N-Benzyl Derivatives of Amino-acids as Peptide Intermediates

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CURRENT views[1,2] on the mechanism of racemisation during the coupling step support the oxazolone hypothesis suggested some time ago to explain the racemisation of typical *N*-acyl derivatives of α-amino-acids by acetic anhydride.[3,4] Although the use of certain types of active esters[5–7] seems to

eradicate the racemisation danger during peptide synthesis, the experimental data accumulated so far do not permit a general acceptance of these esters.

As we have reported,[8] a possible way to avoid, or at least to minimize, racemisation during the coupling step would be the use of *N*-benzyl-L-amino-acid esters instead of the corresponding *N*-unprotected esters, *i.e.*, to transform an α-amino-acid ester into an α-imino-acid ester. This scheme of coupling is justified by the known fact that proline (a natural imino-acid) resists racemisation.[1]

In this Communication we report the synthesis of L-alanyl-L-phenylalanylglycine using *N*-benzyl-L-phenylalanine[9] and building up the tripeptide from the *N*-terminal amino-acid. Coupling of *N*-benzyloxycarbonyl-L-alanine with *N*-benzyl-L-phenylalanine methyl ester hydrochloride by the dicyclohexylcarbodi-imide method in the presence of triethylamine resulted in the formation of the corresponding dipeptide ester. This syrupy ester was saponified and crystalline *N*-benzyloxycarbonyl-L-alanyl-L-(*N*-benzyl)phenylalanine was obtained. The *N*-protected dipeptide was coupled with glycine benzyl ester tosylate by the dicyclohexylcarbodi-imid emethod. A sample of the tripeptide ester thus obtained was subjected to catalytic hydrogenation over palladium black catalyst, but attempted removal of the *N*-benzyl group was unsuccessful. Therefore, reduction with sodium in liquid ammonia was used for the removal of all three protecting groups; the free tripeptide L-alanyl-L-phenylalanylglycine was thus obtained in good yield. The same tripeptide was prepared by a stepwise synthesis starting from glycine benzyl ester tosylate and using the conventional methods of coupling; dicyclohexylcarbodi-imide was the condensing agent used. The optical rotation of the tripeptide obtained *via* *N*-benzyl-L-phenylalanine had the same value as that of the tripeptide synthesized in the conventional way. The use of substituted *N*-benzyl groups (*e.g.*, *p*-methoxybenzyl group) is currently being investigated so that the yield at the final step can be raised and reduction with sodium in liquid ammonia could be avoided.

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[1] For a Review, see I. Antonovics, A. L. Heard, J. Hugo, M. W. Williams, and G. T. Young, "Proceedings, 6th European Peptide Symposium, Athens, 1963, ed. L. Zervas, Pergamon Press, Oxford, 1966, p. 121.
[2] A. Prox, F. Weygand, W. König, and L. Schmidhammer, "Proceedings, 6th European Peptide Symposium, Athens, 1963", ed. L. Zervas, Pergamon Press, Oxford, 1966, p. 139.
[3] M. Bergmann and L. Zervas, *Biochem. Z.*, 1928, **203**, 280.
[4] A. Neuberger, *Adv. Protein Chem.*, 1948, **4**, 297.
[5] S. M. Beaumont, B. O. Handford, and G. T. Young, "Proceedings, 7th European Peptide Symposium, Budapest, 1964" *Acta Chim. Acad. Sci. Hung.*, 1965, **44**, 37; S. M. Beaumont, B. O. Handford, J. H. Jones, and G. T. Young, *Chem. Comm.*, 1965, 53; B. O. Handford, J. H. Jones, G. T. Young, and (in part) T. F. N. Johnson, *J. Chem. Soc.*, 1965, 6814.
[6] H. D. Jakubke, *Z. Naturforsch.*, 1965, **20b**, 273; *Annalen*, 1965, **682**, 244.
[7] S. Bittner, Y. Knofler, and M. Frankel, *Tetrahedron Letters*, 1965, 95.
[8] E. Gazis, D. Borovas, Ch. Hamalidis, G. C. Stelakatos, and L. Zervas, "Proceedings, 6th European Peptide Symposium, Athens, 1963", ed. L. Zervas, Pergamon Press, Oxford, 1966, p. 107.
[9] P. Quitt, J. Hellerbach, and K. Vogler, *Helv. Chim. Acta*, 1963, **46**, 327.