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THE USE OF N-ETHYLBENZISOXAZOLIUM CATION FOR THE CYCLIZATION OF PEPTIDES*

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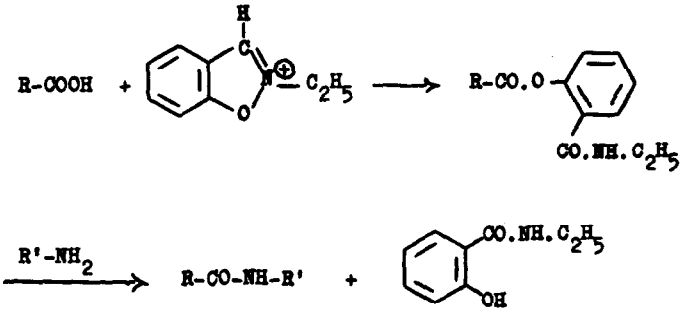
Woodward and Kemp have recently introduced the N-ethylbenzisoxazolium cation as a reagent for peptide coupling[1]. The reaction proceeds in two discrete stages, the first involving the formation of an active ester, and the second, its coupling with the amine component:



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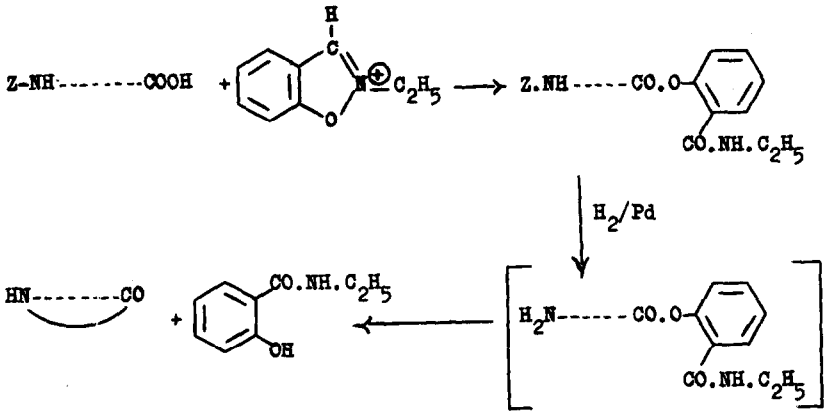
We wish to report the use of this reagent for the cyclization of peptides. The reaction proceeds as follows:



The advantages of this method are: (1) The protecting group can be removed by hydrogenolysis in neutral solution without affecting the active ester; (2) The by-product is easily removed by virtue of its ether and alkali solubility; (3) The yields of the cyclic peptides (see Table) are reasonable and compare favourably with those by other methods. As a specific instance, starting from the tripeptide acid Z.Gly.Phe.Gly.OH the overall yield (2 stages) of the cyclohexapeptide is 37.3%. This seems much superior to the p-nitrophenyl ester method[2], where the overall yield (3 stages) from the same starting compound is only 13.5%.

In the actual cyclization procedure, the N-carbobenzoxypeptide active ester was hydrogenolyzed in DMF solution in presence of Pd/C and then left at room temperature for 24-48 hrs. Evaporation of the solvent, followed by digestion of the residue with ether left the crude cyclic peptide. This was then purified by passage through anion and cation exchange resins.

The following linear tripeptides have been converted to the known cyclohexapeptides by this method: (See Table I).

The infrared spectra of the products were identical with those of authentic specimens or with the corresponding published spectra. Molecular weight determination (mass spectrum[6] and Vaporometric method[7]) confirmed that the compounds were the expected cyclodimers.

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TABLE I

Starting Peptide	Product	Yield %	$[\alpha]_D$ observed	$[\alpha]_D$ reported	Ref.
Z.Gly.Gly.Gly.OH	Cyclo $(Gly)_6$	70			3
Z.Gly.Phe.Gly.OH	Cyclo $(Gly.Phe.Gly)_2$	41	$-68 \pm 1^\circ$ (C, 1 in DMF)	$-79.8 \pm 1^\circ$	4
Z.Gly.Pro.Gly.OH	Cyclo $(Gly.Pro.Gly)_2$	44.4	$+44.2 \pm 2^\circ$ (C, 0.6 in water)	$+49.1 \pm 3^\circ$	5

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6. Kindly taken by Dr. H. Hörseler of CIBA Basle

7. We thank Dr. W. Padowetz of CIBA Basle for the molecular weight determinations.