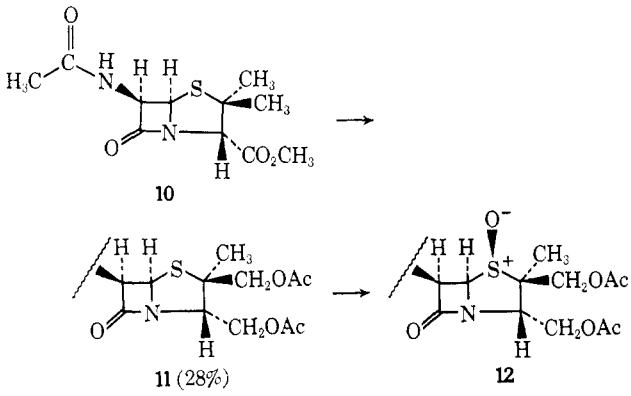
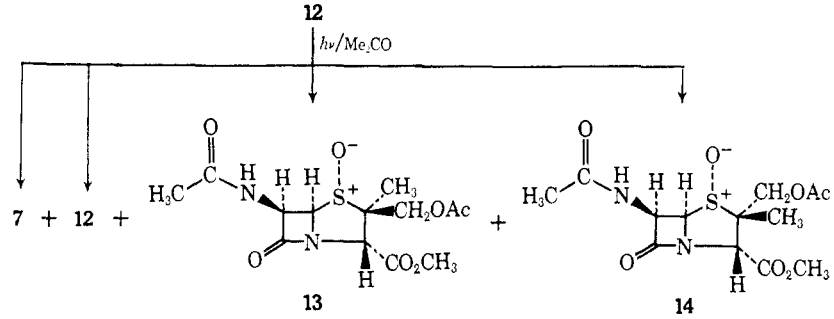


10

11 (28%) 12

mixture of sulfoxides. For example, phenoxymethylpenicillinic acid (1.0×10^{-2} *M*) in 1:1 water–acetone was treated with ozone (3.4 g/hr) for 2.5 hr. Evaporation of acetone gave crystalline, analytically pure β-sulfoxide acid in 49% yield; lyophilization of the aqueous solution gave analytically pure, noncrystalline α-sulfoxide acid in 51% yield. Treatment of sulfide **11** with ozone in 1:1 water–acetone gave **13** and **12** in a 2:1 ratio.

The selective oxidation of 2-methylene-substituted penicillins followed by ring-expansion rearrangement thus allows the conversion of penicillins to cephalosporins.



13 14

The synthesis of **7** is particularly interesting in that it establishes the S_1–C_2 cleavage mechanism for both the photochemical and thermal epimerization of penicillin sulfoxides.

Methylpenicillin methyl ester (**10**) was prepared in 97% yield from 6-aminopenicillanic acid and ketene, followed by esterification with diazomethane. Oxidation to the β-sulfoxide[9] with peracid, followed by acetic anhydride rearrangement, gave **11** which was then oxidized, again with peracid, to the crystalline β-sulfoxide β-methyleneacetoxy compound **12**, mp 184–185°, $[\alpha]_D$ +166° (dioxane).

Irradiation of **12** according to the procedure of Archer,[9] followed by chromatography on silica, led to the isolation of compounds **7**, **12**, **13**, and **14**.

The configurations were determined from nmr chemical shifts and internal NOE[5] (see Table II).

The thermal epimerization of **13** under refluxing benzene (30 min) gave **7** in good yield as the only lactam product.[10] A plausible mechanism to explain this involves S_1–C_2 cleavage to give the olefin–sulfenic acid, followed by S_1–C_5 and C_2–C_3 rotation and subsequent cyclization of the hydrogen-bonded sulfenic acid olefin.[11] The hydrogen bonding of the sulfenic acid with the amide apparently controls the stereochemistry.

To circumvent chromatographic problems associated with the photochemical preparation of the desired penicillin sulfoxide (cis to the methyl and trans to the methylene acetoxy), selective oxidation of the sulfide was investigated.

Ozone, under certain conditions, is an ideal reagent for converting various penicillin acids or esters into a

(9) R. A. Archer and P. V. Demarco, *J. Amer. Chem. Soc.*, **91**, 1530 (1969).

