Anchimeric Acceleration of the Aminolysis of Esters and its Application to Peptide Synthesis

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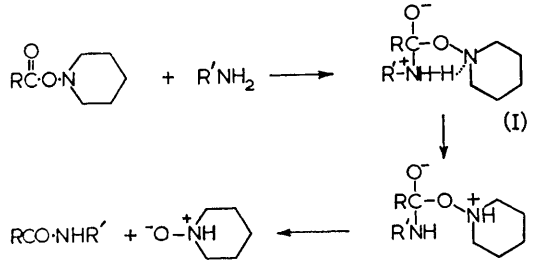
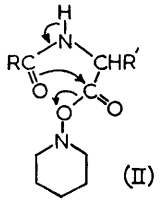
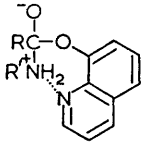
THE uncatalysed reaction of 1-piperidyl esters with highly nucleophilic amines such as benzylamine[1] is unexpectedly rapid for an ester of such a weakly acidic hydroxy-compound (hydroxylamine has been estimated[2] to have pK_a 12—13), and we have suggested[1] that this is due to stabilisation of the transition complex for the formation of the adduct (I) by hydrogen-bonding with the incoming amine; the subsequent elimination would be aided by the transfer of a proton to the piperidyl-nitrogen, as in the Scheme:



We have pointed out[3] that such assistance would not be available for oxazolone formation from an acylamido-ester, because the nucleophilic group bears no hydrogen (see structure II);



(II)



(III)

since racemisation during peptide-coupling reactions is believed to proceed through the intermediate formation of an oxazolone,[4] this would explain the absence of racemisation in such cases. (It should be noted that these uncatalysed reactions are distinct from the acid-catalysed condensations normally used for peptide synthesis).[1]

Recently it has been shown[5,6] that acylamido-esters of 8-hydroxyquinoline (oxine) condense rapidly with benzylamine, and in standard tests couple without racemisation.[7] We have found that the rate of condensation of the oxine ester of benzyloxycarbonyl-L-valine with glycine ethyl ester in dioxan is comparable to that of the corresponding *p*-nitrophenyl ester, although the phenols concerned have pK_a 9·8 and 7·15 respectively;[8] the analogous ester of 1-naphthol (pK_a 9·4[9]) reacts very slowly indeed. The addition of triethylamine to a solution of benzoyl-L-leucine oxine ester in chloroform gave no oxazolone-carbonyl infrared absorption (at 1830 cm.$^{-1}$), although the analogous *p*-nitrophenyl ester gives strong absorption, under the same conditions. These observations can again be explained by acceleration of the aminolysis (but not of oxazolone formation) due to a hydrogen-bonded transition complex for the formation of the adduct (III), with subsequent proton-transfer to the nitrogen of the ring. This explanation of the acceleration of the aminolysis has also been advanced by Jakubke and Voigt.[6]

It appears therefore that selective acceleration of the reaction of active esters with amines, without encouraging oxazolone formation (and hence

racemisation) can be achieved by introducing in a suitable position an atom or group capable of hydrogen-bonding to, and then accepting a proton from, the incoming amine. The behaviour of mono-esters of catechol (pK_a 9·5[8]), known to solvolyse abnormally rapidly,[10] confirm this hypothesis. Phthaloylglycine *o*-hydroxyphenyl ester (m.p. 139—141°), prepared by the action of *o*-phenylene sulphite[11] on phthaloylglycine in pyridine, condensed with glycine ethyl ester hydrochloride and an equivalent of triethylamine in chloroform at room temperature to give a 91% crude yield of peptide in 1 hr.; this indicates a reactivity comparable with that of a *p*-nitrophenyl ester. Benzoyl-DL-leucine *o*-hydroxyphenyl ester (m.p. 145—147°) was prepared by the reaction of the mixed carbonic anhydride of benzoyl-DL-leucine with two equivalents each of catechol and triethylamine. With triethylamine in chloroform it gave no oxazolone-carbonyl infrared absorption, yet with glycine ethyl ester hydrochloride with an equivalent of triethylamine in chloroform it gave an 89% yield of crude peptide after 1·5 hr. at room temperature. We believe that these observations provide a basis for the development of further racemisation-free methods of peptide synthesis.

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