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## Protection of Cysteine and Histidine by the Diphenyl-4-pyridylmethyl Group during Peptide Synthesis

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*Summary* The diphenyl-4-pyridylmethyl group provides acid-stable protection of the thiol group of cysteine and the imidazole-nitrogen of histidine; it is removed by reductive methods (including electrolytic reduction) and from thiols by mercury(II) acetate and by iodine.

THE insertion of a basic residue such as pyridyl into an acid-labile group greatly increases the stability to acid, presumably by distracting the attacking proton on to a non-productive site,<sup>1</sup> a method of modifying reactivity

which appears to have received little attention in organic synthesis. Thus we find that whereas S-tritylcysteine is rapidly cleaved by acid, S-diphenyl-4-pyridylmethyl-Lcysteine (1) can be recovered unchanged after 48 h in trifluoroacetic acid or in 45% hydrogen bromide in acetic acid at room temperature. The protection is removed by mercury(II) acetate in aqueous acetic acid at pH 4 (15 min), by iodine in 80% acetic acid (1.5 h), by zinc and acetic acid (15 min) (all at room temperature), and by electrolytic reduction at a mercury cathode<sup>2</sup> (45 min at 0 °C).

The sulphide (1) was prepared by the reaction of Lcysteine hydrochloride with diphenyl-4-pyridylmethanol<sup>3</sup> and boron trifluoride-ether in acetic acid at 60°C (48 h); it had m.p. 154—157 °C,  $[\alpha]_{D}^{20} + 51^{\circ}$  (c 2·1 in M-HCl). The

Cys-Ala NH2•CH•CO2H I CH<sub>2</sub>•SCPh<sub>2</sub>Py ĊPh<sub>2</sub>Py (2)(1)

Boc-Ile-Ala-Cys-Ala-Cys-Ala-OPic	Ile-Ala-Cys-Asn-Cys-Ala
 CPh <sub>2</sub> Py CPh <sub>2</sub> Py	 CPh <sub>2</sub> Py CPh <sub>2</sub> Py
(3)	(4)

Boc-Gly-His Boc-His-OMe Z-His CPh<sub>2</sub>Py ĊPh<sub>2</sub>Py CPh<sub>2</sub>Py (7)(5) (6)

> Py = 4 - pyridyl;Pic = 4-picolyl

dicyclohexylammonium salts of the t-butoxycarbonyl and benzyloxy carbonyl derivatives had m.p. 202—204 °C,  $[\alpha]_{\rm D}^{20}$ +19°, and m.p. 170-172 °C,  $[\alpha]_{D}^{20}$  + 26° (c 1 in CHCl<sub>3</sub>), respectively; the latter was prepared by the use of benzyl 981

succinimido carbonate and tetramethylguanidine in chloroform. The protected peptides (2), (3), and (4) were synthesised by the picolyl ester method<sup>4</sup> using standard procedures. Deprotection of (2) by means of iodine in 60%acetic acid gave L-cystinyl-di-L-alanine in 91% yield. The removal of the S-diphenyl-4-pyridylmethyl groups from (3) and (4) was effected satisfactorily by means of mercury-(II) acetate in 50% acetic acid and by iodine in 60% acetic acid, respectively.

The same group provides an improved protection of the imidazole-nitrogen of histidine. Diphenyl-4-pyridylmethyl chloride<sup>5</sup> reacted with  $N(\alpha)$ -t-butoxycarbonyl-L-histidine methyl ester and triethylamine in chloroform giving the N(Im)-diphenyl-4-pyridylmethyl derivative (5) (oil;  $[\alpha]_{\mathbf{p}}^{20}$  $+2^{\circ}$ , c 1 in MeOH), and the  $N(\alpha)$ -benzyloxycarbonyl analogue was prepared similarly and was hydrolysed to the acid (6) {m.p. 108—111 °C,  $[\alpha]_{D}^{20} + 13^{\circ}$  (c 1 in Me<sub>2</sub>N-CHO) }. This acid was recovered unchanged from trifluoroacetic acid after 48 h at 21 °C; 45% hydrogen bromide in acetic acid (1 h) removed only the benzyloxycarbonyl group. By standard methods the protected peptide (7) was prepared, from which the diphenyl-4-pyridylmethyl group was removed by hydrogenolysis (Pd-C) in 91% yield. It was removed from (5) by zinc and acetic acid (1.5 h; 91%)yield) and by electrolytic reduction (2.5 h, 0 °C; 87% yield).

It will be noted that this new protecting group has the additional advantage of providing a weakly basic 'handle,' which assists the isolation of the coupling product during peptide synthesis.6

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  <sup>6</sup> For a review, see G. T. Young in 'The Chemistry of Polypeptides,' ed. P. G. Katsoyannis, Plenum Press, New York, 1973, p. 43.