Tetrahedron Letters No. 24, pp 2159 - 2162, 1973. Pergamon Press. Printed in Great Britain.

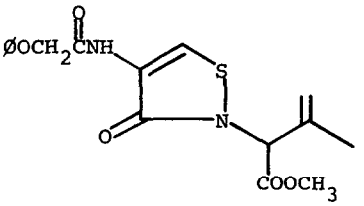
CHEMISTRY OF DEHYDROPEPTIDES. A REARRANGEMENT OF AN ISOTHIAZOLONE.

Robert B. Morin and Eric M. Gordon
School of Pharmacy
University of Wisconsin-Madison
Madison, Wisconsin 53706

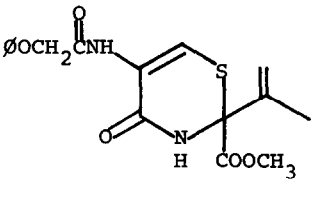
Thomas McGrath and Robert Shuman
The Lilly Research Laboratories
Indianapolis, Indiana

(Received in USA 4 April 1973; received in UK for publication 8 May 1973)

The transformation of penicillin sulfoxides to cephalosporin derivatives and methyl-substituted penicillins is often accompanied by three non-β lactam-containing substances which are in the case of penicillin V sulfoxide methyl ester substances 1, its α-β double bond isomer and 2[1,2]. Isothiazolone 1, whicl is most conveniently prepared by the reaction of Penicillin V sulfoxide methyl

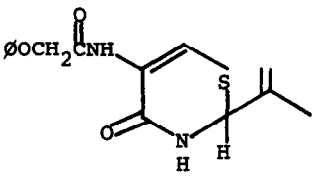


1



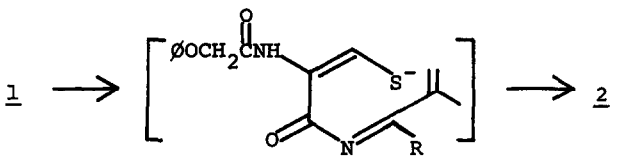
2

ester with a trace of acid in refluxing xylene containing triethylformate, is transformed into 2 by heating in dimethylacetamide solution at 140° for 18 hours. Compound 2 can also be obtained by heating 1 in DMF at reflux temperature but the principal product is 3[3,4] [nmr ($CDCl_3$) δ 1.94 (s, 3H), 4.59 (s, 3H), 5.28 (m, 3H), 7.24 (m, 5H), 8.18 (s, 1H), 8.69 (br.s, 1H); $\nu_{max}^{CHCl_3}$ 3350, 2980, 1665, 1600, 1520 cm^{-1}; λ_{max}^{EtOH} 320 mμ (ϵ 7800); m.p. 157-159°; $[\alpha]_D^{25}$ = 0.00 c = 1.0 $CHCl_3$]. A co-occurring uncharacterized product in the latter case, is an unstable adduct which contains elements of the solvent. The isothiazolone 1 is stable in xylene solution at reflux temperature but is converted into 2 by the subsequent addition of a non-nucleophilic[5] base.



3

A plausible explanation for this rearrangement is a base catalyzed formation from 1 of the acylimine 4a which is then trapped by the neighboring thiol

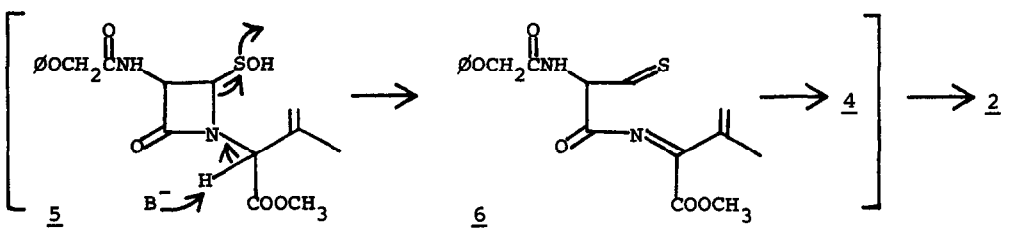


4 a. R = $COOCH_3$

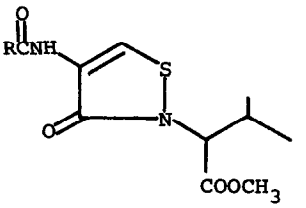
b. R = H

function. In the transformation in DMF the free acid must be formed which undergoes decarboxylation instead of a loss of the α-valyl proton in forming the acylimine, (4b).

Substance 2 is not formed from 1 in the penicillin sulfoxide dehydrative-rearrangement, since under the conditions of the latter reaction 1 does not give 2. An adequate explanation for the formation of 2 from the sulfenic acid derivative 5, which has been implicated as an important intermediate in the penicillin sulfoxide transformations, is the fragmentation reaction, 5 → 6 → 4 → 2[6]. This mechanism[7] emphasizes the similarity to the presently described rearrangement and the importance of acylimines in these transformations.



