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CHEMISTRY OF DEHYDROPEPTIDES. REARRANGEMENT OF PEPTIDE ISOXAZOLIDINONES DERIVED FROM CYCLOSERINE.

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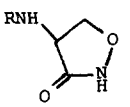
The oxidative studies of acyl cysteinyl valine in relation to penicillin synthesis has led to the isolation of peptide isothiazolidinones in several laboratories[3,4]. This 5-membered heterocyclic ring system bears an obvious relationship to another antibiotic substance, cycloserine, 1 (R = H). Consequently the question whether seryl peptides could be oxidized to derivatives of cycloserine and their transformation to other dehydropeptides became of interest to us.

Oxidation of N-Cbz-L-seryl-L-valine methyl ester, 2[5], did not provide the corresponding cycloserine analog 3 under a variety of oxidizing conditions. Lead tetraacetate oxidation of 2 in benzene afforded the two diastereoisomeric hydroxyglycine peptides 4[5] [one isomer m.p. 111-114°; mass spectrum m/e 388 (M+); p.m.r. ($CDCl_3$) δ 0.95 (d, 6H, J = 7Hz), 2.01 (m, 1H), 3.75 (s, 3H), 4.53 (d of d, 1H, J = 9, 5Hz), 4.95 (broad m, 1H), 5.15 (s, 2H), 5.61 (broad d, J = 7Hz), 6.78 (d, 1H, J = 7Hz, exchangeable with D_2O), 7.26 (broad m, 1H, exchangeable with D_2O), 7.40 (s, 5H)][6] probably via α-cleavage[7] of an oxygen radical with the extrusion of formaldehyde. The broad doublet signal in the nmr at δ 5.61 on exchange



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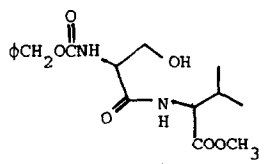

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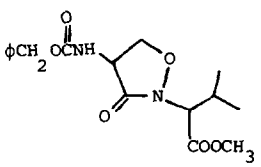

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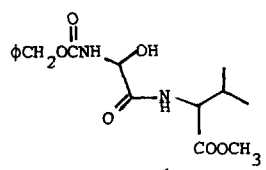

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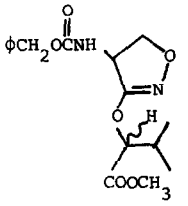
with D_2O initially sharpens and then collapses to a singlet as expected for the assigned structure. Benzyl carbamate was also isolated from this reaction mixture, presumably as resulting from a degradation of the isomeric compounds 4.

In order to facilitate this investigation authentic compound 3 was desired by an alternate synthesis. Alkylation of N-Cbz-D-cycloserine[5] (1, R = Cbz) as the potassium salt with methyl α-bromo isovalerate in DMF at 75° gave, instead of the expected isoxazolidinone 3, two diastereomeric mixtures. The minor, more non-polar pair 5[5] [one isomer $\nu_{max}^{CHCl_3}$ 3420, 2960, 1725, 1625, 1505 cm^{-1}; p.m.r. ($CDCl_3$) δ 4.3 (m, 2H, CH-$\underline{CH_2}$-O-), 4.7 (d, 1H, J = 4Hz, -O-$\underline{CH}$-CO_2CH_3), 5.2 (m, 1H), 5.8 (d, 1H, J = 8Hz, -NH-)][6] was the result of O-alkylation of the Cbz-cycloserine.



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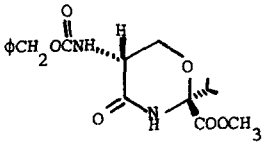

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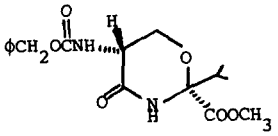

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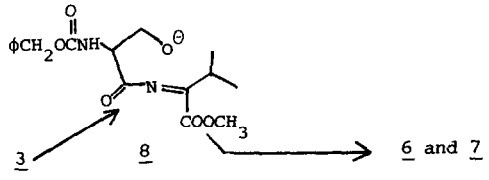
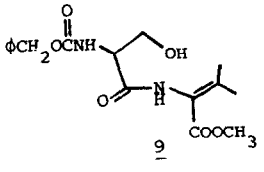
The remaining two substances which could be separated by silica chromatography were the isomeric dihydro-oxazinones 6[5] and 7[5] [one isomer $\nu_{max}^{CHCl_3}$ 3405, 2960, 1739, 1700 cm^{-1}; p.m.r. ($CDCl_3$) δ 4.13 (m, 2H, -CH$\underline{CH_2}$O-), 4.22 (m, 1H, -$\underline{CH}$-CH_2O-), 7.73 (s, 1H, ring NH exchangeable with D_2O)][6]. The p.m.r. spectrum of both substances lacked a proton doublet corresponding to the α-valyl proton but possessed two N-H protons, one of which was a singlet. Further evidence results from double irradiation p.m.r. experiments in which irradiation of the gem dimethyl resonances at δ 0.96 caused a multiplet at δ 2.17 (1H) to collapse to a sharp singlet.



