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FORMATION OF 'DEHYDROPEPTIDES' FROM PEPTIDES

A MODEL SYSTEM ESTABLISHING A MECHANISM FOR THE BIOGENESIS OF PEPTIDE AMIDES AND α-KETO-ACIDS

G.C.Barrett,* L.A.Chowdhury, and A.A.Usmani

(Oxford Polytechnic, Headington, Oxford OX3 0BP)

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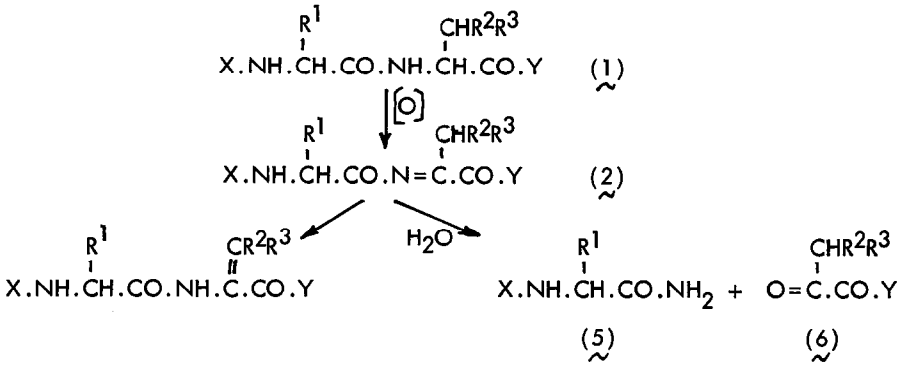
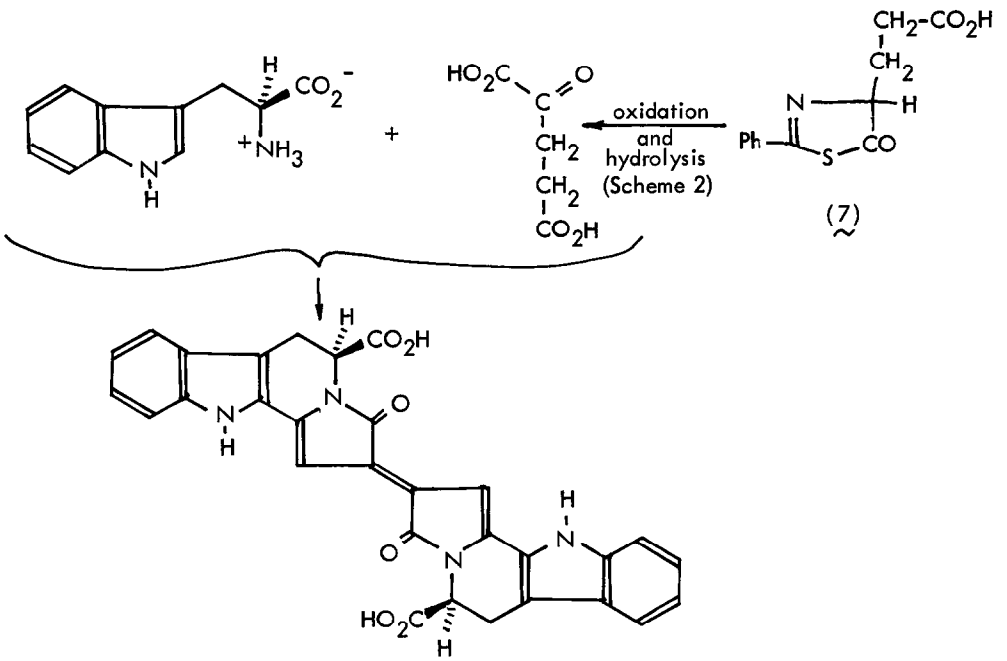
The oxidative conversion of peptides into dehydro-analogues (SCHEME 1) has been proposed[1] to account for the occurrence of αβ-dehydro-amino-acid residues and D-amino-acid residues in microbial peptides. The possible relevance in the early stages of penicillin and cephalosporin biosynthesis of selective oxidation at the C-terminal residue of a cysteinylvaline derivative has also been recognised,[2] but the further significance of this general process in the biogenesis of peptide amides and α-keto-acids has not been pointed out previously



SCHEME 1

The problem posed in these potentially non-enzymic pathways, the discovery of appropriate conditions through which the in vivo conversion of a peptide into an acylimine (2) can be brought about, has not been solved. Morin and Gordon[3] attempted to establish conditions for the oxidation of peptide oxazol-5(4H)-ones (3), reasoning that these are plausible intermediates in the in vivo oxidative conversion of peptides into 'dehydropeptides'. Although selective oxidation at the C-terminal residue of a peptide under biomimetic conditions was not accomplished in this study, some of the reaction products obtained by Morin and Gordon pointed to the intermediacy of acylimines in these oxidation experiments.

