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A PROMISING MODIFICATION OF THE CARBODIIMIDE METHOD USING AN INSOLUBLE CARBODIIMIDE

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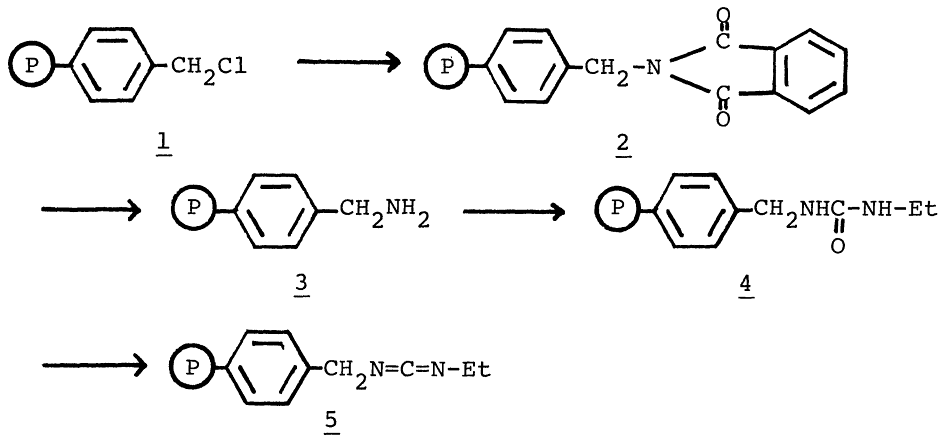
A modified polystyrene-divinylbenzene copolymer, in which ethylcarbodiimidomethyl groups were linked so as to be available as a condensing agent for peptide synthesis, were prepared. This polymer proved of great use in synthesizing some protected peptides without accompanying any troublesome by-product which would otherwise be formed.

As the carbodiimide method[1)] is exceedingly simple in operations, it has been widely used for peptide synthesis. However, because of the formation of acylureas[2)] that is inherent in the method, the desired peptides may occasionally be obtained only in unsatisfactory yields and purities. To get over the difficulties in using the method, an insoluble styrene-divinylbenzene copolymer containing an unsymmetrically substituted carbodiimide group was employed in the place of dicyclohexylcarbodiimide (DCC) and found to give excellent results in peptide synthesis.

Chloromethylated polystyrene[3)] (divinylbenzene 2%, 100-200 mesh, Cl-content 0.86 mmole/g) (1) was smoothly converted within 4 hr to phthalimidomethylated polystyrene (ir 1720 cm^{-1}) (2) with potassium phthalimide in dimethylformamide (DMF), at 40°C. Warming with hydrazine hydrate (in DMF) for 8 hr followed by treating with 0.1N HCl-dioxane for 1 hr produced aminomethyated polystyrene (ir 3350 cm^{-1}, no C=O stretching frequency) (3) of which amino group content (0.6 meq/g) was determined following the method of Dorman[4)] and suggested about 70% conversion of the initial chlorine atoms in 1 to amino groups at this atage. The reaction of ethylisocyanate ($Et_2O-CH_2Cl_2$, room temperature) with 3 afforded ethyl-



carbamidomethylated polystyrene (ir 3350, 1640 cm^{-1}) (4). Finally, ethylcarbodiimidomethylated polystyrene (ir 2130 cm^{-1}) (5) was obtained when 4 was heated at 70°C for 1.5 hr together with pyridine and p-toluenesulfonyl chloride.

The capacity of 5 for producing peptides was estimated by measuring the quantity of Dnps(2,4-dinitrophenylthio)-Gly-L-Val-OMe[5] (λ_{max} 333 nm, $\varepsilon=6.88\times10^3$) produced when a mixture of Dnps-Gly[6] and L-Val-OMe was treated with a smaller quantity of 5 in CH_2Cl_2 for 16 hr. In this case 1 g of 5 could afford 0.43 mmole of the expected peptide.

Thus Dnps-L-Cys(Bzl)-Gly-OEt[5] (mp 165-166°, $[\alpha]_D$ -68.4°) was synthesized in good yield from the reaction in CH_2Cl_2 between Dnps-L-Cys(Bzl) and Gly-OMe via contacting with 5 for 2 hr at room temperature. In similar manners Dnps-L-Arg(Tos)-L-Arg(Tos)-OBzl[7] (mp 103-105°, $[\alpha]_D$ -35.2°) was afforded from Dnps-L-Arg(Tos) and L-Arg(Tos)-OBzl. Since in all cases above no by-product was detected in the solutions, which would be linked to the insoluble polymer if actually formed, the isolation of the desired dipeptides were remarkably easy.

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