Tetrahedron Letters No. 24, pp 2163 - 2166, 1973. Pergamon Press. Printed in Great Britain.

CHEMISTRY OF DEHYDROPEPTIDES. FORMATION OF DEHYDROPEPTIDES BY OXIDATION OF PEPTIDE OXAZOLONES.

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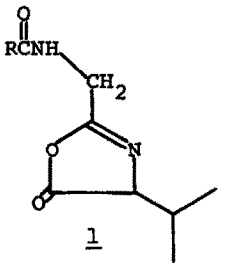
(Received in USA 5 March 1973; received in UK for publication 8 May 1973)

Many important biologically active natural products are derivatives of small molecular weight dehydropeptides[1], penicillin, an important example, derives formally from a bis-dehydro-acyl cysteinyl valine. Evidence indicates that the normal amino acids, L-α-aminoadipic acid, L-cysteine and L-valine are incorporated into a tripeptide which subsequently undergoes biological oxidation and cyclization[2]. Other natural dehydropeptides likely arise from intact peptides which are formed from amino acid residues having the normal L-configuration. Due to the importance of these substances and the lack of understanding of their formation in biological systems, we have initiated a chemical program to prepare dehydropeptides related to certain antibiotics from the corresponding peptides by various oxidative reactions.

Oxazolones, often implicated[3] in the racemization occurring during peptide synthesis, activate the α-hydrogen of the C-terminal amino acid residue. Earlier work[4] has indicated that oxazolones of simple acyl amino acids could be oxidized at this α-center by several different means. Consequently the C-terminal residue of an intact peptide chain might be selectively subject to oxidation via the oxazolones. Treatment of the oxazolone of Cbz glycyl valine 1[5], (R = $\emptyset CH_2O-$) with lead tetraacetate in benzene at room temperature, provided after chromatography on silica, Cbz glycyl amide[6], a result consistent with the oxidation and subsequent hydrolytic cleavage of the valine residue. Oxidation of the oxazolone, 1, (R = $\emptyset CH_2O-$) with mercuric acetate in benzene at room temperature provided a mixture from which the Cbz formyl imide 2[6], the hydroxy-oxazolone, 3[7], m.p. 147-148, and the diacetyl compound, 4[8], [$\nu_{max}^{CHCl_3}$ 1805, 1760,

1733, 1715, 1648 cm^{-1}; nmr ($CDCl_3$) δ 1.95 (s, 3H, $C\underline{H}_3COO$—), 2.04 (s, 3H, $C\underline{H}_3COO$—), 6.77 (d, 1H, J = 10 Hz, —NHC<u>H</u>OAc)] were isolated.



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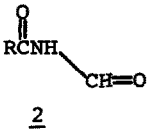

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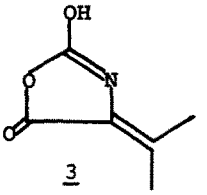

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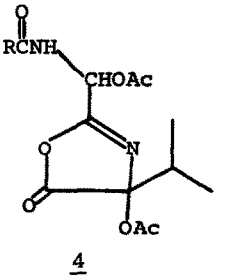

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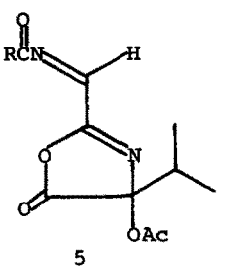
Benzoyl glycyl valine oxazolone, 1[5], (R = Ø) gave on lead tetraacetate oxidation compound 2[6], and acylimine 5[9] [m.p. 97-99, $\nu_{max}^{CHCl_3}$ 1825, 1759, 1670 cm^{-1}; nmr ($CDCl_3$) δ 2.15 (s, 3H, $C\underline{H}_3COO$—), 6.49 (s, 1H, <u>H</u>—C═N—); $\lambda_{max}^{Et_2O}$ 239 mμ (ε 7500)]. A similar acylimine, 5, (R = $\emptyset CH_2O$) is a likely intermediate in the formation of 4.



