N^{in}-MESITYLENE-2-SULFONYLTRYPTOPHAN, A NEW TRYPTOPHAN DERIVATIVE, AND ITS APPLICATION FOR PEPTIDE SYNTHESIS

Nobutaka Fujii, Shiro Futaki, Kouichi Yasumura, Kenichi Akaji and Haruaki Yajima

Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto 606, Japan

It has been known that the indole moiety of tryptophan(Trp) is sensitive to several side reactions, such as alkylation, oxidation, carboline-formation, and dimerization, under the acidolytic cleavage of N^{α}-protecting groups in peptide synthesis.

In order to find a suitable method for the solution synthesis of biologically active peptides containing Trp redidues, the indole alkylation, the most serious side reaction observable during TFA treatment of Boc-Trp-OH and Z(OMe)-Trp-OH, was first examined. Among scavengers, soft nucleophiles, so far examined, ethanedithiol was found most effective to suppress the alkyl cation attack at its indole moiety. Several Trp-containing peptides, such as gastrin releasing peptides (porcine and chicken) were synthesized by this improved method.

Next, in order to improve the situation further by reduction of the nucleophilicity of the indole moiety of Trp, we introduced an electron-withdrawing group, mesitylene-2-sulfonyl(Mts) group, at the N^{in}-function of Trp (Fig. 1.). The Mts group of Trp is stable under the TFA N^{α}-deblocking conditions, and well resists against the attack of alkyl cations during this treatment. It can be readily removed by 1M trifluoromethanesulfonic acid-thioanisole (1:1) in TFA without accompanying any sizable amount of side products. Usefulness of this new Trp-derivative has been demonstrated by the synthesis of tetragastrin, as an example. (Fig. 2.).

Fig. 1. N^{in}-mesitylene-2-sulfonyltryptophan [Trp(Mts)]

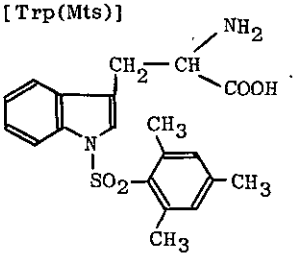

Fig. 2. Synthetic scheme of tetragastrin