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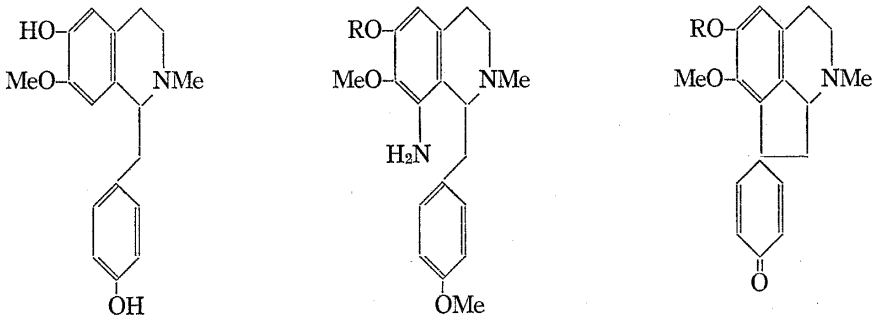
Total Synthesis of *dl*-Homolinearisine

Homolinearisine, $C_{18}H_{19}O_3N$, melted at 220°, was isolated from *Croton linearis* Jacq.[1] and chemical and spectral investigation led to the proposed structure (I) by Haynes and his co-workers.[2]



V

Ⅲ : R=H
Ⅳ : R=Me

I : R=H
Ⅱ : R=Me

Chart 1

The phenolic oxidation is a useful method for synthesizing proaporphine type compound,[3] but coupling occurs only at the position *para* or *ortho* to the hydroxyl group. However, homolinearisine has a hydroxyl group at the position *meta* to the site of carbon-carbon coupling, and therefore, homolinearisine can not be synthesized by the phenolic oxidation of 1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-7-methoxy-2-methyl-6-isoquinolinol (V).[4]

In a preceding communication,[5] we reported that deamination of 8-amino-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (IV) gives three components, one of which is a proaporphine type compound, *dl*-pronuciferine (II).

In this communication, we wish to report the synthesis of *dl*-homolinearisine by the Pschorr reaction of 8-amino-1,2,3,4-tetrahydro-7-methoxy-1-(4-methoxybenzyl)-2-methyl-6-isoquinolinol (III)[6] under alkaline condition.[7]

8-Amino compound (III) was diazotized with a slight excess of sodium nitrite in 5% sulfuric acid solution at 5° and decomposition of the resulting diazonium salt with an excess of sodium acetate at room temperature over a period of three hours afforded two compounds.

The mixture of these two compounds was chromatographed on silica gel and eluted with chloroform–methanol (30:1) to give a small amount of 2-hydroxy-1,12-dimethoxyaporphine and *dl*-homolinearisine in 10% yield. The latter was identified with the natural product by the infrared (in chloroform) spectral comparison.

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Studies on the Synthesis of Proinsulin. I. Synthesis of Partially Protected Tritriacontapeptide related to the Connecting Peptide Fragment of Porcine Proinsulin[1]

Recently, Chance and coworkers[2] have proposed an amino acid sequence of the connecting peptide fragment of porcine proinsulin. This polypeptide chain connects the carboxy-terminus of the B chain to the amino-terminus of the A chain of insulin molecule.

B chain ⟶ Arg-Arg-Glu-Ala-Gln-Asn-Pro-Gln-Ala-Gly-Ala-Val-Glu-Leu-Gly-Gly-Gly-
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

Leu-Gly-Gly-Leu-Gln-Ala-Leu-Ala-Leu-Glu-Gly-Pro-Pro-Gln-Lys-Arg ⟶ A chain
18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33

Amino Acid Sequence of Connecting Peptide Portion of Porcine Proinsulin

The present communication describes the synthesis of partially protected tritriacontapeptide related to the connecting peptide fragment of porcine proinsulin.

Thus, we subdivided the connecting peptide chain into four fragments of proper size and synthesized the protected peptides, Z-Arg(NO_2)-Arg(H^+)-Glu-Ala-Gln-Asn-Pro-Gln-Ala-Gly-NHNH-BOC (I), Z-Ala-Val-Glu(OBu^t)-Leu-Gly-Gly-Gly-Leu-Gly-NHNH-BOC (II), Z-Gly-Leu-Gln-Ala-Leu-Ala-Leu-Glu(OBu^t)-Gly-NHNH-BOC (III) and Z-Pro-Pro-Gln-Lys(F)-Arg-(H^+)OH (IV), as intermediates for the construction of the entire sequence. This approach is similar to that on the synthesis of fragments of ribonuclease T_1.[3]

The absence of sulfur-containing amino acid residues in the connecting peptide led us to use Z group as α-amino protecting group of the intermediates, which was removed readily by catalytic hydrogenolysis. Preparation of these peptide fragments was conducted mostly by stepwise elongation starting from the C-terminus with the desired Z-amino acid N-hydroxysuccinimide[4] or 2,4,5-trichlorophenyl[5] esters. To avoid the complexity of increasing coupling stages, some intermediates of these peptides were prepared by fragment condensation using Z-tetra-, Z-tri- or Z-dipeptide azides and in certain instances by Anderson's mixed anhydride procedure[6] with Z-dipeptides terminating with glycine. The ε-amino group of lysine was pro-

1) The amino acids except glycine are L-configuration. The abbreviations used to denote amino acid derivatives and peptides are those recommended by IUPAC-IUB Commission on Biochemical Nomenclature; *Biochemistry*, **5**, 2485 (1966). The following abbreviations are used: F=formyl; NO_2=nitro; TFA=trifluoroacetic acid; DMF=dimethylformamide; AP-M=aminopeptidase M. Solvent systems used for thin-layer chromatography are as follows: Rf^{I}, Partridge system (S.M. Partridge, *Biochem. J.*, 42, 238 (1948)); Rf^{II}, 1-butanol-pyridine-acetic acid-water (30:20:6:24). Rf^{III} value refers to the system of 1-butanol-pyridine-acetic acid-water (30:20:6:24) on paper chromatography.

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