The Biosynthesis of Alkaloids.

Introduction

Alkaloids are non-peptidic, non-nucleosidic compounds containing nitrogen, abundant in higher (flowering) plants, insects, amphibians and fungi. They are mainly produced from α-amino acids including ornithine, lysine, tyrosine, phenylalanine and tryptophan.

Part 1 – Alkaloids from ornithine and lysine

These two amino acids are mainly involved in the biogenesis of aliphatic alkaloids, for example cocaine (Figure 1).

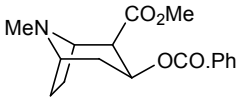
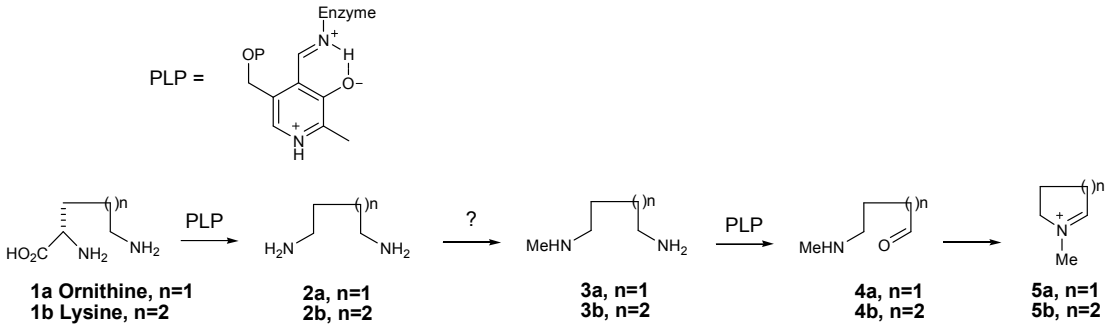


Figure 1: Cocaine

The early stages of the biosynthetic pathways of ornithine and lysine are shown below (Scheme 1).



Scheme 1: Early stages of ornithine and lysine biosynthetic pathways.

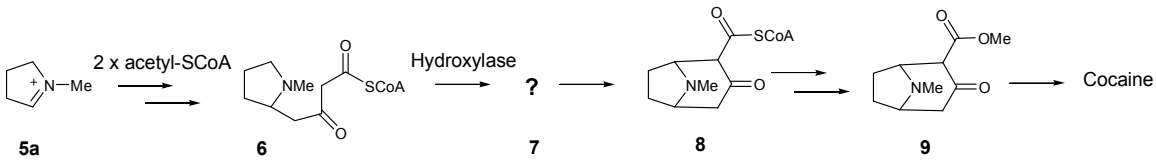
Qu 1: The first step in the biosynthesis is a pyridoxal phosphate (PLP) dependant decarboxylation; suggest the mechanism for this step.

Qu 2: Suggest a suitable co-substrate for the methylation of **2** to give **3**.

Qu 3: Suggest the mechanism of the oxidative deamination of **3** to **4**.

Qu 4: How would you synthesise compounds **5** from readily available starting materials synthetically, giving suitable reagents.

Feeding studies have shown that symmetrical diamines **2** and iminium salts **5** can be incorporated by the plant *Erythroxylum coca* to synthesise cocaine. The biosynthesis of cocaine is shown below (Scheme 2).



Scheme 2: Biosynthesis of cocaine.

Qu 5: Suggest a *retro*-synthesis and forward synthesis of cocaine, different from the biosynthesis.

Qu 6: Give the mechanism of the formation of **6** from iminium salt **5**.

Qu 7: What is the structure of intermediate **7**?

Qu 8: Give the mechanism for the transformation of **7** to **8**.

Part 2 – Alkaloids from phenylalanine and tyrosine.

These two amino acids make up alkaloids with ArC_2N units. The major classes include monocyclic alkaloids, benzylisoquinolines alkaloids and amaryllidaceae alkaloids.

Morphine is member of the benzylisoquinoline class of alkaloids (Figure 2), biosynthetically derived from two molecules of tyrosine.

