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A NOVEL PEPTIDE SYNTHESIS

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IT has recently been shown by one of us (Z.A.) that N,N-dimethylformamide gives with carbonyl chloride an immonium chloride of the structure $\left[(CH_3)_2N{:}CH.Cl\right]^+ Cl^-$ which has been successfully applied as a reagent in the Vilsmeier-Haack aldehyde synthesis[1-3]. We have now been able to show that this compound is also an effective reagent for the synthesis of peptide bonds.

The reaction is carried out by treating one mole of the protected amino-acid or peptide with one mole of reagent in suitable solvent (e.g. chloroform, dichloromethane, dimethylformamide) with cooling (-5 to -10°) and adding the reaction mixture to a cooled (0°) solution of an amino-acid ester or peptide ester hydrochloride (one mole) containing three moles of a tertiary base. The reaction can be performed at temperatures as low as -70°.

Peptide derivatives synthesised in this way are listed in the Table. The results indicate that no racemisation took place when S-benzyl-N-benzyl-

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[1] Z. Arnold and F. Šorm, Chem. listy 51, 1082 (1957); Coll. Czech. Chem. Comm. 23, 452 (1958).

[2] Z. Arnold, Chem. listy 52, 2013 (1958); Coll. Czech. Chem. Comm. 24, 4048 (1959).

[3] Z. Arnold and F. Šorm, Czechoslovak Patent 90,045 (1956).

TABLE

Product	Yield percent	M.p.
Phthaloylglycylglycine ethylester	86	194° [4]
Toluene-p-sulphonyl-L-leucylglycine methyl ester	78	116-117°
Benzyloxycarbonylglycylglycine methyl ester	77	66-67° [5]
S-Benzyl-N-benzyloxycarbonyl-L-cysteinylglycine methyl ester	80	106-107° [a]
S-Benzyl-N-benzyloxycarbonyl-L-cysteinylglycine ethyl ester	74	99-100° [b, 6]
N^{α}-Benzyloxycarbonyl-N^{ϵ}-toluene-p-sulphonyl-L-lysylglycine ethyl ester	75	153-154° [7]
N^{α}-(Benzyloxycarbonyl-L-prolyl)-N^{ϵ}-toluene-p-sulphonyl-L-lysylglycine ethyl ester [c]	88	151-152° [7]

[a] $[\alpha]_D^{23}$ -26.4 ± 0.5° (c 6, glacial acetic acid).

[b] $[\alpha]_D^{23}$ -26,8 ± 0.5° (c 6, glacial acetic acid); the literature[6] gives $[\alpha]_D^{20}$ -26.8° (c 6, glacial acetic acid).

[c] From benzyloxycarbonyl-L-proline and the dipeptide ethyl ester hydrobromide.

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[4] R.A. Boissonnas, Helv. Chim. Acta 34, 874 (1951).

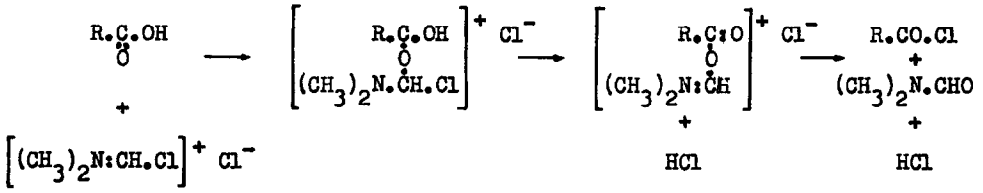
[5] N.F. Albertson and F.C. McKay, J. Amer. Chem. Soc. 75, 5323 (1953).

[6] S. Goldschmidt and Ch. Jutz, Chem. Ber. 86, 1116 (1953).

[7] R. Roeske, F.H.C. Stewart, R.J. Stedman and V. du Vigneaud, J. Amer. Chem. Soc. 78, 5883 (1956).

oxycarbonyl-L-cystein was used as the carboxyl component, but the synthesis of acetyl-L-leucylglycine ethyl ester (cf. 8) by the same procedure (-10°) was accompanied by extensive racemisation.

The way in which the carboxyl group is activated in this reaction has not so far been fully elucidated. In principle, the following reaction sequence may be envisaged:



The last stage of this reaction sequence is formulated as the reverse of the reaction between an acyl chloride and dimethylformamide[9]. The acyl chloride may in fact be isolated from the reaction mixture in suitable cases (e.g. phthaloylglycine) (cf. also 10). Neverthless it is possible that, at any rate at low temperatures, some of the postulated intermediates actually reacts as the species with an activated carboxyl group.

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[8] M.B. North and G.T. Young, Chem. & Ind. 1597 (1955); M.B. North, N.A. Smart and G.T. Young, Abstracts Proc. 19th Internat. Congr. Pure and Appl. Chem. Paris 1957 Vol. II, p. 238.

[9] H.K. Hall, J. Amer. Chem. Soc. 78, 2717 (1956).

[10] H.H. Bosshard, R. Mory, M. Schmid and H. Zollinger, Helv. Chim. Acta 42, 1653 (1959).

The structural similarity between $\left[(CH_3)_2N{:}CH.Cl\right]^+ Cl^-$ and the dimethylformamide-SO_3 complex[11] prompts the question whether the mechenism of peptide synthesis with the latter reagent[12,13] is analogous to that of the synthesis described here. Indeed this is a plausible alternative to the mechanism originally proposed[12,13] for the formation of the intermediate acyl sulphate, but further experimental evidence would be required to distinguish between them[14].

Since the reagent is readily accessible and stable in chloroform solution, the reaction conditions mild, the procedure simple and the yields generally high we believe that the new method may prove convenient, especially for the synthesis of relatively simple peptides on a large scale.

We wish to thank Academician F. Šorm for his support of this work.

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[11] S. Coffey, G.W. Driver, D.A.W. Fairweather and F. Irving, Brit. Patents 610,117 (1948) and 642,206 (1950).

[12] G.W. Kenner and R.J. Stedman, J. Chem. Soc. 2069 (1952).

[13] D.W. Clayton, J.A. Farrington, G.W. Kenner and J.M. Turner, ibid. 1398 (1957).

[14] We are indebted to Professor Kenner for discussion on this point.