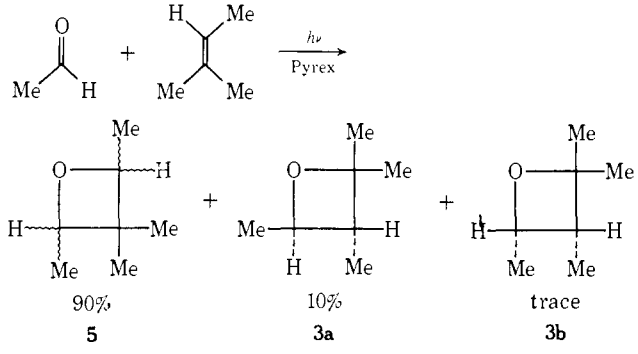
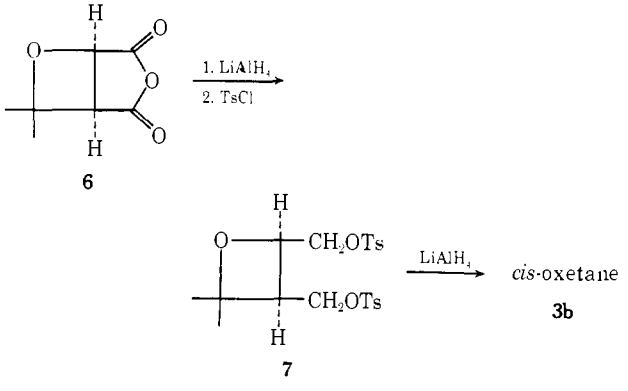
and a carbon–hydrogen analysis[5] demand the hydrogenated photoproduct to be one of the two *cis–trans* isomers of oxetane **3**.

Attempts to synthesize oxetane **3** by base-catalyzed hydrogen chloride or bromide elimination from a diastereomeric mixture of 4-halo-2,3-dimethylpentan-2-ols were unsuccessful. Irradiation of a cooled pentane solution of acetaldehyde and 2-methylbut-2-ene, however, did give approximately a 10% yield (vpc collected) of oxetane **3**,[5] but it is evidently the other *cis–trans* isomer: nmr (δ, CCl_4) 4.19 (1 H, pentet, J = 6.5 Hz), 2.17 (1 H, multiplet), 1.30 (3 H, s), 1.27 (3 H, d, J = 6.5 Hz), 1.22 (3 H, s), 1.00 (3 H, d, J = 6.5 Hz).[4] A major easily observable ir spectral difference between the two oxetanes was the absence of a small peak at 1029 cm^{-1} for the Patterno–Büchi reaction product. The major (2 + 2) addition photoproduct (*ca.* 90% yield) appears to be a *cis–trans* mixture of oxetane **5**[5] which shows a two-proton multiplet centered at δ 4.37 in the nmr in addition to the other expected absorptions for this material. Significantly, the vpc-collected oxetane **5** which showed a symmetrical peak on several vpc columns exhibited weak-impurity nmr absorptions due to the hydrogenated photoproduct from ketone **1**. We subsequently determined that the hydrogenated photoproduct has the same vpc retention time as oxetane **5**.



Proof that the hydrogenated photoproduct has structure **3b** was finally obtained by a simple stereospecific synthesis of the *cis*-oxetane. Photochemical (2 + 2) addition of acetone to maleic anhydride gave the known adduct **6**.[6] Reduction and ditosylate formation gave **7**,[5] mp 106–107°, which was reduced in a low yield to



3b. No trace of the *trans* isomer **3a** was observed by vpc analysis. The major reduction product of **7** was shown to be 2,3-dimethylpentan-2-ol[7] which was independently synthesized by a Grignard reaction of 2-bromobutane and acetone.

