CHEM 109, LECTURE 16

Alkaloid Natural Products – Opioid Family – Morphine

- Pharmaceuticals, -kinetics, and –dynamics
- Biosynthesis

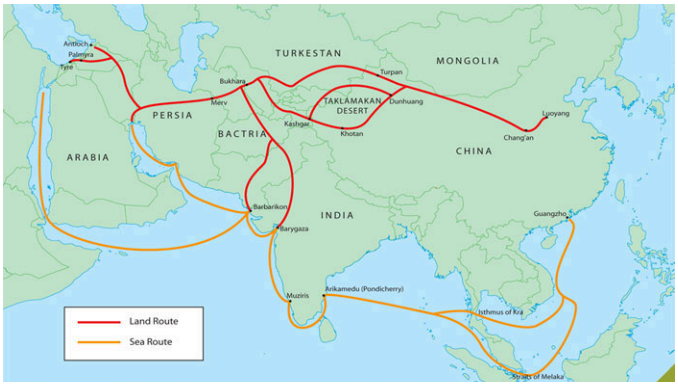
HW – Carry out the 9 starred mechanisms using acids (H^+) and bases (:B) – not for credit, but for exam prep!

Poppy – *Papaver somniferum* – "flower of joy"
- Sap from seed pod = crude opium (schedule II drug)
- Central Asia
- Latin America – Columbia & Mexico

Morphium – Greek god of dreams

1803 – Extraction of Morphine
10x more powerful – "miracle drug"
analgesic (pain relief)

1820's – commercial production (Merck)
1874 – Heroine synthesis from morphine
1898 – 1924 - medicinal use of heroine

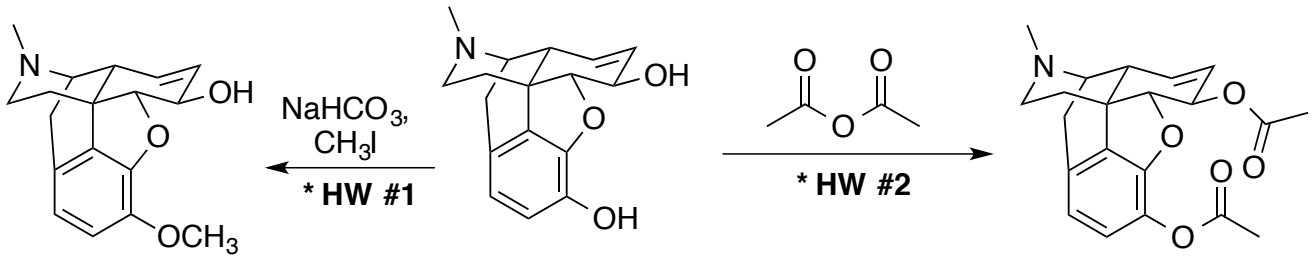


DEA Controlled Substances Act (1970)

"Schedules" based on medical use, abuse potential, and dependence

Schedule I	No currently accepted medical use, lack of accepted safety for use under medical supervision, high potential for abuse	Heroin, LSD, Marijuana, peyote, MDMA
Schedule II	High potential for abuse, several psychological or physical dependence	Dilaudid, methadone, oxycodone, fentanyl, codeine, hydrocodone
Schedule III	Less potential for abuse, moderate-to-low physical dependence, high psychological dependence	Tylenol with <90 mg codeine per dose, ketamine, anabolic steroids
Schedule IV	Low potential for abuse	Xanax, valium
Schedule V	Lower potential for abuse	Cough medicine with <200mg/100mL codeine

http://www.deadiversion.usdoj.gov/schedules/#define



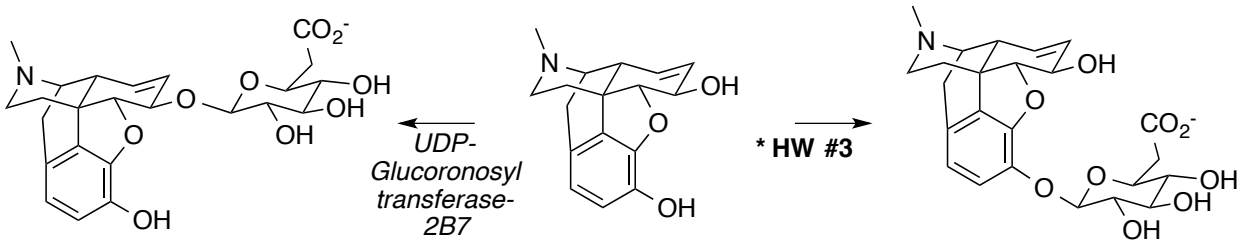
Codeine **Morphine** **Heroine**

Morphine - Pharmaceutical Phase

- Enteral or parental – IV and inhalation ("chasing the dragon") most common
    - Administered as HCl salt

