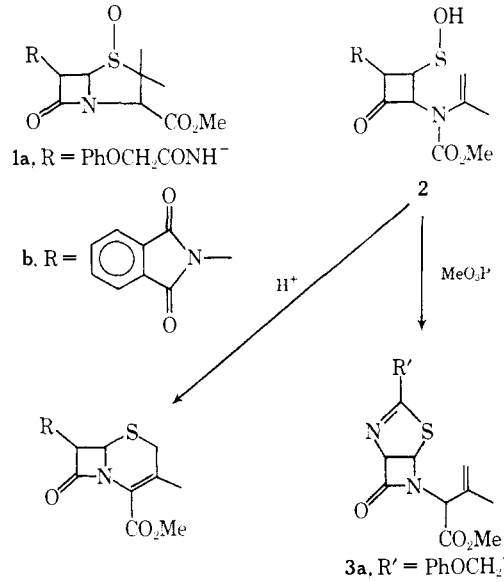
Structural Studies on Penicillin Derivatives. V. Penicillin Sulfoxide–Sulfenic Acid Equilibrium

Sir:

In the rearrangement of penicillin sulfoxide **1a**, discovered by Morin, *et al.*,[1] the intermediacy of a sulfenic acid **2a** was proposed. This same intermediate has been envoked in the rearrangement of **1a** into the thiazoline **3a**.[2] Another instance in the literature of its possible intermediacy is in the very facile inversion of methyl penicillin (*R*)-sulfoxide methyl ester, which was reported as converting to the (*S*)-sulfoxide in refluxing benzene.[3] The alternate possibilities in this latter case of pyramidal inversion[4] or homolytic scission–recombination[5] mechanisms, although extremely unlikely due to their far greater energy requirements, cannot as yet be rigorously excluded.[6]

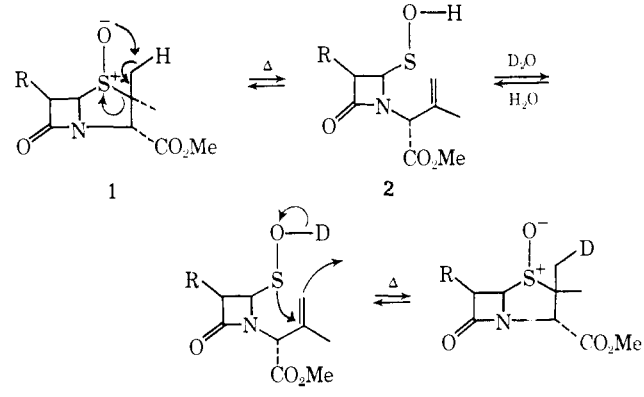


We have observed that on heating (*ca.* 80°) a solution of penicillin V sulfoxide methyl ester (β-sulfoxide) **1a** in benzene containing a large excess of deuterium oxide for 24 hr, the recovered sulfoxide (recovery 100%) contains an average of one deuterium atom located only in the *β-methyl group* (as shown by nmr).[7,8] The mass spectrum of the deuterated product shows a mixture of 45% d_0, 43% d_1, 11% d_2, and 1% d_3 products.

Similar treatment of phthalimidopenicillin sulfoxide ester (α-sulfoxide) (**1b**) gave deuterium incorporation only in the *α-methyl group*.[7,9] The product contained a mixture of 0% d_0, 24% d_1, 52% d_2, and 24% d_3 isomers.

We interpret these results to indicate the existence of a thermal equilibrium between the sulfoxide and the sulfenic acid. When this is established in the presence of deuterium oxide, hydrogen–deuterium exchange occurs in the sulfenic acid with consequent deuterium incorporation into the methyl group(s) of the sulfoxide **1** (see Scheme I).

Scheme I



(1) 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); *ibid.*, **91**, 1401 (1969).

(2) R. D. G. Cooper and F. L. Jose, *ibid.*, **92**, 2575 (1970).

(3) R. A. Archer and P. V. DeMarco, *ibid.*, **91**, 1530 (1969).

(4) D. R. Rayner, A. J. Gordon, and K. Mislow, *ibid.*, **90**, 4854 (1968).

(5) E. G. Miller, D. R. Rayner, H. T. Thomas, and K. Mislow, *ibid.*, **90**, 4861 (1968).

(6) Dr. P. Sammes has kindly informed me, prior to publication, that from deuterium-incorporation studies he has strong evidence for the intermediacy of a sulfenic acid in this inversion.

(7) Identification of the methyl signals in the nmr has been assigned previously by nuclear overhauser effects.[8,9]

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

(9) R. D. G. Cooper, P. V. DeMarco, and D. O. Spry, *ibid.*, **91**, 1528 (1969).

We have previously suggested[2] that the formation of a sulfenic acid can be considered a reversible thermal six-electron sigmatropic rearrangement. This is allowable as the hydrogen atom involved in transfer from the methyl group to the sulfoxide oxygen has a symmetrical electron distribution (s orbital). Thus effective orbital overlap can be established between the oxygen p orbitals and the hydrogen atom in the forward sense, and the carbon–carbon double-bond π orbitals and the hydrogen atom in the reverse sense.