(10) Similar conditions on **14** do not result in **12**.

(11) I am indebted to Dr. B. B. Molloy of these laboratories for this explanation.

Acknowledgment. I wish to acknowledge the many helpful discussions with my colleagues, in particular Drs. B. B. Molloy, R. A. Archer, R. D. G. Cooper, R. B. Morin, and A. Pohland.

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Azabicyclobutanes. Solvolytic Cleavage of 3-Phenyl-1-azabicyclo[1.1.0]butane

Sir:

Current conjecture concerning the role of 1-aza-, 1-oxa-, and 1-thiabicyclobutonium ions as intermediates in solvolytic reactions of 2-halomethyl and 2-arenesulfonyloxymethyl aziridines,[1] 3-substituted azetidines,[1] and related oxacyclic[2] and thiacyclic[3] systems prompts us to report our observations regarding the mechanism of acid-catalyzed reactions of 3-phenyl-substituted 1-azabicyclobutanes, **1a–c**.

It has previously been noted that **1a** is extremely sensitive to decomposition under acidic conditions,[4] and that other azabicyclobutanes can undergo facile addition of a variety of reagents to yield 3-substituted azetidines *via* cleavage of the 1,3 bond.[5]

Cleavage reactions of **1a–c** can be conveniently followed by measuring the decrease in uv absorption

(1) J. A. Deyrup and S. C. Clough, *J. Amer. Chem. Soc.*, **91**, 4590 (1969); J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968); V. R. Gaertner, *ibid.*, 5919 (1968).

(2) H. G. Richey and D. V. Kinsman, *ibid.*, 2505 (1969).

(3) J. C. Martin and D. J. Anderson, Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961, p 31-O.

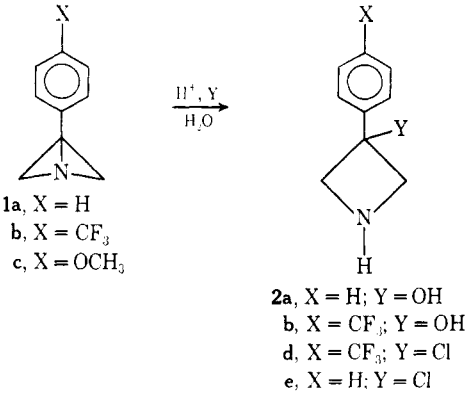
(4) A. G. Hortmann and D. A. Robertson, *J. Amer. Chem. Soc.*, **89**, 5974 (1967); A. G. Hortmann and J. E. Martinelli, *Tetrahedron Lett.*, 6205 (1968).

(5) W. Funke, *Angew. Chem.*, **81**, 35 (1969); *Chem. Ber.*, **102**, 3148 (1969).

near 2300 Å where **1a–c** absorb strongly (log ϵ *ca.* 4) and the corresponding azetidines do not. In aqueous solutions of dilute buffers, the hydrolysis of **1a** follows the rate law

$$-\frac{d[\mathbf{1a}]}{dt} = k_{\psi}[\mathbf{1a}] = k_{1a}a_{H}[\mathbf{1a}] \qquad (1)$$

where a_H is the hydrogen ion activity determined by pH meter measurements. The only detectable product of hydrolysis of **1a** is 3-phenylazetidin-3-ol (**2a**) as evidenced by the following: addition of **1a** (1.00 g) in dioxane (90 ml) to H_2O (1 l.) followed, after 12 hr, by evaporation of the solvent *in vacuo* gave a quantitative yield of crude **2a** which had ir and nmr spectra which were essentially identical with those of analytically pure **2a**.[6] Isotope dilution analysis of the product from **1a** was carried out by adding weighed amounts of both **1a** and **2a**-*2,2*-d_2[7] to borax buffer (pH *ca.* 9.4) and determining the deuterium content[8] of the carefully purified **2a** product; the yield of **2a** from **1a** was calculated to be 91 ± 5%.



