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CHEMISTRY OF DEHYDROPEPTIDES. FORMATION OF ISOTHIAZOLONES AND ISOTHIAZOLIDONES FROM CYSTEINYL PEPTIDES

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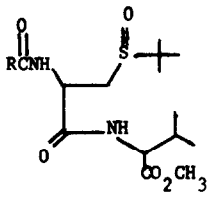
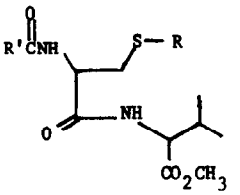
The work reported from our laboratories[3] and others[4] has established the importance of sulfenic acids in the transformations of penicillins. Since sulfenic acids can be envisaged as proximate oxidation products of cysteinyl peptides, this chemical function or a derivative might further be important in the biochemical formation of penicillin from a precursor acyl cysteinyl valine. The ready formation of isothiazolones in penicillin sulfoxide rearrangements[3] and their thermal rearrangement to dihydrothiazines[5], suggest that an isothiazolidone formed from a cysteinyl valine sulfenic acid may be important in the formation of penicillin. The formation and chemical transformations of isothiazolidones and isothiazolones from acyl cysteinyl valine peptides is described.



1 R=$C_6H_5CH_2O$- or $C_6H_5OCH_2$-



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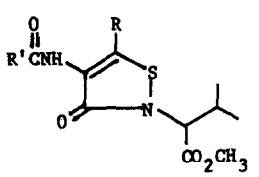
Thermolysis[6] of 1 under various conditions has led to a variety of products, some of which must derive from the sulfenic acid, 2 (R=OH). The desired substance 9 was not isolated in these experiments. However, in one instance the isothiazolone, 3[7] (R'=$C_6H_5OCH_2$-, R=H), was obtained in low yield suggesting the intermediacy of 9.

Direct oxidation of acyl cysteinyl valine ester, 2 (R=H), under a variety of conditions led primarily to the corresponding symmetrical disulfides and to only minor amounts of other products. Interestingly, the disulfides exist in a preferred conformation in non polar organic solvents. This is particularly evident with the phenoxyacetyl

derivative, 2 (R=]$_2$, R'=$C_6H_5OCH_2$-), in which the methylene of the acyl function is found in the n.m.r. as an AB quartet in contrast to the singlet found in all penicillin V and its transformation products.

Halogenation of carbobenzyloxycystinyl valine methyl ester has led to isothiazolones and isothiazolidones. Treatment of 2 (R=]$_2$, R'=$C_6H_5CH_2O$-) with N-chlorosuccinimide gave the isothiazolones, 3[7] (R=H, R'=$C_6H_5CH_2O$-), [m.p. 81-83°; λ_{max}^{MeOH} 290nm (ε 9400); $\nu_{max}^{CHCl_3}$ 1737, 1640, 1510 cm^{-1}; n.m.r. ($CHCl_3$)δ 5.10 (d, 1H, J=10Hz), 8.22 (s,1H)] and 3[7] (R=Cl, R'=$C_6H_5CH_2O$-), [λ_{max}^{MeOH} 284nm (ε 11,300); $\nu_{max}^{CHCl_3}$ 1740, 1730, 1650, 1610, 1500 cm^{-1}; n.m.r. ($CDCl_3$)δ 5.08 (d, 1H, J=10Hz), 5.16 (s, 2H), 7.62 (s, 1H, exchangable with D_2O)]. Chlorination using chlorine at -78° in pyridine - methylene chloride - carbon tetrachloride provided four substances: carbobenzyloxy-β-chloroalanylvaline methyl ester, m.p. 122°; 4[7] [$\nu_{max}^{CHCl_3}$ 2940, 1733(br), 1720, 1710, 1700 cm^{-1}; n.m.r. ($CDCl_3$)δ 2.45 (m, 1H), 5.92(br. s, 1H), 6.06(br. s, 1H)]; 5[7] (predominantly one stereoisomer) [$\nu_{max}^{CHCl_3}$ 1735, 1720(br.), 1495 cm^{-1}; n.m.r. ($CDCl_3$)δ 3.39(d, 1H, J=3Hz), 3.74(s, 3H), 4.80(d, 1H, J=8Hz), 5.08(m, 1H), 5.92(d, 1H, J=6Hz, exchangable with D_2O)], and 6[7] [m.p. 128-130°; $\nu_{max}^{CHCl_3}$ 1738, 1718, 1675, 1497, 1049 cm^{-1}; n.m.r. ($CDCl_3$)δ 4.55(d of d, 2H, J=9, 9Hz), 5.10(m(br), 2H), 5.15(s, 4H), 6.22(d, 2H, J=8Hz, exchangable with D_2O), 7.61(m(br), 2H, exchangable with D_2O)]. Likely, compound 4 is derived from 7 by the mechanism indicated, followed by displacement on sulfur by the urethane nitrogen and further oxidation. Hydrolysis of 7 will provide the isothiazolidone oxide 5.