To our knowledge this is the second report in which a simple unfluorinated stable oxetene product has been definitely verified by spectral data and hydrogenation to an oxetane. The first reported simple oxetene was prepared by photoisomerization of cyclooctatetraene oxide.[8]

The rapid formation of oxetene **2** is most likely facilitated by a significant cisoid population of ketone **1**.[9] This aspect plus the fact that the reaction is initiated by irradiation of the π–π^* absorption is reflected in similar features of the substituted acrylic acids studied by Chapman.[10] In the latter case nonisolable oxetene formation was postulated upon irradiation. The possibility exists, therefore, that oxetene formation may be a general photochemical reaction of α,β-unsaturated carbonyl compounds just as cyclobutene formation is a general reaction from conjugated dienes.[11] We are investigating this possibility plus the questions concerning the multiplicity of this photochemical reaction.

Acknowledgments. The authors are grateful for Research Grant GP-8878 from the National Science Foundation.

(5) A satisfactory carbon and hydrogen analysis was obtained.
(6) N. J. Turro, P. Wriede, J. C. Dalton, D. Arnold, and A. Glick, *J. Amer. Chem. Soc.*, 89, 3950 (1967).
(7) L. Schmerling and E. Meisinger, *ibid.*, 75, 6217 (1953).
(8) J. M. Holovka, P. D. Gardner, C. B. Strow, M. L. Hill, and T. V. Van Auken, *ibid.*, 90, 5041 (1968). See also D. F. Bowman and F. R. Hewgill, *Chem. Commun.*, 524 (1964); D. R. Arnold, *Advan. Photochem.*, 6, 301 (1968); H. J. T. Bos and J. Boleiji, *Rec. Trav. Chim. Pays-Bas*, 88, 465 (1969).
(9) R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).
(10) O. L. Chapman and W. R. Adams, *J. Amer. Chem. Soc.*, 90, 2333 (1968).
(11) R. Srinivasan, *ibid.*, 85, 4045 (1963).
(12) To whom inquiries should be addressed.

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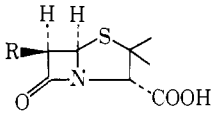
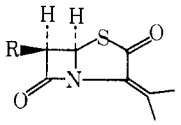
Reversal of the Anhydropenicillin Rearrangement

Sir:

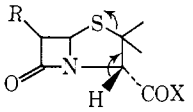
Conversion of the carboxyl group of a penicillin (**1**) into an acid chloride or mixed anhydride and treatment with base result in rearrangement to an anhydropenicillin (**2**).[1] The process has been represented[1] as a reverse Michael opening of the thiazolidine ring (**3** → **4a**), followed by recyclization at the acyl carbon (**4a** → **2**). Reversal of the sequence, *i.e.*, **2** → **4b,c** → **1**, is of interest because of its synthetic and biosynthetic implications, but there are several stages at which the reaction might fail. It is necessary to hydrolyze selectively an α,β-unsaturated γ-thiolactone in the presence of a β-lactam; the resulting sulfhydryl grouping must then effect a conjugate addition to a double bond whose reactivity toward nucleophilic attack is uncertain because, if viewed as an α,β-unsaturated acid, it is activated, and, as an enamine, it is deactivated;[2] if con-

(1) S. Wolfe, J. C. Godfrey, C. T. Holdrege, and Y. G. Perron, *Can. J. Chem.*, 46, 2549 (1968); S. Wolfe, *ibid.*, 46, 459 (1968); S. Wolfe, U. S. Patent 3,311,638 (1967).
(2) The unusual chemical and spectroscopic properties of anhydropenicillins have been explained[1] in terms of partial enamine character of the exocyclic double bond. The attendant decreased basicity of the β-lactam nitrogen could then have the opposing effects of permitting

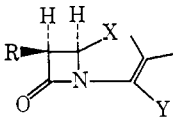




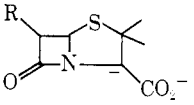
1a, R = R′CONH 2a, R = R′CONH
b, R = $C_6H_4(CO)_2N$ b, R = $C_6H_4(CO)_2N$



