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Studies on Peptides. XXXVI.[1] Chloro-substituted 8-Hydroxyquinoline Derivatives, as Racemization Suppressing Reagents in Peptide Synthesis

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As an active ester in peptide synthesis, the 8-hydroxyquinolyl ester of N-protected amino acids was first introduced by Jakubke[3] in 1965. This bifunctional active ester, as examined in detail by the same authors,[4] suppresses the rate of racemization during the aminolysis.

Applying the system of Bodanszky and Conklin,[5] known as one of convenient and sensitive tests for racemization, we have measured the degree of racemization which occured during the coupling reaction of Ac-L-Ile-OH with H-Gly-OEt by dicyclohexylcarbodiimide (DCC) plus 8-hydroxyquinoline or its commercially available chloro-derivatives: 5-chloro or 5,7-dichloro-8-hydroxyquinoline. As shown in Table I, racemization decreases as the number of chlorosubstituents of these reagents increases. It appears, therefore, that the pK_a values of these reagents[6] are closely associated with this tendency.

Under identical conditions, the reaction of DCC alone gave a racemate in 27.4%,[7] while DCC plus N-hydroxybenztriazole[8] gave only 2.4%. These results suggest that 5,7-dichloro-8-hydroxyquinoline is an effective racemization-depressant nearly comparable to N-hydroxybenztriazole, known as the most effective reagent for the racemization-free peptide synthesis.

TABLE I. Degree of Racemization

Reagent	8-Hydroxy-quinoline	5-Chloro-8-hydroxy-quinoline	5,7-Dichloro-8-hydroxy-quinoline
Racemization %	21.3	12.4	5.3

Experimental

Ac-Ile-Gly-OEt——To a solution of Ac-L-Ile-OH (0.87 g, 0.5 mmole) in dimethylformamide (20 ml), H-Gly-OEt (prepared from 0.7 g of the hydrochloride with 0.7 ml of triethylamine) in dimethylformamide (10 ml) was combined. To this solution, DCC (0.5 mmole) and 8-hydroxyquinoline or 5-chloro-8-hydroxyquinoline or 5,7-dichloro-8-hydroxyquinoline (0.5 mmole each) was added. The solution, after stirring at 20° for 18 hr, was filtered and then evaporated *in vacuo* under 45°. The residue was dissolved in AcOEt, which after washing with 10% citric acid, 5% Na_2CO_3 and H_2O–NaCl, was dried over Na_2SO_4 and then evaporated. The solid residue was dried over P_2O_5 *in vacuo*. The racemate, allo-D-Ile-OH, was determined quantitatively, after acid hydrolysis with 6N HCl for 18 hr, by the amino acid analyzor (Spackman–Stein–Moore method).[9] Acid hydrolysate of the starting Ac–L-Ile–OH gave no measurable racemate and the results were listed in Table I.

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