Synthesis and Use of N^{im}-Tosyl-L-histidine*1

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Recently, great progress has been made in peptide synthesis, but the synthesis of histidine peptides requires further improvement.[1] This paper will describe a new procedure for the protection of the imidazole residue with a tosyl group. Generally, the tosyl group in peptide derivatives is stable and can only be removed by treatment with sodium in liquid ammonia.[2] However, a tosyl group attached to a guanido group in an arginine residue can, exceptionally, be removed by treatment with anhydrous HF at 0°C for 30 min, although it is stable with HBr in acetic acid.[3] The N^{im}-tosyl group was found to be removed more easily, not only by short treatment with anhydrous HF, but also under the conditions used for ester saponification. This group was also partially decomposed with anhydrous HCl or HBr in organic solvents. Further, the N^{im}-tosyl group was found to be unaffected by treatment with trifluoroacetic acid at room temperature under the conditions used for removing Nps-, Boc-, Aoc-, or Z(OMe)-groups. These properties all suggest that this group might be used for the synthesis of histidine peptides.

The tosyl group was introduced into N^{α}-protected histidine derivatives with tosyl chloride under the conditions of the Schotten-Baumann reaction, using sodium carbonate as the base. Thus the following compounds were synthesized and obtained as crystals: Z-L-His(Tos)-OH·DCHA, yield 62%, mp 150—152°C (decomp.), $[\alpha]_D^{17}$ +19.2° (*c* 1, DMF); Aoc-L-His(Tos)-OH (I), yield 75%, mp 109—111°C (decomp.), $[\alpha]_D^{17}$ +10.0° (*c* 1, pyridine); Nps-L-His(Tos)-OH (II), yield 75%, mp 140—141°C (decomp.), $[\alpha]_D^{17}$ +39.9° (*c* 1, DMF). Elemental analyses gave correct values for these compounds within the expected limits of error. These compounds were soluble in the organic solvents for usual acylated amino acids. Compounds I and II were coupled with the glycine benzyl ester by the DCC method and by the mixed anhydride method; Aoc-L-His(Tos)-Gly-OBzl (III) and Nps-L-His(Tos)-Gly-OBzl (IV) were thus both obtained in 80% yields. III: oily compound. IV: mp 164—165°C, $[\alpha]_D^{18}$ +57.5° (*c* 1, DMF). Found: C, 55.03; H, 4.19; N, 11.24; S, 10.44%. Calcd for $C_{28}H_{27}N_5O_7S_2$: C, 55.16; H, 4.46; N, 11.48; S, 10.51%. The Aoc- or Nps-group was removed by dissolving III or IV in trifluoroacetic acid in a presence of anisole at room temperature; after 30 min, the product was coupled with Nps-L-alanine using DCC. The product, Nps-L-Ala-L-His(Tos)-Gly-OBzl, was recrystallized from ethyl acetate and *n*-hexane as needles; yield 50%, mp 88—89°C, $[\alpha]_D^{17}$ −30.0° (*c* 1, AcOEt). Better results were obtained by the *N*-hydroxysuccinimide method, in which case the yield was 75%. Found: C, 54.43; H, 4.53; N, 12.35; S, 9.43%. Calcd for $C_{31}H_{32}N_6O_8S_2$: C, 54.69; H, 4.73; N, 12.34; S, 9.42%. All the protective groups could be removed from IV by treatment with anhydrous HF[4] at 0°C for 1 hr; L-His-Gly·½H_2O was thus obtained, as expected; yield 55%, mp 190°C (decomp.), $[\alpha]_D^{17}$ +24.6° (*c* 1, water). Reported,[5] mp 190°C (decomp.), $[\alpha]_D$ +25±1° (*c* 2, water).

Thus, the procedure was demonstrated to be useful for histidine peptide syntheses. The new histidine derivatives, I and II, should be especially useful in the solid-phase method. This possibility is now being investigated in our laboratory.

*1 The abbreviations used conform with those tentatively proposed by the IUPAC-IBC: *J. Biol. Chem.*, **241**, 2491 (1966).
DCHA=dicyclohexylamine DMF=dimethylformamide
Aoc=*t*-amyloxycarbonyl

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