Chemical Communications

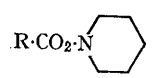
NUMBER 4/1965 24 FEBRUARY

The Use of Esters of *NN*-Dialkylhydroxylamines in Peptide Synthesis and as Selective Acylating Agents

By (Miss) S. M. Beaumont, B. O. Handford, J. H. Jones, and G. T. Young

(*The Dyson Perrins Laboratory, Oxford University*)

Bittner, Knobler, and Frankel have reported[1] the condensation of esters of *NN*-diethylhydroxylamine with amino-esters to yield peptides, but the reaction was slow ("some days" were required for completion at room temperature). We had previously reported the use of esters of 1-hydroxypiperidine in peptide synthesis,[2] and further work has confirmed our conclusion that when used under our conditions esters of dialkylhydroxylamines have considerable usefulness not only in this field but also as selective acylating agents.



(I)

1-Piperidyl esters (I) of acylamino-acids can be formed by the condensation of the acid with 1-hydroxypiperidine by use of dicyclohexylcarbodi-imide (method A), by treating an ethereal solution of the hydroxypiperidine with the acid chloride (method B), or by reaction of the carbonic mixed anhydride with 1-hydroxypiperidine (method C). In method B, the ester hydrochloride is precipitated; addition of aqueous sodium carbonate to the mixture liberates the free ester, which passes into the ether and is isolated in the usual way. The reaction of benzyloxycarbonyl-L-leucine 1-piperidyl ester with glycine ethyl ester (1·2 molar proportions) in dioxan is slower than is desirable for use in peptide synthesis, but the addition of 1·2 equivalents of acetic acid greatly reduces the time required (presumably *N*-protonation activates the piperidyl ester), and the use of glycine ethyl ester hydrochloride with an equivalent of sodium acetate trihydrate gives an 85% yield of pure peptide after a reaction time of only 2 hr. These last conditions, which have now proved successful in a considerable number of examples, provide a coupling reaction somewhat faster than with the analogous *p*-nitrophenyl ester. High yields of peptide (70–85% after recrystallisation) have also been obtained by the condensation of benzyloxycarbonylamino-acid 1-piperidyl esters with the sodium salts of amino-acids in aqueous dioxan (reaction time, 15–24 hr.). We also have made the ester of benzyloxycarbonylglycine with *NN*-diethylhydroxylamine mentioned by Bittner *et al.*,[1] and we have prepared the ester of phthaloylglycine with *NN*-dimethylhydroxylamine; the latter couples rapidly with glycine ethyl ester hydrochloride and sodium acetate (work with Mr. T. F. N. Johnson).

[1] S. Bittner, Y. Knobler, and M. Frankel, *Tetrahedron Letters*, 1965, 95.

[2] (Miss) S. M. Beaumont, B. O. Handford, and G. T. Young, Proc. 7th European Peptide Symposium, Budapest, 1964, to be published.

A coupling method is of restricted use if racemisation occurs (see *e.g.* ref. 3), and a remarkable feature of these active esters lies in their optical stability. A solution of benzoyl-L-leucine 1-piperidyl ester in chloroform containing one equivalent of triethylamine had an unchanged optical rotation after 14 days, and the solution showed no oxazolone-carbonyl infrared spectral absorption; under similar conditions, the corresponding *p*-nitrophenyl ester racemises rapidly and oxazolone is formed.[4] Further, in our racemisation test[3] (the condensation of benzoyl-L-leucine 1-piperidyl ester with glycine ethyl ester) no racemate was detected; the analogous coupling with the sodium salt of glycine also occurred without racemisation. In combining optical stability with high activity under optimum conditions these esters are rivalled only by acid azides. In our experience so far, the products of reaction from 1-piperidyl esters are remarkably pure, the co-product, 1-hydroxypiperidine, being very readily washed out by acid, and soluble in all common solvents. It should be noted, however, that, as in the case of all other active esters, no procedure is yet available by which an acyldipeptide can be converted directly into its active ester without danger of racemisation.

Wider application of such esters is suggested by the use of benzyl 1-piperidyl carbonate and its *p*-nitrobenzyl analogue (conveniently prepared by method B) for the preparation of benzyloxycarbonyl- and *p*-nitrobenzyloxycarbonyl-amino-esters (using the amino-ester hydrochloride and sodium acetate trihydrate in dioxan). The acylation of amines by means of 1-piperidyl esters is markedly selective. Whereas, for example, strongly nucleophilic amines such as benzylamine and n-butylamine react completely with 1-benzoyloxypiperidine at 24° within 48 hr., aniline and the sterically-hindered t-butylamine are unattacked, and cyclohexylamine and isopropylamine are only slightly attacked, in that time.

(*Received, January 18th,* 1965.)

[3] M. W. Williams and G. T. Young, *J.*, 1963, 881.
[4] M. W. Williams and G. T. Young, *J.*, 1964, 3701.