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

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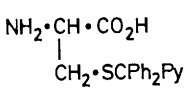
*Summary* The diphenyl-4-pyridylmethyl group provides acid-stable protection of the thiol group of cysteine and the imidazole-nitrogen of histidine; it is removed by reductive methods (including electrolytic reduction) and from thiols by mercury(II) acetate and by iodine.

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,[1] 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-L-cysteine (**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[2] (45 min at 0 °C).

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



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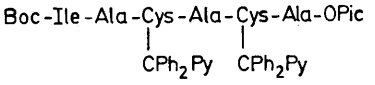

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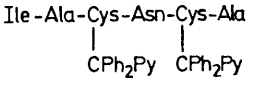

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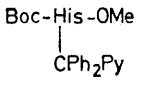

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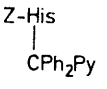

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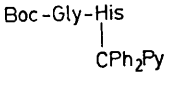

(7)

Py = 4-pyridyl; Pic = 4-picolyl

dicyclohexylammonium salts of the t-butoxycarbonyl and benzyloxycarbonyl derivatives had m.p. 202—204 °C, $[\alpha]_D^{20}$ +19°, and m.p. 170—172 °C, $[\alpha]_D^{20}$ + 26° (*c* 1 in $CHCl_3$), respectively; the latter was prepared by the use of benzyl succinimido carbonate and tetramethylguanidine in chloroform. The protected peptides (**2**), (**3**), and (**4**) were synthesised by the picolyl ester method[4] 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[5] reacted with *N*(α)-t-butoxycarbonyl-L-histidine methyl ester and triethylamine in chloroform giving the *N*(Im)-diphenyl-4-pyridylmethyl derivative (**5**) (oil; $[\alpha]_D^{20}$ +2°, *c* 1 in MeOH), and the *N*(α)-benzyloxycarbonyl analogue was prepared similarly and was hydrolysed to the acid (**6**) {m.p. 108—111 °C, $[\alpha]_D^{20}$ + 13° (*c* 1 in $Me_2N$-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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[6] For a review, see G. T. Young in 'The Chemistry of Polypeptides,' ed. P. G. Katsoyannis, Plenum Press, New York, 1973, p. 43.