An approach to the Synthesis of Oxytocin from cystine

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ABSTRACT

Oxytocin is a single chain oligopeptide containing nime amino acid residues with one disulfide bridge. The amino acid sequence of oxytocin is as follows: Cys-Tyr- Ile-Gln-Asn-Cys-Pro-Leu-GlyNH2 ｜ ｜ └──────────┘ A synthetic approach to cystine-containing peptide Using cystine as a starting material is disclosed in the thesis. Emphasis is placed on enzymatic ca talyzed condensation and liquid phase method to study the synthesis of oxytoci n. Enzyme catalyzed peptide synthesis was explored first. Ficin was able to catalyzed the condensation of (Boc-Cys)2 with amino acid ester and triethylam ine to form asymmetric cystine peptide. The reactions were performed at pH 5.7 5 and shaked at 24 ℃ for 4 hours. Mono coupled cystine peptide was afforded in the yield of 73.7 %. However, the coupling of (Boc-Cys)2- TyrOMe and Pro-Leu-G lyNH2 was not successful. Therefore, condensation of (Boc-Cys)2 with Pro-Le u-GlyNH2 was studied as an alternative pathway. Boc-Pro and LeuOBn were conden sed with DCC to form Boc-Pro-LeuOBn, which was hydrogenated to obtain Boc-Pro- Leu. Pro-Leu-GlyNH2 was synthesized by coupling of Boc-Pro-Leu with GlyNH2 usi ng DCC and DMAP. Removal of the Boc group by TFA generated Pro-Leu- GlyNH2. (Bo c-Cys)2-Pro-Leu-GlyNH2 was synthesized smoothly by using DCC as condensing age nt. The other segment, Tyr-Ile-Gln-AsnOMe, was also synthesized by a stepw ise mothod using DCC. Cbz-Asn was reacted with dimethyl sulfate to form Cbz-As nOMe, which was hydrogenated to remove Cbz group. The resulting compound was t hen coupled with Cbz-Gln to form Cbz-Gln-AsnOMe, which was hydrogenated to rem ove Cbz group and obtain Gln-AsnOMe. Boc-Tyr was reacted with IleOBn to form B oc-Tyr-IleOBn, which was hydrogenated to obtain Boc-Tyr-Ile. Coupling of Boc-T yr- Ile with Gln-AsnOMe and removal of the Boc group by TFA affored Tyr-Ile-Gln -AsnOMe. Unfortunately, the tetrapeptide and the pentapeptide were unable to form a protected nonapeptide with various coupling reagents.

Keywords : oxytocin ; cystine ; liquid phase synthesis ; enzymatic catalyst

Table of Contents