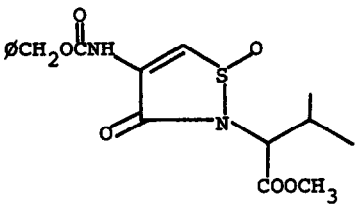
Since isothiazolones are readily formed from cysteinyl peptides by oxidation[8], this rearrangement might provide a means of selectively oxidizing, via the intermediacy of an acylimine[9] the amino acid residue adjacent to cysteine[10] towards the C-terminal end of a peptide chain. Unfortunately the isothiazolones 7a or 7b[8] do not undergo this rearrangement under conditions utilized for the earlier transformation[10]. Apparently in this case the double bond in the valine



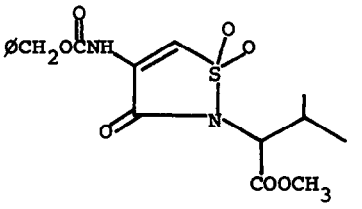
7 a. R = $\emptyset OCH_2-$

b. R = $\emptyset CH_2O-$

portion is needed to stabilize an anion or free radical generated in the α position. Similarly, compound 8[3] [nmr ($CDCl_3$) δ 0.90 (d, 3H, J = 7 Hz), 1.08 (d, 3H, J = 7 Hz), 2.65 (m, 1H), 3.61 (s, 3H), 4.41 (d, 1/2H, J = 10), 4.71 (d, 1/2H, J = 9 Hz), 5.22 (s, 2H), 7.39 (s, 5H), 7.68 (br.s, 1H), 8.05 (br.s, 1/2H), 8.15 (br.s, 1/2H); $\nu_{max}^{CHCl_3}$ 3380, 2950, 1745, 1710, 1640, 1510 cm^{-1}; M^+ 380; λ_{max}^{MeOH} 280 mμ (ϵ 3100), 230 mμ (ϵ 6600)], formed from 7b by a controlled peracid oxidation is stable to acid and base at elevated temperatures. Substance 9[3], [nmr ($CDCl_3$) δ 0.96 (d, 3H, J = 7 Hz), 1.11 (d, 3H, 7 Hz), 2.80 (m, 1H), 3.71 (s, 3H), 4.28 (d, 1H, J = 10 Hz), 5.26 (s, 2H), 7.30 (s, 1H), 7.40 (s, 5H); $\nu_{max}^{CHCl_3}$ 3380, 2950, 1739 br., 1650, 1510; M^+ 396; m.p. 82-84; $[\alpha]_D^{25}$ = -25°, c = 3.1 $CHCl_3$; λ_{max}^{MeOH} 237 mμ (ϵ 17,000), 2761 (ϵ 4500)], formed by oxidation of 7b or 8 likewise was stable. Compound 8 is a mixture of two isomers both of which can be oxidized to 9. Substance 8 was surprisingly non-polar relative to other mono oxidized sulfur derivatives, particularly in comparison to the similar derivative of the isothiazolidone[10].



8



9

Acknowledgement: We wish to thank Eli Lilly and Company and the National Institutes of Health (Grant Al-10519) for support of this research.

References

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

2. R. D. G. Cooper and D. O. Spry in "Cephalosporins and Penicillins: Chemistry and Biology," Edwin H. Flynn, Ed., Academic Press, New York, N.Y., 1972, Chapter 5.

3. This compound gave a satisfactory elemental analysis.

4. Cf., D. H. R. Barton et al., Chem. Comm., 1137(1971).

5. 1,8-Cis-(dimethylamino)-naphthalene.

6. An interesting alternative possibility for a subsequent reaction of intermediate 6 is the 4+2 cycloaddition to provide a cephem ring system. Such products are formed in these transformations.

7. Alternate mechanisms for this reaction are discussed in reference 2.

8. R. B. Morin, E. M. Gordon, and J. Lake, unpublished results.

9. B. W. Bycroft, Nature, 224, 595(1969). R. B. Morin and E. M. Gordon, Tetrahedron Lett., in press.

10. Isothiazolidones might represent "masked" sulfenic acids, the expected primary oxidation products of the easily oxidizable sulfhydryl groups of cysteinyl residues, and therefore would be of greater interest in this rearrangement. Experience has shown that derivatives of peptide isothiazolidones are considerably more reactive than the corresponding isothiazolones. Further of interest, is the fact that the analogous peptide isoxazolidone also undergoes this base catalyzed rearrangement, unpublished results, R. B. Morin and E. M. Gordon.