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The Chemical Conversion of *C*-Terminal Glycines in Peptides into Taurine

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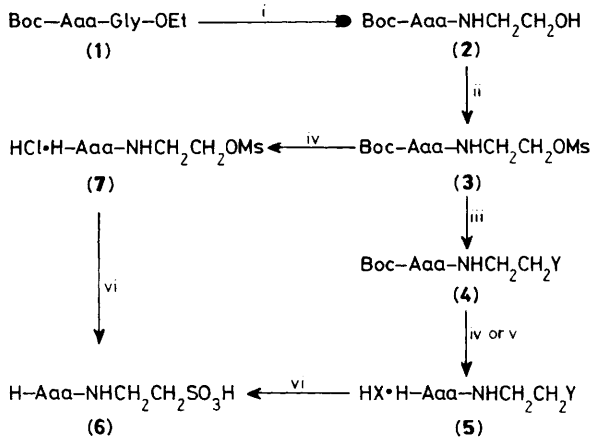
The first chemical conversion of *C*-glycine in dipeptides into taurine has been achieved using a general substitution of a sulpho group for a halogeno or mesyl group *via* the corresponding amino acid 2-halogenoethyl- or 2-methanesulphonyloxyethyl-amides, each of which was prepared from the ethanolamide obtained by $LiBH_4$ reduction of a protected dipeptide containing a *C*-glycine ester.

Although taurine itself has been thoroughly investigated, studies on its derivatives such as taurine-peptides have been limited. However, the discovery of γ-Glu-Tau (glutaurine) in mammalian parathyroids[1] promoted studies on such intrinsic taurine-peptides.[1—3] Several synthetic studies,[4—8] mostly based on conventional coupling of taurine with an amino acid or peptide, have also been documented. During our studies on the immunocross reactivities of a series of taurine-oligopeptides with haptenic taurine- and glutaurine-antisera,[3,7—10] we have previously shown[7,8] that substitution *via* amino acid β-halogenoethylamides is useful as an alternative general synthetic method without racemization. Since a *C*-terminal glycine can therefore be a precursor of a 2-hydroxyethylamide[11] which can be converted to the halogenoethylamide, we have combined these independent techniques into a conversion route from glycine-peptide to taurine-peptide.

Boc-Val-Gly-OEt (**1a**) (50 mmol) was reduced (Scheme 1) in ethanol (140 ml) to give crystalline Boc-Val-$NHCH_2CH_2OH$ (**2a**), m.p. 89—90 °C, in 95% yield by using $LiBH_4$,[11] prepared from $NaBH_4$ (100 mmol) and LiCl (100 mmol) in tetrahydrofuran (THF) (70 ml). The ethanolamide (**2a**) was converted to an intermediate, Boc-Val-$NHCH_2CH_2OMs$ (**3a**), m.p. 87—89 °C, by reaction of the ethanolamide (**2a**) and methanesulphonylchloride (50 mmol) with triethylamine (52 mmol) in dichloromethane (200 ml) in 90% yield. Val-Tau (**6a**) was synthesized by two routes; *via* halogenoethylamides (**4a**) and (**5a**) or deprotected *O*-mesylethanolamide (**7a**). The mesylate (**3a**) (20 mmol) was reacted with NaI (100 mmol) in acetone (50 ml) to yield Boc-Val-$NHCH_2CH_2I$ (**4a**), m.p. 123—124 °C (89%), which was deprotected with HCl (4 M) in dioxane (50 ml) to give a hygroscopic powder, HCl·H-Val-$NHCH_2CH_2I$ (**5a**) (95%). Without further purification, the iodoethylamide (**5a**) (10 mmol) was reacted with sodium sulphite (20 mmol) in water (20 ml) to give analytically pure crystalline Val-Tau (**6a**) (81%) {m.p. 318—320 °C (decomp.), $[\alpha]_D^{20}$ +40.7° (*c* 1, H_2O)}.

The preparation of (**6a**) from (**7a**) was not so successful. The substitution reaction between (**7a**) (hygroscopic oil, 10 mmol) and sodium sulphite (20 mmol) in water (20 ml) gave (**6a**), m.p. 317—319 °C (decomp.), in only 10% yield, although (**7a**) was obtained in 97% yield by deprotection of the key intermediate (**3a**). Both samples Val-Tau (**6a**) prepared by the two different routes were identical with the authentic specimen {m.p. 315—316 °C (decomp.), $[\alpha]_D^{20}$ +40.5° (*c* 1, H_2O)}.[7]



a; Aaa = Val
b; Aaa = Phe
c; Aaa = Ser (Bzl)
d; Aaa = Ser (Ac)
e; Aaa = Ser

a; X = Cl, Y = I
b; X = Cl, Y = I
c; Y = Br
d; X = Y = Br

Boc = t-Butoxycarbonyl
Ms = Mesyl
Bzl = Benzyl

Scheme 1. *Reagents and conditions:* i, $NaBH_4$, LiCl, THF, EtOH, room temp., 20 h; ii, MsCl, Et_3N, CH_2Cl_2, −5 °C, 30 min; iii, NaI or LiBr, Me_2CO, room temp.; iv, HCl, dioxane, room temp., 1 h; v, HBr, AcOH, room temp.; vi, Na_2SO_3, H_2O, room temp., 20 h.

Similarly, Phe-Tau (**6b**) and Ser(Ac)-Tau (**6d**) were prepared from the corresponding dipeptides containing a glycine ethyl ester at the *C*-terminal [(**1b**) and (**1c**)] by the route shown in Scheme 1; net yields from (**1**) *via* (**5**) were 32 and 23%, respectively. Although Phe-Tau (**6b**) can be obtained from neither the bromo nor the chloro derivative as previously reported,[7] iodoethylamide (**5b**) gave (**6b**) {m.p. 305—307 °C (decomp.), $[\alpha]_D^{20}$ +68.0° (*c* 1, H_2O); [lit.,[7] m.p. 306—308 °C (decomp.), $[\alpha]_D^{20}$ +69.2° (*c* 1, H_2O)]}. The naturally occurring Ser-Tau (**6e**) {m.p. 264—266 °C, $[\alpha]_D^{20}$ +9.6° (*c* 1, H_2O); lit.,[7] m.p. 265—267 °C (decomp.), $[\alpha]_D^{20}$ +10.1° (*c* 1, H_2O)]}, was obtained by a mild ethanolic saponification of (**6d**) [prepared by the sequence (**1c**) → (**2c**) → (**3c**) → (**4c**) → (**5d**) → (**6d**)].

Since the methods described herein can be generalized to convert a *C*-terminal amino acid in general peptides to a corresponding optically active 2-substituted taurine, such a synthetic approach giving a variety of taurine-peptide derivatives is potentially useful.

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