3 → 8 → 6 and 7



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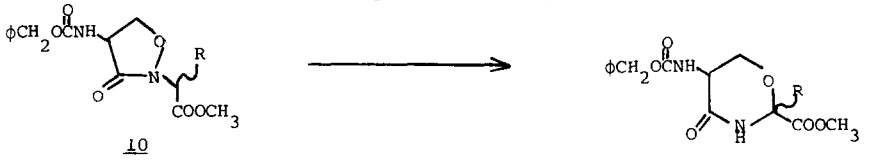
A plausible mechanism for the formation of 6 and 7 is the formation of the originally desired product 3, a base catalysed opening to the acylimine 8 and subsequent ring closure to give the dihydro-oxazinones. Apparently, the trapping of the acylimine by the

neighbouring hydroxyl group proceeds faster than tautomerization as little evidence could be found for the presence of compound 9. Use of different bases, solvents and temperatures did not provide conditions for isolation of 3.

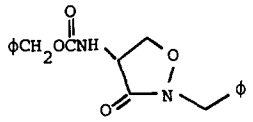
In order to investigate the generality of this rearrangement N-Cbz-cycloserine (1, R = Cbz) was treated with other alkylating agents. In contrast to the isovaleryl group discussed above, several of the new examples gave the cycloserine analog in good yield.



10 11

Alkylation of N-Cbz-cycloserine with methyl bromo-acetate (using KOt in DMSO at room temperature) gave 10[5](R=H) [m.p. 107°, $\nu_{max}^{CHCl_3}$ 3420, 3020, 2960, 1750, 1715, 1505 cm^{-1}; p.m.r. ($CDCl_3$) δ 4.1 (m, 1H), 4.3 (s, 2H, $-\underline{CH_2}CO_2CH_3$), 4.7 (m, 2H)] in good yield with only a trace amount of isomeric 11[5] (R = H). Under these conditions the α-bromo isovalerate gave only the rearranged product 11 (R = isopropyl). With methyl α-bromo propionate and methyl α-bromo-n-butyrate a mixture of 10[5] and 11[5] (R = methyl and ethyl respectively) was obtained. Likewise treatment with methyl α-bromo-β-phenyl propionate gave a mixture of 10[5] and 11[5] (R = $CH_2\phi$), but in contrast, methyl α-bromo-α-phenyl acetate yielded only the rearranged product 11[5] (R = φ). Minor amounts of O-alkylated products were formed in each case. The O-alkylated products could be identified by the presence of a peak at 1630 cm^{-1} in the i.r.[8] and their characteristic c.m.r. spectra.

The N-alkylated products 10[5] rearranged readily under basic conditions to the dihydro-oxazinones 11[5]. The results from the study of the conditions needed for rearrangements of 10 and the relative yields of 10 and 11 in the alkylations, indicate that bulkier R-groups or a group stabilizing an anion facilitate the rearrangement. Alkylation of 1 (R= Cbz) with benzyl bromide provided in good yield compound 12 which was resistant to rearrangement. Under the conditions of our experiments the N-Cbz-seryl-dehydrophenyl alanine derivative 13 could not be found among the rearrangement products of 10 (R = $CH_2\phi$). This is somewhat surprising due to the potential stabilizing effect of the phenyl group and the known ease of tautomerization of acylimines having a β-hydrogen.



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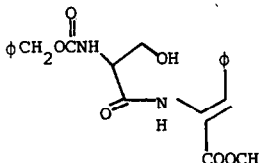

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The rearrangement of isoxazolidinones is in direct analogy to isothiazolones[9] and represents an interesting reaction of O-alkylated hydroxamic acids. Since amides bearing an electronegative substituent on nitrogen and an adjacent proton undergo a similar elimination to acylimines[10] and since enzymatic N-hydroxylation of secondary amides to hydroxamic acids is a known phenomenon[11], the latter group of substances and their derivatives might represent, in general, the primary intermediates in the formation of dehydropeptides.

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