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THE USE OF β-METHYLTHIOETHYL ESTERS FOR THE PROTECTION OF CARBOXYL GROUPS IN PEPTIDE SYNTHESIS: REMOVAL THROUGH THE β-METHYLSULPHONYLETHYL ESTER

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The β-methylthioethyl ester group has been advocated for use in carboxyl protection in peptide syntheses, being readily removed at room temperature, in aqueous solution at pH 10-10.5, after conversion into the methiodide by the action of methyl iodide (1). Although this method has proved successful and useful in a number of applications in these laboratories, it failed with a series of N-t-butoxycarbonyl-glutamic acid peptides in which the side-chain carboxyl group was protected as the benzyl ester; treatment of the methylthioethyl esters of these gave poor yields of the methiodides, contaminated with considerable amounts of side-products and difficult to purify. We now report an alternative procedure which has given excellent yields in these cases and which may well prove to be more generally convenient than the earlier method.

The new method depends on the finding (2) that β-methylsulphonylethyl esters (I) resemble the corresponding methiodides in being readily split at room temperature in mildly alkaline solution to the corresponding carboxylic acids:

$$\underset{\text{(I)}}{R.CO_2CH_2.CH_2.SO_2.Me} + OH^- \longrightarrow R.CO_2^- + CH_2{:}CH.SO_2.Me + H_2O$$

The yields in both stages of the new procedure (oxidation to the methylsulphonylethyl esters and alkaline fission) are excellent and the intermediate methylsulphonylethyl esters are highly crystalline and readily purified.

Uncatalysed oxidation of the methylthioethyl esters with hydrogen peroxide gave only the sulphoxides, which are not readily split by alkali (2). Catalysis with ammonium molybdate (3), however, gave the required sulphones. The β-methylthioethyl ester (10 mmol) is dissolved in acetone (50 ml.) and water (10 ml.) and treated with hydrogen peroxide (30%; 21 ml.), mixed with 0.3 M-ammonium molybdate (3 ml.). After 2 hr at room temperature, the acetone is removed under reduced pressure and the residue partitioned between chloroform (50 ml.) and water (50 ml.). The water layer is extracted with more chloroform (50 ml.) and the mixed chloroform solutions washed thrice with saturated brine, dried over magnesium sulphate and evaporated. The crude product contains a little sulphoxide, detectable by thin-layer chromatography (chloroform:methanol; 95:5), but this is easily removed by recrystallisation. The yields of recrystallised, chromatographically pure, β-methylsulphonylethyl ester in five cases were between 80 and 95%.

This ester (10 mmol) is dissolved in acetone (50 ml.) and water added to incipient turbidity. Aqueous 0.25 M-sodium hydroxide is added dropwise, with stirring, at room temperature, at such a rate as to maintain the pH between 10 and 11, conveniently with an automatic titrator; the lower half of this pH range should be used if the solution contains 30% or more of water, the upper half if it contains less. Consumption of the theoretical amount of alkali (40 ml.) requires 12-24 hr. The mixture is then brought to pH 7 with N-hydrochloric acid and the acetone removed under reduced pressure. Acidification, to pH 3, with more hydrochloric acid and extraction with ether, or other suitable solvent, gives the peptide acid, which is purified by recrystallisation. The yields of chromatographically pure material in five cases were between 85 and 90%. The procedure fails with aspartic acid peptides containing side-chain ester groups owing to loss of these by way of the imide (4).

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