The deuteration is remarkably stereospecific. As a consequence of the sigmatropic rearrangement, the readdition of the sulfenic acid to the olefin gives of necessity deuterium in the methyl group cis to the sulfoxide. The configuration of the products can be controlled by two possible factors. The first, which we prefer, is the thermodynamic stability of the product, since in all cases the recovered sulfoxides have the same stereochemistry as the starting sulfoxides, which we have previously shown[7,8] to be resistant to isomerization. An alternative viewpoint would concern the intermediate sulfenic acid which due to hydrogen bonding to the NH in the amido side chain has a restricted conformation. Ring closure would then occur on the β face of the molecule, except in the case of no NH in the side chain (phthalimido) when steric effects would operate[10] and ring closure occur on the α side.

In qualitative terms, temperature requirements for deuterium incorporation are less, and the degree of incorporation more, for **1b** than for **1a**. This could be from one or both of two effects:[11] either the presence of hydrogen bonding in **1a** would decrease the electron density of the sulfoxide oxygen and thereby decrease the effective orbital overlap with the hydrogen of the methyl group; or alternatively, the greater electron-withdrawing power of the phthalimido group weakens the sulfur–carbon bond and lowers the activation energy of the process.[12]

Acknowledgments. I wish to acknowledge valuable discussions with Dr. L. D. Hatfield and Dr. B. B. Molloy of these laboratories and Dr. J. E. Baldwin of Massachusetts Institute of Technology.

(10) Steric control was previously suggested[9] as the reason for the formation of the α-sulfoxide from the oxidation of phthalimidopenicillin.

(11) A referee has suggested the possible alternate explanation that the rate difference is due to the higher ground-state energy of the phthalimido derivative because of considerable steric interaction of the β-methyl group with a carbonyl function of the phthalimido group.

(12) Experiments with a suitably substituted series of side chains are in progress to test this hypothesis and to obtain a value for the activation energy.

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Book Reviews

The Chemistry of the Isoquinoline Alkaloids. By TETSUJI KAMETANI, Tohoku University, Aobayama, Sendai, Japan. Hirokawa Publishing Co., Inc., 27-14 Hongo 3-chome, Bunkyo-ku, Tokyo. 1968. 265 pp. 18 × 26 cm. $18.90.

The number of recorded isoquinoline alkaloids, already impressively large, is constantly expanding because of the availability of vastly improved methods of isolation and characterization. Consequently, the task of establishing the novelty of newly discovered alkaloids can assume heroic proportions. Under these circumstances the greatest boon to those interested in the field is access to a reliable and systematic description of what is already known. This is precisely what Professor Kametani has provided in his new book (also to be made available soon by American Elsevier Publishing Co.), which is a compilation of an enormous amount of informative data, readily accessible and attractively printed. The first chapter is an introduction which is a masterful condensation of background material covering structural determination, chemical synthesis, biogenesis, and biosynthesis of the isoquinoline alkaloids. This is followed by 23 chapters of concisely presented data for the alkaloids which are grouped according to structure and/or biogenesis. The data in the text are complete through 1966 and are updated through 1967 with an appendix.

Unfortunately, no undertaking of this scope can be completely free of errors and oversights. Examination of Chapter 17, "Emetine and Related Alkaloids," pp 160–166, reveals the following. (1) Representation of the sterochemistry at C-1′ is not consistent—it is given for tubulosine and some other alkaloids and omitted for cephaeline and others. (2) Almarckine does *not* occur in *A. lamarckii* as indicated. (3) The empirical formula for emetine is $C_{29}\ldots$, *not* $C_{20}\ldots$. (4) Reference 119 is incomplete—two authors are omitted. A more serious criticism is the deviation from the stated organization of the book, namely, "The compounds are arranged with respect to their molecular weight." Unfortunately this arrangement, the value of which is enhanced by the wide application of mass spectra, is not always followed (see pp 90, 131, 162, and 163 as random examples).

Despite these critiques, Professor Kametani's contribution is monumental. Everyone working with isoquinoline alkaloids owes him a debt of gratitude for this monograph which is a valuable addition to the existing library on alkaloids. It is this reviewer's fervent wish that Professor Kametani will augment its usefulness by frequent and regular updating.

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BOOKS RECEIVED. *June, 1970*

FRANK BRESCIA, JOHN ARENTS, HERBERT MEISLICH, and AMOS TURK. "Fundamentals of Chemistry, a Modern Introduction." Second Edition. Academic Press, Inc., 111 Fifth Ave., New York, N. Y. 1970. 796 pp. $12.50.

J. F. DANIELLI, A. C. RIDDIFORD, and M. D. ROSENBERG, Editors. "Recent Progress in Surface Science." Volume 3. Academic Press, Inc., 111 Fifth Ave., New York, N. Y. 1970. 346 pp. $17.50.