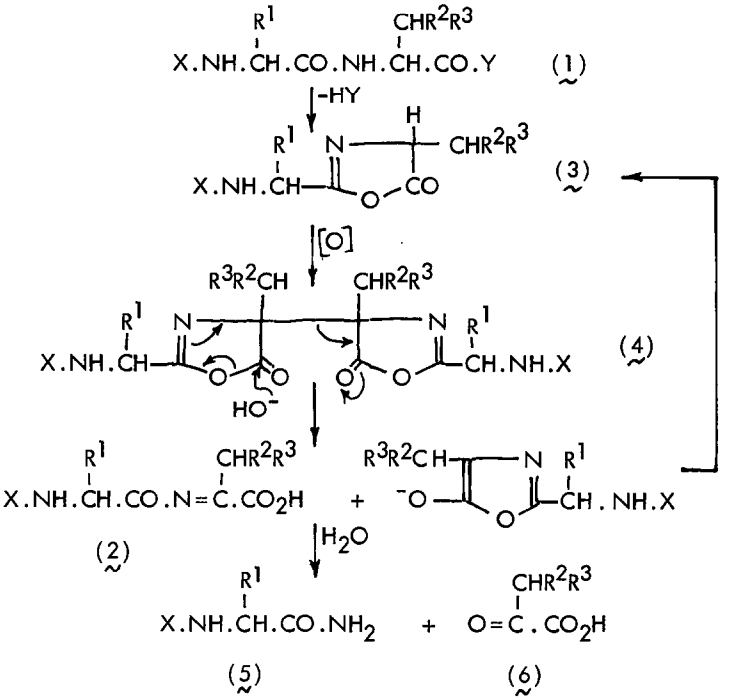
Since Kapadia and Rao[11] have demonstrated a biomimetic synthesis (SCHEME 3) of the blue pigment trichotomine from L-tryptophan and α-ketoglutaric acid in aqueous suspension, using atmospheric oxygen as oxidant, we reasoned that the generation of this pigment in a reaction mixture containing L-tryptophan and 4-(2-carboxyethyl)-2-phenylthiazol-5(4H)-one (7), a model for the oxazol-5(4H)-one generated from a peptide carrying a C-terminal glutamic acid residue, would provide compelling support for the biogenesis of α-keto-acids from peptides.



SCHEME 3

The blue pigment which separated after two weeks from a solution of L-tryptophan and the thiazolone (7) in water-dioxan (5:1) was identical with trichotomine, formed (within five days) from L-tryptophan and α-ketoglutaric acid as described by Kapadia and Rao.[11] The longer reaction time is consistent with the relatively slow oxidative dimerisation of 4-alkyl-substituted 2-phenylthiazol-5(4H)-ones in air,[10] but the clean reaction mixture (in contrast with that resulting from the reaction conditions described by Kapadia and Rao[11]) and the further deposition of trichotomine during the two weeks or so following its first appearance in the L-tryptophan - thiazolone reaction mixture, is notable. The yield of crude trichotomine (17%) obtained *via* the thiazolone was marginally greater than that reported by Kapadia and Rao.[11]

Steglich[4] has established that oxazol-5(4H)-one dimers (4) formed by mercury(II) acetate oxidation of oxazol-5(4H)-ones[5] can be hydrolysed to acylimines, from which an α-keto-acid and an amide can be formed by a further hydrolysis step. Extending this sequence to peptide oxazol-5(4H)-ones (3), as shown in SCHEME 2, a biogenetic route to acylimines (2), peptide C-terminal amides (5) and α-keto-acids (6) from peptide 'active esters' (1; Y = electron-withdrawing grouping) can be proposed; this route depends only on the establishment of appropriate conditions for the in vivo oxidative dimerisation of peptide oxazol-5(4H)-ones (known[4] to be readily formed from peptide 'active esters') and for the subsequent hydrolytic steps.



SCHEME 2

Oxidative dimerisation of 4-substituted 2-benzyloxy-thiazol-5(4H)-ones[6] and of 2-phenyl analogues[7] can be brought about using iodine and triethylamine.[6,7] We have accounted for the changes observed[8] in the UV spectra of dioxan solutions of 2-phenylthiazol-5(4H)-ones in terms of the same oxidative dimerisation, brought about by peroxides generated by photo-oxygenation of the solvent.[9,10] The dimers (analogues of (4) with S in place of ring O) are slowly hydrolysed in neutral aqueous dioxan at room temperature in accordance with Steglich's scheme (see SCHEME 2) for oxazol-5(4H)-one dimers.

Trichotomine was not formed in aqueous dioxan under air from L-tryptophan alone, with L-glutamic acid, or with N-thiobenzoyl-L-glutamic acid.

We have established that peptide oxazol-5(4H)-ones (3) also undergo oxidative dimerisation, either by treatment with iodine - triethylamine or by oxygenation in aqueous dioxan, and that the dimers undergo hydrolysis in neutral aqueous solution following the steps in SCHEME 2. Thus, N-benzoyl-glycinamide was formed from N-benzoyl-glycyl-L-phenylalanine by oxygenation of the derived oxazol-5(4H)-one in neutral aqueous dioxan.

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