1a, X = H
b, X = CF_3
c, X = OCH_3

2a, X = H; Y = OH
b, X = CF_3; Y = OH
d, X = CF_3; Y = Cl
e, X = H; Y = Cl

The value of the second-order rate constant, k_{1a}, was measured at 7.8°, 25.0°, and 45.0°; its temperature dependence implied $\Delta H^{\pm} = 5.6 \pm 0.3$ kcal/mol, $\Delta S^{\pm} = -10.5 \pm 0.9$ gibbs. The value of k_{1a} when D_2O is the solvent was also measured at all three temperatures, using values of a_D calculated from pH meter readings;[9,10] an inverse solvent isotope effect was observed; values of k_{1a}^{D}/k_{1a}^{H} fell within the range 3.15 ± 0.1 at all three temperatures. The second-order rate constant (eq 1) increases sharply when a *p*-OCH_3 substituent is introduced on the phenyl ring ($k_{1c}/k_{1a} = 1.5 \times 10^2$ at 25°) and decreases upon introduction of a *p*-CF_3 substituent ($k_{1b}/k_{1a} = 4.6 \times 10^{-2}$ at 25°). Representative rate data are given in Table I.

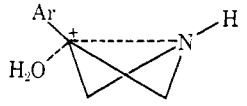
Equation 1 requires that the rate-determining activated complex contain hydrogen ion. Since protonation of tertiary amines in aqueous solution is accompanied by an increase in standard entropy of *ca.* 15 gibbs,[11] the observed $\Delta S^{\pm}$ suggests that the remainder of the activation process results in an entropy loss of *ca.* 25 gibbs. Such a large negative entropy change is in the range commonly interpreted as implying nucleophilic participation of solvent.[12] The observed inverse solvent isotope effect lies in the range which would be expected for the isotope effect on the equilibrium protonation of the substrate,[13] and is inconsistent with any mechanism involving rate-determining proton transfer. It also suggests that nucleophilic participation of solvent is sufficiently weak to produce no significant secondary isotope effect arising from positive charge on the nucleophilic oxygen in the transition state. The substituent effect correlates well with σ^+, but not with σ, and leads to $\rho = -2.57 \pm 0.17$, which implies that the positive charge on the benzyl moiety in the transition state is near unity.[14]

Table I. Observed Rates of Substrate Disappearance

Substrate	*T*, °C	pH	*I*[a]	k_{ψ},[b] sec^{-1}	k_{ψ}/a_H, M^{-1} sec^{-1}
1a	25.0	9.18[c]	0.05	1.74×10^{-3}	2.64×10^6
1a	25.0	7.77[d]	0.03	4.72×10^{-2}	2.78×10^6
1a	7.8	6.93[e]	0.08	1.60×10^{-1}	1.37×10^6
1a	45.0	9.02[c]	0.05	4.75×10^{-3}	4.98×10^6
1b	25.0	9.18[c]	0.05	7.92×10^{-5}	1.20×10^5
1b	25.0	8.04[d]	0.05	1.17×10^{-3}	1.28×10^5
1c	25.0	11.73[f]	0.05	7.1×10^{-4}	3.8×10^8
1c	25.0	10.98[g]	0.05	4.0×10^{-3}	4.2×10^8
1b	25.0	6.80[e]	0.25[h]	3.4×10^{-2}	2.2×10^5
1b	25.0	6.74[e]	0.25[i]	$(5.2 \times 10^{-2})^j$	$(2.8 \times 10^5)^j$
				$(0.7 \times 10^{-2})^k$	$(0.4 \times 10^5)^k$

[a] Ionic strength; unless otherwise noted, the only salts present are $NaClO_4$ and the buffer. [b] Defined by eq 1. [c] Borate buffer. [d] Tris(hydroxymethyl)aminomethane buffer. [e] Phosphate buffer. [f] Sodium hydroxide, *ca.* 0.01 *F*. [g] Piperidine buffer. [h] 0.21 *F* KF. [i] 0.21 *F* KCl. [j] Initial rate constant. [k] Final rate constant.

These observations suggest that the hydrolysis proceeds *via* prior equilibrium protonation of the substrate followed by a reaction in which the structure of the rate-determining activated complex may be represented by **3**, where both dotted bonds have



3

covalent orders near zero. It is currently assumed that the species formed in the prior equilibrium is the protonated azabicyclobutane; however none of the evidence presently available excludes the possibility that it is the corresponding carbonium ion formed by cleavage of the 1,3 C–N bond. Similarly, the activated complex, **3**, is consistent with attack by solvent either directly on protonated substrate or on the carbonium ion.

