Protection of Thiol and Phenolic Hydroxy-groups as their 4-Picolyl Ethers, Cleaved by Electrolytic Reduction

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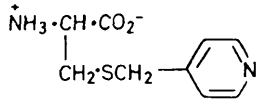
Summary The 4-picolyl group, removable by electrolytic reduction, has been used to protect the thiol group of cysteine and the hydroxy-group of tyrosine during peptide synthesis.

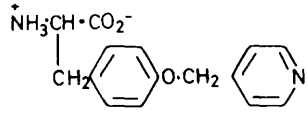
PROTECTING groups removable by reductive methods are especially valuable in peptide synthesis. Catalytic hydrogenation usually fails in the presence of sulphur, but we found earlier[1] that the nitro-group could be cleaved smoothly from nitroarginine by electrolytic reduction at a mercury cathode, even in the presence of cysteine and methionine residues. We have since shown that the piperidino-oxycarbonyl amino-protecting group[2] and the 4-picolyl carboxy-protecting group,[3] can be removed similarly,[4] and we now report the extension of this series with the use of 4-picolyl for the protection of the thiol group of cysteine and the phenolic group of tyrosine.

S-4-Picolyl-L-cysteine (I) was prepared by the reaction of purified 4-picolyl chloride with the solution obtained by the reduction of L-cystine by sodium in liquid ammonia; after recrystallisation from methanol–water the yield was 68%; m.p. 210—211°, $[\alpha]_D^{20}$ −10° (*c* 1 in N-HCl). It was

completely stable for 7 days at room temperature in trifluoroacetic acid or in 32% hydrogen bromide in acetic acid. Electrolytic reduction[1] of a solution in 0·5N-sulphuric acid gave L-cysteine (88% yield); in a similar experiment the reduced solution was reoxidised by air at pH 8 and pure L-cystine was recovered. The Scheme outlines the use of (I) in the synthesis of L-cystinyl-bis-glycine.

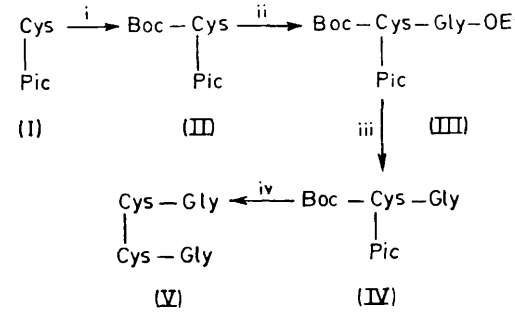


(I)



(VI)

Following preliminary work with Dr. A. Kotai, we have also used *O*-4-picolyltyrosine in synthesis. The nickel complex of L-tyrosine was alkylated by 4-picolyl chloride and sodium hydroxide in aqueous ethanol; nickel was removed by means of ethylenediaminetetra-acetic acid, and the crude *O*-4-picolyl-L-tyrosine (VI) was converted into the t-butoxycarbonyl derivative, m.p. 180—181°, $[\alpha]_D^{20}$ −12° (*c* 1·1 in Me_2NCHO). By a series of reactions analogous to those shown in the Scheme, *N*-t-butoxycarbonyl-*O*-4-picolyl-L-tyrosylglycine, m.p. 187°, $[\alpha]_D^{20}$ −7° (*c* 1 in Me_2N-CHO), was synthesised, and the action of trifluoroacetic acid followed by electrolytic reduction gave authentic L-tyrosylglycine of $[\alpha]_D^{20}$ +81° (*c* 1 in H_2O); lit.[5], $[\alpha]_D^{23}$ +82·6° (*c* 2 in H_2O).



SCHEME

Reagents: Boc = *t-butoxycarbonyl*, i, Boc-N_3, *yield* 87%; ii, Gly-OEt *and dicyclohexylcarbodi-imide, yield* 98%; iii, N-NaOH *in dioxan, yield* 83%; iv, $CF_3{\cdot}CO_2H$, *electrolytic reduction, and oxidation by air, yield* 75%. *Compound* (II), m.p. 138—139°, $[\alpha]_D^{20}$ −42°; (III), *m.p.* 90—91°, $[\alpha]_D^{20}$ +24° (c 1·2 *in* $CHCl_3$); (IV), m.p. 179—181°, $[\alpha]_D^{20}$ −34°; (V), $[\alpha]_D^{20}$ −98° (c 0·1 *in* 0·1 N-HCl). *Optical rotations are in dimethylformamide* (c 1) *unless otherwise stated. New compounds had satisfactory elemental analyses.*

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[3] R. Camble, R. Garner, and G. T. Young, *J. Chem. Soc.* (*C*), 1969, 1911.
[4] Unpublished work with D. Stevenson and W. B. Watkins
[5] J. L. Bailey, *J. Chem. Soc.*, 1950, 3461.