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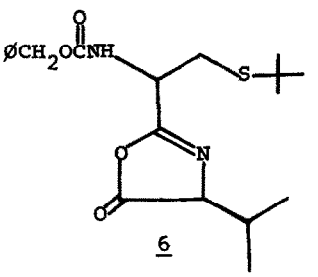

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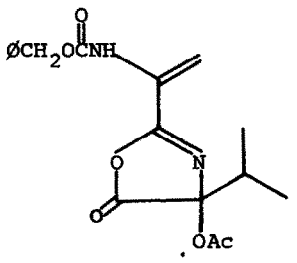
Mercuric acetate oxidation of Cbz t-butyl cysteinyl valine oxazolone 6[5] gave Cbz amide and the bis-dehydroalanyl valine oxazolone, 7[9], [$\nu_{max}^{CHCl_3}$ 1839, 1730, 1659, 1612 cm^{-1}; nmr ($CDCl_3$) δ 2.10 (s, 3H, $C\underline{H}_3COO$—), 5.78 and 6.50 (br. s 1H, each, N—C═C<u>H</u>$_2$); $\lambda_{max}^{Et_2O}$ 250 mμ (ε 3000)], resulting from a β-elimination of the sulfur function. Oxidation of the peptide oxazolone 6[5] with lead tetraacetate provided the Cbz bis-dehydro t-butyl cysteinyl valine oxazolone 8[9],

[$\nu_{max}^{CHCl_3}$ 1815, 1731, 1675 (sh), 1620 cm^{-1}; $\lambda_{max}^{Et_2O}$ 301 mμ (ϵ 8400); nmr ($CDCl_3$) δ2.08 (s, 3H, $C\underline{H}_3COO$—), 7.65 (s, 1H, =C$\underline{H}$S—)]. Interestingly this compound was optically active ($[\alpha]_D^{25}$ -20°, c = 1.1 $CHCl_3$). Likely the substance results from an intermediate acylimine which undergoes tautomerism.



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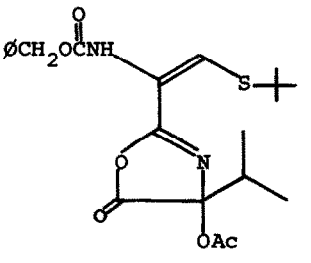

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Results of this work clearly indicate that oxazolones provide intermediates for the oxidation of the C-terminal residues of peptides, particularly for the synthesis of bis-dehydro derivatives in which the ultimate and penultimate amino acid residues have been oxidized. This latter reaction might prove useful in the synthesis of dipeptide derivatives in which both hydrogens in the α-position have been substituted by an electronegative substituent, for example substances like gliotoxin.

These oxidative procedures also provide a means of synthesis of acylimines which are attracting increasing interest as possible intermediates in the biosynthesis of dehydropeptides and formation of D-amino acid residues in peptides[10]. They have also been implicated as intermediates in the oxidations of β-lactam antibiotics[11], penicillin-related compounds[12], and other amide containing substances[13]. Substance 5 is a stable, crystalline, acylimine derived from a peptide. This material upon warming in chloroform, underwent ready isomerization about the carbon-nitrogen double bond [appearance of a second imino hydrogen at δ 6.6 (s) in the nmr].

The oxazolones utilized in this study were conveniently prepared from the corresponding peptide by treatment with the water soluble carbodiimide derivative CMCI[14] in a mixture of pure methylene chloride and ether. The peptide

oxazolones are oxidized by other reagents such as t-butyl hypochlorite, and DDQ however the nature of the products have not been determined. These various oxidizing agents under the conditions utilized (with the exception of the formation of the sulfoxide of the t-butyl cysteinyl derivative on treatment with lead tetraacetate) do not affect the peptide precursors.

Acknowledgement: We thank Hoffmann-LaRoche Laboratories and the National Institutes of Health (Grant AI-10519) for support of this research.

References

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5. These were characterized by IR and NMR and were free of starting peptide, reagent, and resulting urea.

6. Compared with a synthetic sample.

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9. This compound gave satisfactory analysis and spectra.

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