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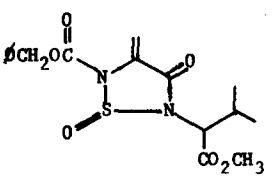

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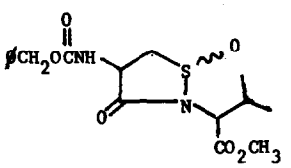

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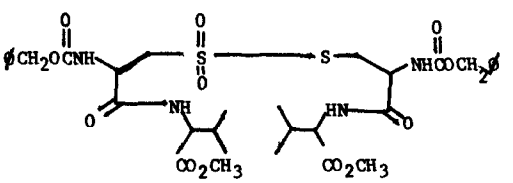

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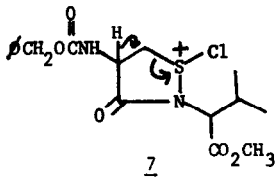

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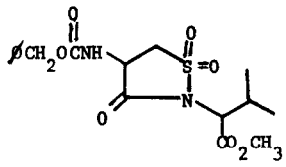
Bromination of 2(R=)$_2$, R'=$C_6H_5CH_2O$-) with bromine in the presence of silver oxide in pyridine - methylene chloride in the cold, gave the isothiazolone, 3[7](R=Br, R'=$C_6H_5CH_2O$-) [$\nu_{max}^{CHCl_3}$1735, 1650 1500 cm^{-1}; λ_{max}^{MeOH} 283nm (ε=10,000)], and an isothiazolidone oxide, 5', [m.p. 111-113°; $\nu_{max}^{CHCl_3}$ 1735, 1715(br), 1501 cm^{-1}; n.m.r. ($CDCl_3$)δ 3.03(m, 1H), 3.43(m, 1H), 3.77(s, 3H), 4.54(d, 1H, J=9Hz), 4.92(m, 1H)], that differs from that isolated in the chlorination experiment by the configuration at sulfur[8]. This latter statement is demonstrated by the fact that both isomers give on oxidation the same isothiazolidone dioxide, 8[7], [$\nu_{max}^{CHCl_3}$ 1725(br), 1495 cm^{-1}; mass spectrum m/e 398(M^+); n.m.r. ($CDCl_3$)δ 4.00(d, 2H, J=7Hz), 4.26(d, 1H, J=9Hz)].



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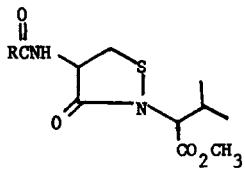

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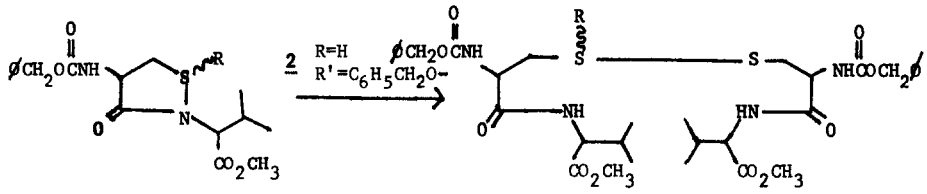
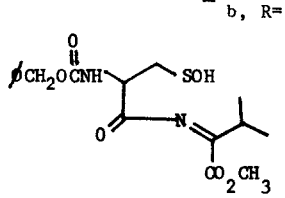
TLC analysis of the chlorination product indicated presence of the other isomer, produced stereospecifically in the bromination experiment. Bromination experiments without the silver oxide led to the same monoxide but additionally in good yield to the desired isothiazolidone, 9[7], (R=$C_6H_5CH_2O$-), [m.p. 65°; mass spectrum m/e 366(M^+); n.m.r. ($CDCl_3$)δ 3.62(m, 2H), 4.60(m, 1H), 4.66(d, 1H, J=9Hz), 5.65(d(br), 1H)].



5 a, R= 
b, R=

10 a, R= 
b, R=



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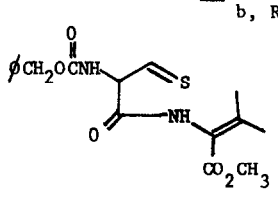

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The isothiazolidone monoxides, 5a and 5b, react stereospecifically with thiol, 2 (R=H, R'=$C_6H_5CH_2O$-), to form the diastereomeric thiosulfinates, 10a and 10b, thus providing a convenient method of preparing thiosulfinates of a specific configuration at sulfur[8]. Studies are currently under way concerning the thermolysis of the monoxides, 5a and 5b, which might provide penicillin via the intermediates 11 and 12 on the basis of analogy to earlier work[5,9].

The isothiazolidone, 9 (R=$C_6H_5CH_2O$-), can be considered a masked sulfenic acid and might be expected to undergo reactions characteristic of this function. Indeed, it reacts with thiol, 2 (R=H, R'=$C_6H_5CH_2O$-), to form the disulfide[10,11]. Isothiazolidone, 9, can be expected to form a dehydrovaline peptide in analogy to the isoxazolidone analog and the unsaturated system. Oxidation of 9 (R=$C_6H_5CH_2O$-) with peracid gave an equal mixture of the monoxides, 5a and 5b.

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References:

1. Henry S. Wellcome Memorial AFPE Fellow 1972-73, Department of Chemistry, Yale University, New Haven, Conn.

2. The described work was carried out at the School of Pharmacy, University of Wisconsin, Madison, Wisconsin.

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5. R. B. Morin and E. M. Gordon, T. McGrath and R. Shuman, Tetrahedron Lett., 2159 (1973).

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7. This compound gave satisfactory elemental, IR, NMR, and mass spectral analyses.

8. The configuration at sulfur has not yet been ascertained in these compounds.

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10. This relates closely to the work of Harpp; see D. N. Harpp and T. G. Back, Tetrahedron Lett., 5313(1972).

11. Isothiazolidones, if present naturally in proteins and enzymes, could thus provide a mechanism for disulfide interchange.