Piperidinoxycarbonylamino-acids: a New Amino-protecting Group

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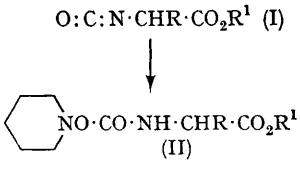
THE reaction of α-isocyanato-esters[1](I) with 1-hydroxypiperidine in light petroleum has given piperidinoxycarbonylamino-esters (II), which were hydrolysed by sodium hydroxide to piperidinoxycarbonylamino-acids. These are conveniently isolated and stored as their dicyclohexylammonium salts (see Table). Piperidinoxycarbonyl-L-phenylalanine methyl ester has also been prepared directly by the reaction of *p*-nitrophenyl-1-piperidyl carbonate (m.p. 79—80°, prepared from *p*-nitrophenyl chloroformate and 1-hydroxypiperidine in ether, by Method B in ref. 2) with L-phenylalanine methyl ester in dioxan.

The piperidinoxycarbonyl group is unexpectedly stable to acid; for example, piperidinoxycarbonyl-L-phenylalanine methyl ester was recovered unchanged in 92% yield from a solution of 6N-hydrogen bromide in acetic acid after 3 hr. at room temperature, and after 24 hr. of such treatment no phenylalanine methyl ester could be detected by



thin-layer chromatography. The same piperidinoxycarbonyl derivative was recovered unchanged in similar yield after 24 hr. in trifluoroacetic acid, in dioxan containing hydrogen chloride (7N), or in chloroform containing hydrogen chloride (0·44N), at room temperature. The piperidinoxycarbonyl group can be removed by brief heating with 50%

TABLE

Piperidinoxycarbonylamino-acids, esters, and salts[a]

(II)				Dicyclohexylammonium salt	
R	R^1	m.p.°	$[\alpha]_D^{20}$[b]	m.p.°	$[\alpha]_{365}^{20}$[c]
H	H	119—120°	—	145—150° (d)	—
H	Et	53—54°	—	—	—
Me_2CH	H	92—94°	+25·5°	139—141°	+40·7
$Me_2CH{\cdot}CH_2$	H	—	—	141—143°	+5·4°
$Me_2CH{\cdot}CH_2$	Me	52—53°	−11·9°	—	—
$PhCH_2$	H	79—81°	−16·9	140—141°	+67·7
$PhCH_2$	Me	79°	−27·8°	—	—
$PhCH_2{\cdot}S{\cdot}CH_2$	H	—	—	109—110°	−6·1°
$PhCH_2{\cdot}S{\cdot}CH_2$	Et	55—56°	−53·2°	—	—

[a] Satisfactory elemental analyses were obtained for each compound.
[b] *c* 1·0 in $HCO{\cdot}NMe_2$.
[c] *c* 1·0 in EtOH.

acetic acid, but cleaner products are obtained under reducing conditions, *e.g.*, zinc and aqueous acetic acid or sodium dithionite in aqueous acetic acid. Conveniently, it can be removed by electrolytic reduction in a mixture of 1N-sulphuric acid and tetrahydrofuran (1 : 1) in the simple cell used earlier for the electrolytic removal of the nitro-group from nitroarginine and its derivatives.[3] The sulphuric acid was removed by Dowex-3 (AcO^-) resin, and, for example, from piperidinoxycarbonyl-glycine and -L-phenylalanine the amino-acid was recovered in 93% and 90% yield, respectively. Hydrogenation in 50% acetic acid, in the presence of palladium on charcoal, is equally effective (95% yield of amino-acid from piperidinoxycarbonyl-L-phenylalanine). The difference in the stability between the piperidinoxycarbonyl group and the amino-protecting groups in common use (*e.g.*, benzyloxycarbonyl is rapidly removed by hydrogen bromide in acetic acid, but is stable to electrolytic reduction[3]) may prove valuable when selective protection is required, particularly during peptide synthesis.

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