In the presence of salts of weakly nucleophilic anions (*e.g.*, F^-, ClO_4^-), the observed rate of disappearance of substrate remains first order and shows a normal salt effect. However, addition of nucleophiles can modify that behavior. For example, in the presence

(6) Mp 150–154° dec; ir ($CHCl_3$) 3600 and 3350 cm^{-1}; nmr (DMSO-d_6) δ 3.72 (4, sym A_2B_2 pattern), 4.12 (s, br, 2), and 7.2–7.8 (m, 5). *Anal.* Found: C, 72.71; H, 7.40; N, 9.43; mol wt 149 (mass spec).

(7) Obtained by hydrolysis of **1a**-*2,2*-d_2 prepared as described earlier (ref 4).

(8) Deuterium analyses were performed by Mr. Josef Nemeth, Urbana, Ill.

(9) R. Gary, R. G. Bates, and R. A. Robinson, *J. Phys. Chem.*, **68**, 3806 (1964).

(10) P. K. Glasoe and F. A. Long, *ibid.*, **64**, 188 (1960); P. Salomma, L. L. Schaleger, and F. A. Long, *J. Amer. Chem. Soc.*, **86**, 1 (1964).

(11) P. Paoletti, J. H. Stern, and A. Vacca, *J. Phys. Chem.*, **69**, 3759 (1965).

(12) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

(13) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 188.

(14) P. R. Wells, "Linear Free Energy Relationships," Academic Press, London, 1968, Chapter 2.

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.

(16) To whom correspondence should be addressed.

(17) National Institutes of Health Predoctoral Fellow, 1969–1970.

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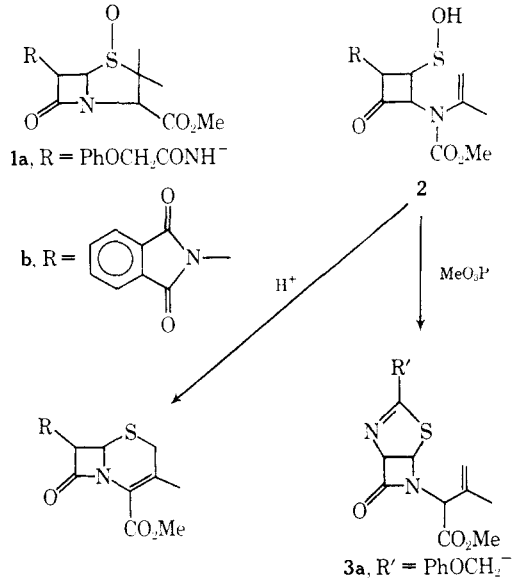
Structural Studies on Penicillin Derivatives. V. Penicillin Sulfoxide–Sulfenic Acid Equilibrium

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]

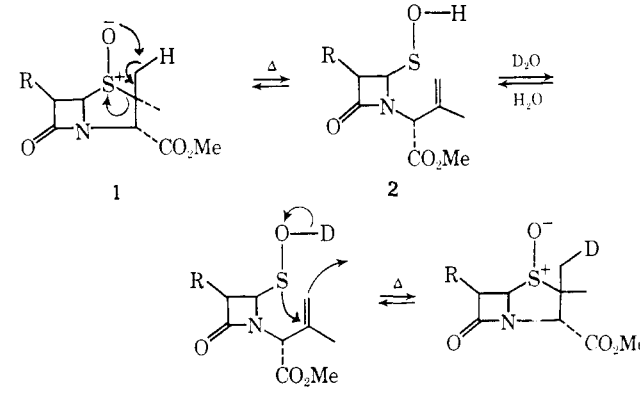


We have observed that on heating (*ca.* 80°) a solution of penicillin V sulfoxide methyl ester (β-sulfoxide) **1a** in benzene containing a large excess of deuterium oxide for 24 hr, the recovered sulfoxide (recovery 100%) contains an average of one deuterium atom located only in the *β-methyl group* (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).