New Method for the Cleavage of the *S*-*p*-Methoxybenzyl and *S*-t-Butyl Groups of Cysteine Residues with Mercury(II) Trifluoroactate

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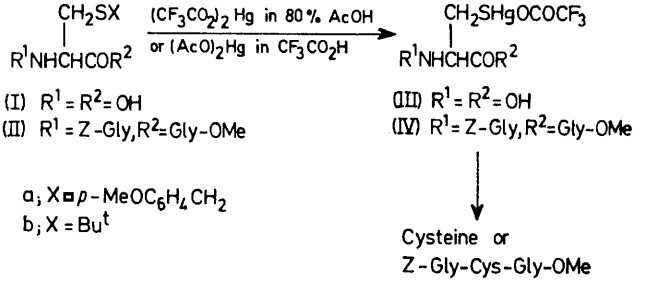
Summary Sulphydryl protecting groups (*p*-methoxybenzyl and t-butyl), for cysteine are cleanly removed by the action of mercury(II) trifluoroacetate in aqueous acetic acid or mercury(II) acetate in trifluoroacetic acid; treatment of the sulphides formed with thiols regenerates the cysteine derivatives.

THE *p*-methoxybenzyl (MBzl) protecting group[1] for the thiol function is now widely used in peptide chemistry. This group is usually removed with strong acids such as hydrogen fluoride[2] or trifluoromethanesulphonic acid.[3] However, treatment with a strong acid makes selective removal difficult. The t-butyl sulphides of cysteine derivatives can be easily prepared[4] but a method for the cleavage of this group has not yet been found.[5]

We have now demonstrated that mercury(II) trifluoroacetate[6] can be used to cleave the S-MBzl and S-Bu^t groups. When the S-MBzl or the S-Bu^t derivatives of cysteine (Ia, Ib) or Z-Gly-Cys-Gly-OMe (IIa, IIb) were treated with *ca.* 1 equiv. of mercury(II) trifluoroacetate in aqueous acetic acid (20 °C, 2—3 h) or mercury(II) acetate in trifluoroacetic acid (0 °C, 10—30 min), the starting material (I) or (II) smoothly reacted almost quantitatively to give the corresponding sulphides (III) or (IV), the thiol function of which was easily regenerated by standard procedures such as treatment with hydrogen sulphide or mercaptoethanol to give cysteine or Z-Gly-Cys-Gly-OMe in nearly quantitative yield.†

This method for the cleavage of the S-MBzl or the S-Bu^t group can be applied to the synthesis of complicated peptides since the reaction is very selective and proceeds rapidly under mild conditions. Thus, the biologically



active peptide, oxytocin, was obtained by this new method in good yield and good quality from the protected nonapeptide amide, Boc-Cys (MBzl)-Tyr-Ile-Gln-Asn-Cys(MBzl)-Pro-Leu-Gly-NH_2.‡

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† Satisfactory analytical data were obtained for all products.

‡ The protected peptide was prepared by Miss C. Kitada using the solid-phase method.

[1] S. Akabori, S. Sakakibara, Y. Shimonishi, and Y. Nobuhara, *Bull. Chem. Soc. Japan*, 1964, **37**, 433.
[2] S. Sakakibara, Y. Shimonishi, Y. Kishida, M. Okada, and H. Sugihara, *Bull. Chem. Soc. Japan*, 1967, **40**, 2164.
[3] H. Yajima, N. Fujii, H. Ogawa, and H. Kawatani, *J.C.S. Chem. Comm.*, 1974, 107.
[4] F. M. Callahan, G. W. Anderson, R. Paul, and J. E. Zimmermann, *J. Amer. Chem. Soc.*, 1965, **87**, 4922; A. Schöberl, J. Borchers, H. Gräfje, and V. Grewe-Pape, *Angew. Chem. Internat. Edn.*, 1966, **5**, 249.
[5] M. Friedman, in 'The Chemistry and Biochemistry of the Sulfhydryl Group in Amino Acids, Peptides and Proteins,' Pergamon, Oxford, 1973, pp. 230.
[6] M. S. Newman and A. Arkell, *J. Org. Chem.*, 1959, **24**, 385.