3, X = Cl, OCOR, OSO_2R

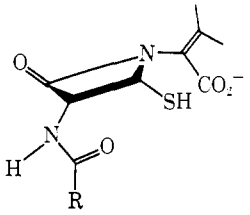


4a, R = R′CONH, $C_6H_4(CO)_2N$; X = S^-; Y = COCl, CO_2COR, CO_2SO_2R
b, R = R′CONH; X = SH; Y = CO_2^-
c, R = $C_6H_4(CO)_2N$; X = SH; Y = CO_2^-

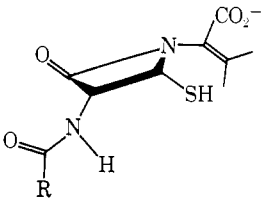


5

formation A of **4b** dominates over conformation B, or if addition to the carbonyl group of the acylamino side chain is facile, the mercaptan might bond in the wrong direction; finally, protonation of carbanion **5** may generate the natural configuration (D) or its epimer.[3]



A

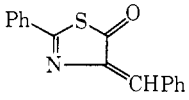


B

The latter possibility was not expected to cause difficulties because the D configuration at C-3 corresponds to the more stable *exo* stereochemistry. In order to reduce problems associated with the side chain, anhydro-6-N-phthaloylaminopenicillin (**2b**) was selected as the substrate for the experimental work.

the desired selective hydrolysis and preventing the Michael addition. It seemed likely, however, that the enamine character was a property of the constrained bicyclic system and would not persist in the monocyclic intermediates **4b** or **4c**.

(3) There is analogy for the proposed reverse anhydropenicillin rearrangement in the hydrolyses **6** → **7**[4] and **8** → **9**.[5]



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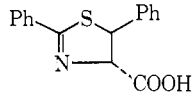

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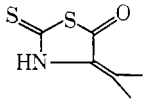

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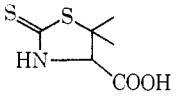


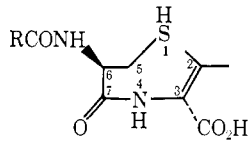
9

(4) J. Sicher, M. Svoboda, and J. Farkas, *Collection Czech. Chem. Commun.*, 20, 1439 (1955).

(5) R. Chatterjee, A. H. Cook, I. Heilbron, and A. L. Levy, *J. Chem. Soc.*, 1337 (1948).

A general screening procedure was devised in which **2b**, dissolved in 1 ml of solvent, was treated with 0.2 ml of buffer. At suitable intervals samples were removed for analysis by tlc and uv.[6] The expected product **1b** was unstable above pH 8.5; in the pH range 7.1–8.5,[7] **1b** was stable for at least 48 hr in the various solvent mixtures used for the hydrolysis studies.[8]

Over 600 runs were performed with systematic variation of the solvent, solvent composition, pH, time, and initial concentration of **2b**. An active substance, R_f 0.05, was finally obtained from a mixture of 1 mg of **2b** in 1 ml of 80:20 DMSO–H_2O to which 0.2 ml of pH 7.4 buffer was added. During a period of 5 hr the uv maximum at 274 nm decreased and a new maximum appeared at 372 nm; after 5 hr the maximum at 372 nm began to decrease and antibacterial activity could be detected.[9] Preparative experiments were then performed under the same conditions with the quantities increased 100-fold. After 20 hr at room temperature 61% of unreacted **2b** was recovered, together with 37 mg of an acid which, as its triethylammonium salt, melted at 147–148° and proved to be identical in all respects (tlc, mixture melting point, ir, specific rotation, and antibacterial spectrum[10]) with **10**.[11] Based on recovered anhydropenicillin the yield of **10** is 86%.[12]



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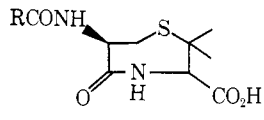

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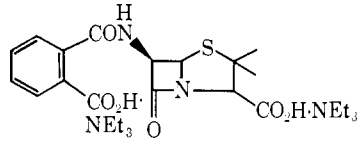

