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THE SYNTHESIS OF A PROTECTED HEPTAPEPTIDE RELATED TO EVOLIDINE: N-BENZYLOXYCARBONYL-L-LEUCYL-L-PROLYL-L-VALYL-L-ASPARAGINYL-L-LEUCYL-L-SERYL-L-PHENYLALANINE BENZYL ESTER

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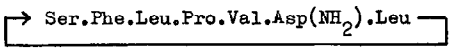
EVOLIDINE was isolated from the leaves of Evodia xanthoxyloides by Hughes, Neill and Ritchie[1], shown to be a peptide by Eastwood, Hughes and Ritchie[2], and to have the cyclic structure I by Law, Millar and Springall[3].



I[4]

The first attempts at synthesis[5] encountered intermediates which were difficult to purify, but we report now the synthesis of the protected heptapeptide N-benzyloxycarbonyl-L-leucyl-L-prolyl-L-valyl-L-asparaginyl-L-leucyl-L-seryl-L-phenylalanine benzyl peptide ester. The scheme is

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[1] G. K. Hughes, K. G. Neill and E. Ritchie, Austral.J.Agric.Res. A5, 401 (1952).

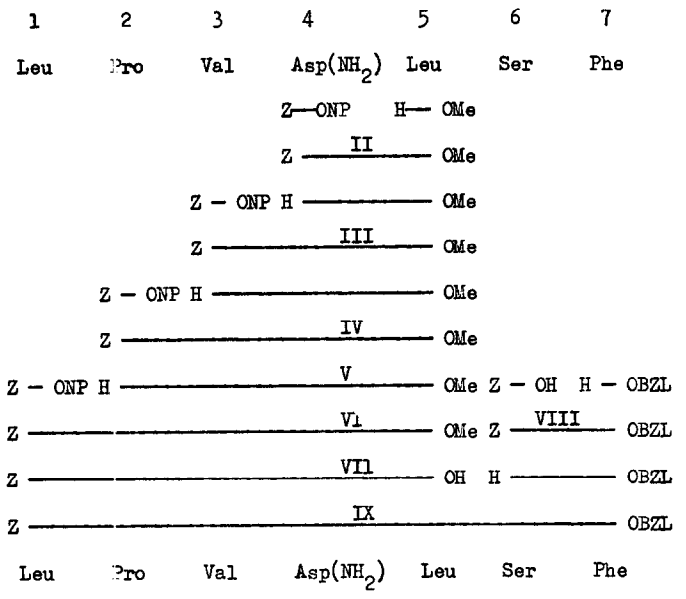
[2] F. W. Eastwood, G. K. Hughes and E. Ritchie, Austral.J.Chem. 8, 552, (1955).

[3] H. D. Law, I. T. Millar and H. D. Springall, J.Chem.Soc. 1961, 279.

[4] The abbreviations for the amino-acids are those recommended in the Tentative Rules for Abbreviations and Symbols for Chemical Names of Special Interest in Biological Chemistry, published as Appendix B to Information Bulletin No.12 of the International Union of Pure and Applied Chemistry.

[5] J. B. Capindale and G. T. Young, unpublished work.

set out below.



II: m.p. 179-181°, $[\alpha]_D^{22}$ -13.0° (Lit.[6]: m.p. 177.5-178.5°);

III: m.p. 239-241°, $[\alpha]_D^{22}$ -39.0°; IV: m.p. 230-232°, $[\alpha]_D^{22}$ -87.5°;

V: m.p. 184-186°, $[\alpha]_D^{22}$ -66.4°; VI: m.p. 176-178°, $[\alpha]_D^{22}$ -89.5°;

VII: m.p. 138-140°, $[\alpha]_D^{24}$ -88.0°; VIII: m.p. 129-130°, $[\alpha]_D^{24}$ -10.5°;

IX: m.p. 205-207°, $[\alpha]_D^{24}$ -75.5°.

Compounds III-IX are new; in each case satisfactory elemental analyses were obtained; specific rotations refer to 1% solutions in 95% acetic acid.

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[6] R. B. Woodward, R. A. Olofson and H. Mayer, J.Amer.Chem.Soc. 83, 1010 (1961).

The key peptide VI was built up by the p-nitrophenyl ester method[7]; at each stage, the benzyloxycarbonyl group was removed by catalytic hydrogenation, and the resulting peptide ester was used, without isolation, for the next coupling. Compound VIII was prepared by the use of dicyclohexylcarbodi-imide[8], and the benzyloxycarbonyl group was removed by means of hydrogen bromide in trifluoracetic acid[9]. The dipeptide ester so obtained was condensed with VII by means of dicyclohexylcarbodi-imide in dimethylformamide, giving crystalline protected heptapeptide IX.

The removal of the protecting groups and the cyclisation of the peptide so obtained are now being investigated.

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[7] see e.g. M. Bodanszky, Ann.N.Y.Acad.Sci. 88, 655 (1960).

[8] J. C. Sheehan and G. P. Hess, J.Amer.Chem.Soc. 77, 1067 (1955).

[9] St. Guttmann and R. A. Boissonnas, Helv.Chim.Acta 42, 1257 (1959).

[10] K. Vogler, H.C. Studer, W. Lergier and P. Lanz, Helv.Chim.Acta 43, 1751 (1960).