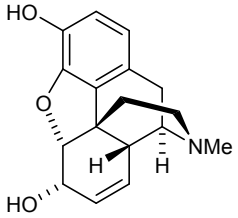
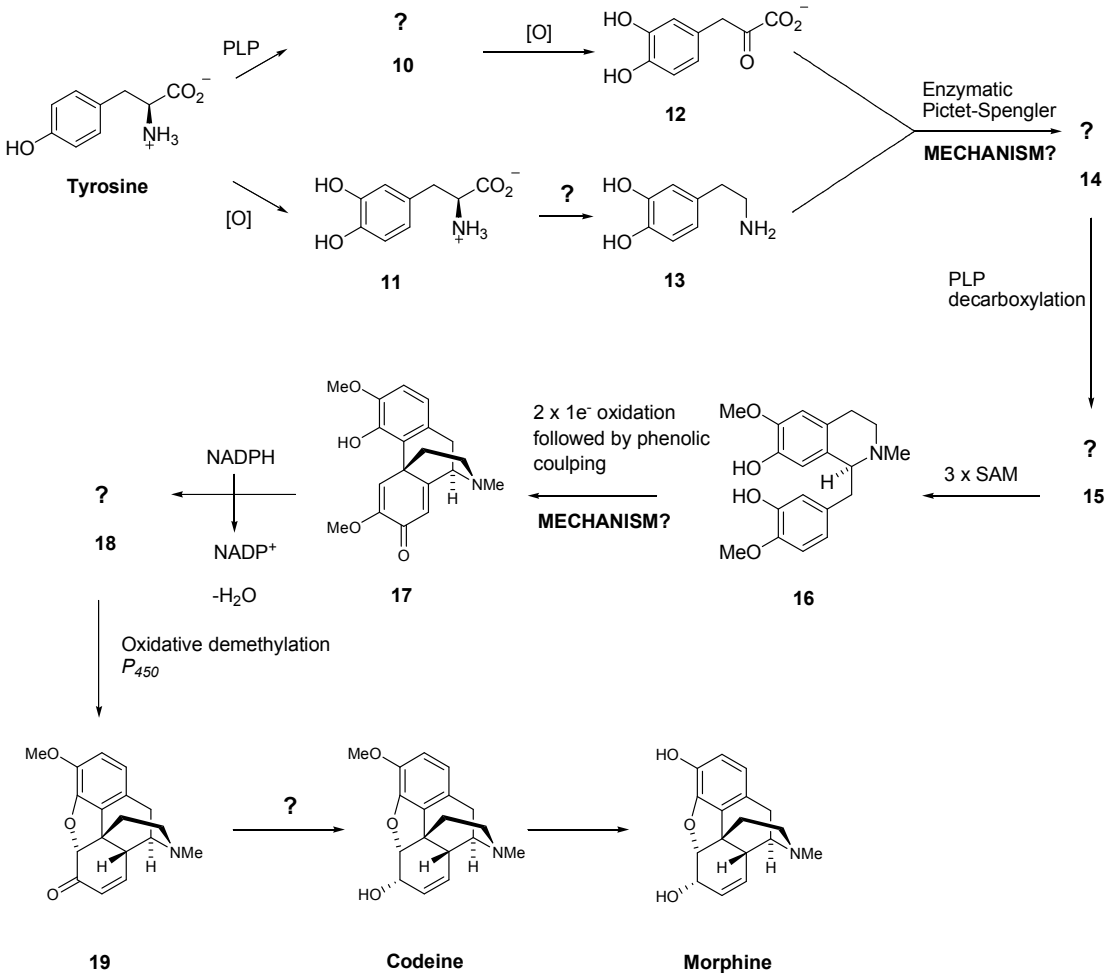


Figure 2: Morphine

Qu 9: Assign each stereocentre in morphine as R or S.

Qu 10: Suggest a *retro*-synthesis and forward synthesis of morphine, not related to the biosynthesis.

The biosynthesis of morphine has been shown below (Scheme 3).



Scheme 3: Biosynthesis of morphine.

Qu 11: Work through scheme 3, filling in missing structures, coenzymes and suggest mechanisms for the highlighted steps.