10

The bicyclic nucleus of penicillin is derived biosynthetically from L-cysteine and L-valine.[13] Since the configuration of penicillin at C-3 is D, oxidative ring closure of a peptide containing a cysteinyl-α,β-dehydrovaline unit has been suggested as a possible biosynthetic mechanism.[14] In one of the suggested routes (I), the final stage is formation of the 4–5 bond (*i.e.*, **11** → **12** → **1a**), and in another (II, **11** → **4b** → **1a**), it is the 1–2 bond which forms last. Route I has been tested, but no conclusive results have yet been presented.[15] A test

(6) A. 0.12-ml aliquot was diluted to 2 ml with water, and the spectrum was run against a blank of the same solvent composition. Disappearance of the maximum at 274 nm[1] was monitored initially.

(7) The buffers employed were boric acid–borax (pH 7.1–7.8) and boric acid–sodium hydroxide (pH 7.8–8.5).

(8) These were DMSO–H_2O, DMF–H_2O, THF–H_2O, dioxane–H_2O. The proportions of solvent to water were 25:75, 50:50, 70:30, 80:20, 90:10, and 95:5.

(9) The uv spectral changes and their pH dependence will be discussed in more detail in a subsequent publication.

(10) We thank Dr. C. T. Claridge of Bristol Laboratories for the microbiological determinations.

(11) Y. G. Perron, W. F. Minor, L. B. Crast, and L. C. Cheney, *J. Org. Chem.*, 26, 3365 (1961).

(12) The timing of the hydrolysis of the phthaloylamino group has not been established.

(13) H. R. V. Arnstein, *Ann. Rept. Progr. Chem.* (Chem. Soc., London), 54, 339 (1957).

(14) H. R. V. Arnstein and J. C. Crawhall, *Biochem. J.*, 67, 180 (1957).

(15) For a discussion of the relevant literature, see N. J. Leonard and G. E. Wilson, Jr., *J. Am. Chem. Soc.*, 86, 5307 (1964); N. J. Leonard and R. Y. Ning, *J. Org. Chem.*, 31, 3928 (1966).

of route II has not been reported. Since the cyclization which occurs during the reverse anhydropenicillin rearrangement represents chemical precedent for this pathway, it seems desirable to subject route II to more direct tests. Appropriate experiments are in progress.

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Evidence for Intermediates during Hydrogenation over Zinc Oxide

Sir:

Hydrogenation of ethylene over solid catalysts appears to be a two-step surface process[1,2]

$$C_2H_4\cdot S + H\cdot S \rightleftharpoons \underset{\mathrm{I}}{CH_3CH_2\cdot S}$$

$$CH_3CH_2\cdot S + H\cdot S \longrightarrow C_2H_6(\mathrm{gas})$$

The infrared spectrum of hydrogen-treated, adsorbed ethylene on nickel suggests the presence of a C_2H_5–S species, but this species appears too stable in hydrogen to be the reactive intermediate, I.[3,4] Thus, to date, direct physical evidence (as opposed to mechanistic inference) for I is lacking. We report in this letter infrared observations during the hydrogenation of ethylene over zinc oxide that provide physical evidence for I. Zinc oxide gives simpler results than metals insofar as the formation of I appears to be irreversible;[5] hence the reaction with deuterium would lead to formation of a single species CH_2DCH_2–S rather than the multiplicity of species ($C_2H_{5-x}D_x$–S) expected for nickel.

When ethylene is circulated over zinc oxide, prominent bands due to adsorbed ethylene (readily reversible) appear in the C–H region at 3060 and 2980 cm^{-1}.[6] If gaseous deuterium is then admixed with the ethylene ($D_2:C_2H_4$ = 116:12 mm) reaction commences, and the band at 2980 cm^{-1} broadens and decreases as new bands appear at 2905 and 2145 cm^{-1} along with bands ascribable to adsorbed deuterium.[7,8] If the ethylene is trapped out but deuterium circulation is continued, the new bands decrease initially at a rapid rate and then more slowly. The initial rate of removal of this species is comparable to the rate of the catalytic reaction.[9]

