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THE PREPARATION OF N-FORMYL DERIVATIVES OF AMINO-ACIDS USING N,N'-DICYCLOHEXYLCARBODI-IMIDE

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There have been several examples of the use of formyl groups for the protection of amino functions in peptide synthesis.[1-3] In these cases N-formylation of the free amino-acids was achieved without racemisation, by treatment with a mixture of excess formic acid and acetic anhydride at 5-15°.[4] Clearly, this method cannot be used with sensitive hydroxyamino-acids such as serine and threonine, or with amino-acid derivatives incorporating acid-labile protecting groups such as O-t-butyl. In this connection we have established that it is possible to effect N-formylation of amino-acid benzyl esters, without racemisation and in good yield, using N,N'-dicyclohexylcarbodi-imide[5] (DCCI).

Amino-acid benzyl esters were liberated from their p-toluenesulphonate salts in chloroform by the addition of triethylamine (1 molar equiv.). The free base, so formed, was formylated *in situ* at 0° using formic acid (1 molar equiv.) in the presence of DCCI (1 molar equiv.). In the case of serine the side-chain hydroxyl group was converted to the O-t-butyl derivative[6] before N-formylation. The N-formyl benzyl esters of glycine, β-alanine and L-leucine were obtained as oils in 60-90% yield (based on the p-toluenesulphonate salts); O-t-butyl-N-formyl-DL-serine benzyl ester (65% yield) was a crystalline solid, m.p. 74-75°. They all gave single ninhydrin-negative, iodine-positive spots on thin-layer chromatography (Kieselgel G) using ethyl acetate. Satisfactory C, H and N analyses were obtained for O-t-butyl-N-formyl-DL-serine benzyl ester, and for O-t-butyl-N-formyl-DL-serine (m.p. 160-163°) and N-formyl-β-alanine (m.p. 74-75°) which were obtained from the corresponding benzyl esters by hydrogenolysis. N-Formyl-L-leucine, similarly prepared, had m.p. 139-142°,

$[\alpha]_D^{20}$ - 18.6° ± 0.2° (c 10 in ethanol). The same compound, when prepared by resolution of the racemate using brucine, was reported[7] as having m.p. 141-144°, $[\alpha]_D^{20}$ - 18.5° ± 0.2° (c 10 in ethanol). Evidently no racemisation occurred during the course of formylation using DCCI.

N-Formyl groups are usually removed by mild acid hydrolysis[3,4,7] or alcoholysis.[8] We have found that acetyl chloride in benzyl alcohol as suggested by Bricas,[9] will deformylate N-formyl amino-acid benzyl esters in good yield during 24 hr. at 20°, or 3 hr. at 60°. Oxidative cleavage using hydrogen peroxide[10] might prove useful for selective removal of an N-formyl group in the presence of other acid-sensitive groups, such as t-butyl ethers and esters.

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