# The Preparation of β-Amino-acid Peptides using Oxazinones

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*Summary* Using normal peptide coupling agents it has proved extremely difficult to prepare peptides of 3-amino-3-methylbutanoic acid; however aminolysis of the intermediate oxazinone proceeds smoothly, yielding the required compounds.

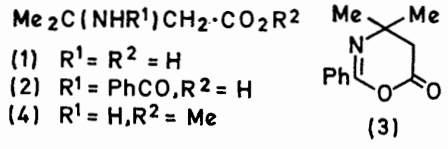
ATTEMPTS to prepare simple peptides from suitably *N*- and *C*-terminal protected derivatives of 3-amino-3-methylbutanoic acid (1) failed using conventional coupling reagents.†

Ollis and Baker[1] prepared the benzoyl derivative (2) of (1) and characterised the derivative oxazinone (3) as the anilide. This, and the analogy to oxazalones of sterically hindered amino-acids,[2] suggested to us that oxazinones of 3,3-dialkyl-β-amino-acids might prove to be useful coupling agents.

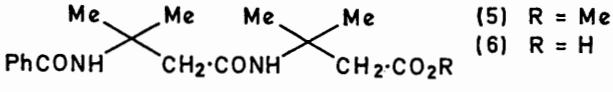
We found that aminolysis of (3) with the methyl ester (4) proceeded readily under reflux conditions yielding the protected dipeptide (5). Hydrolysis of (5) gave the dipeptide acid (6) which on treatment with acetic anhydride afforded the dipeptide oxazinone (7). Aminolysis of (7) with (4) gave the protected tripeptide (8) in an overall yield of 50%, a series of reactions in which all the intermediates were crystalline and analysed correctly.

The scope of the reaction will be increased by the substitution of other *N*-terminal acylprotecting groups, which is in hand, although the benzoyl group can be cleaved in the presence of peptide linkages by electrolysis.[3]

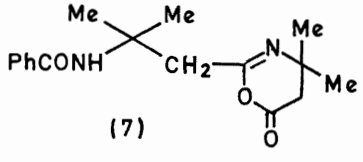
One of us (J.L.) thanks the I.L.E.A. for a studentship.



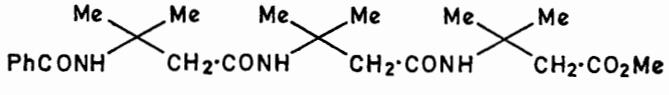

(3)




(5) R = Me
(6) R = H




(7)




(8)

(*Received, May 4th,* 1970; *Com.* 668.)

† *NN'*-Dicyclohexylcarbodi-imide, Woodward's reagent, isobutyl chloroformate.

[1] W. Baker and W. D. Ollis, *J. Chem. Soc.*, 1949, 345.
[2] M. T. Leplawy, D. S. Jones, G. W. Kenner, and R. C. Sheppard, *Tetrahedron*, 1960, **11**, 39; D. S. Jones, G. W. Kenner, J. Preston, and R. C. Sheppard, "Proc. 6th European Peptide Symposium, Athens, 1963," ed. L. Zervas, Pergamon, London, 1963, p. 313; *J. Chem. Soc.*, 1965, 6227; G. W. Kenner, J. Preston, and R. C. Sheppard, *ibid.*, p. 6239.
[3] L. Horner and H. Neumann, *Chem. Ber.*, 1965, **95** 3462.