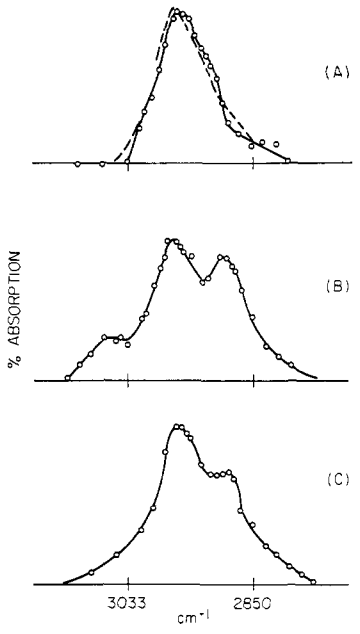

Figure 1. Spectra during reaction in the C–H region (spectral slit width 18 cm^{-1}): (A) 100% conversion (the dotted line is the spectrum of gaseous CH_2DCH_2D with the transmission scaled so that the peak intensities coincide); (B) 60% conversion; (C) 95% conversion.

Subsequent evacuation through a liquid nitrogen trap for 30 min reveals a residual band at 2145 cm^{-1} (and 2905 cm^{-1}) but, even when the catalyst is reexposed to the trapped out ethylene and dideuterioethane, this band has only one-third the intensity it had under reaction conditions. Resumption of the reaction by admission of a charge of deuterium brings about immediate restoration of the band intensities.

Figure 1 shows the difference spectra in the C–H region during reaction in a circulating system.[10] Spectra were computed by using as background the spectra of zinc oxide after reaction was complete and hydrocarbons had been trapped out for 4 min. Use of this "background," which includes a residual peak at 2905 cm^{-1}, results in a difference spectrum for 100% conversion (Figure 1A) essentially identical with the spectrum of gaseous 1,2 dideuterioethane under comparable conditions with the per cent transmission scaled to give the same peak intensity (dashed line). Under reaction conditions (Figure 1B) three peaks are seen. The 3060-cm^{-1} peak is ascribable to adsorbed ethylene and shows a gradual decline as the run proceeds; the center peak contains contributions from adsorbed ethylene (2980 cm^{-1}) and the product ethane (2980 cm^{-1}), and changes relatively little as the run proceeds. The species giving rise to bands at 2905 cm^{-1} (and 2145 cm^{-1}) is an intermediate; it appears at the onset of the reaction, stays roughly constant until the reaction is about 70% complete, and then starts a slow decline. These bands, however, are still apparent even when the reac-

(1) G. C. Bond, "Catalysis by Metals," Academic Press, New York, N. Y., 1962, pp 229–279.
(2) R. L. Burwell, Jr., A. B. Littlewood, M. Cardew, G. Pass, and C. T. H. Stoddard, *J. Amer. Chem. Soc.*, **82**, 6272 (1960).
(3) R. P. Eischens and W. A. Pliskin, *Advan. Catal.*, 10, 1 (1958).
(4) L. H. Little, "Infrared Spectra of Adsorbed Species," Academic Press, New York, N. Y., 1966, pp 100–137.
(5) W. C. Conner, R. A. Innes, and R. J. Kokes, *J. Amer. Chem. Soc.*, **90**, 6858 (1968).
(6) Band positions were determined at higher resolution than that for Figure 1 and are accurate to about 10 cm^{-1}.
(7) R. P. Eischens, W. A. Pliskin, and M. J. D. Low, *J. Catal.*, **1**, 180 (1962).
(8) A. L. Dent and R. J. Kokes, *J. Phys. Chem.*, 73, 3772, 3781 (1969).
(9) In this estimate we assume that the species responsible for the new bands is present in amounts comparable to the initially adsorbed ethylene. This assumption is supported by the relative intensity of the 2905-cm^{-1} band compared with the initial intensity of the 2980-cm^{-1} band.
(10) These spectra were run on a Perkin-Elmer Model 112c spectrometer with the expanded scale procedure similar to that described in ref 3, p 50. The per cent absorption of the strongest peak is about 10%.