Pharmacokinetics

- *Adsorption* – crosses membranes, including BBB
- *Distribution* – detected in plasma after 20 min IV or 30 min oral
    - 40-50% reaches central nervous system
- *Metabolism* - Subject to first pass metabolism



Morphine-6-glucoronide
pain relief

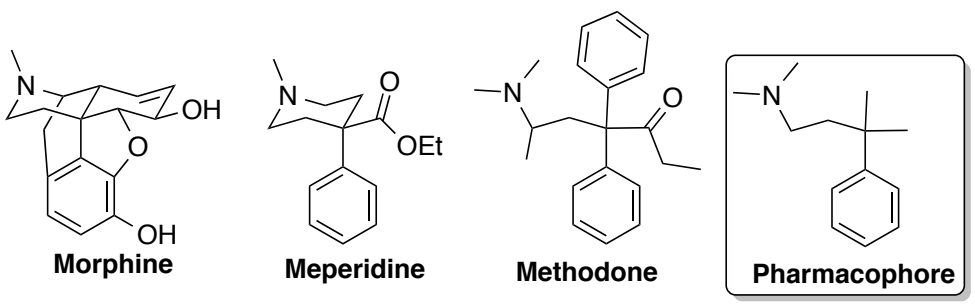
Morphine

Morphine-3-glucoronide
not active

- *Excretion* - Half-life of 120 minutes

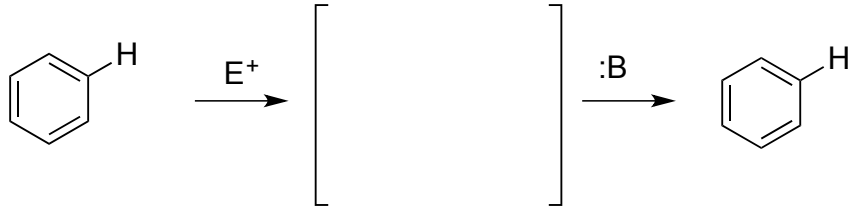
Pharmacodynamics

- Multiple opioid receptors for endogenous opioids (ex. endorphins = "endogenous morphine")
    - Pain inhibition



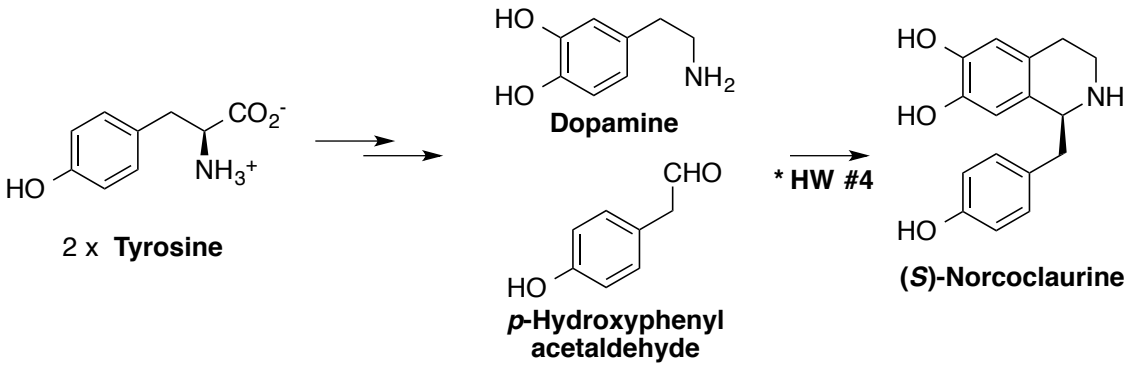
Morphine **Meperidine** **Methodone** **Pharmacophore**

Electrophilic Aromatic Substitution (EArS)

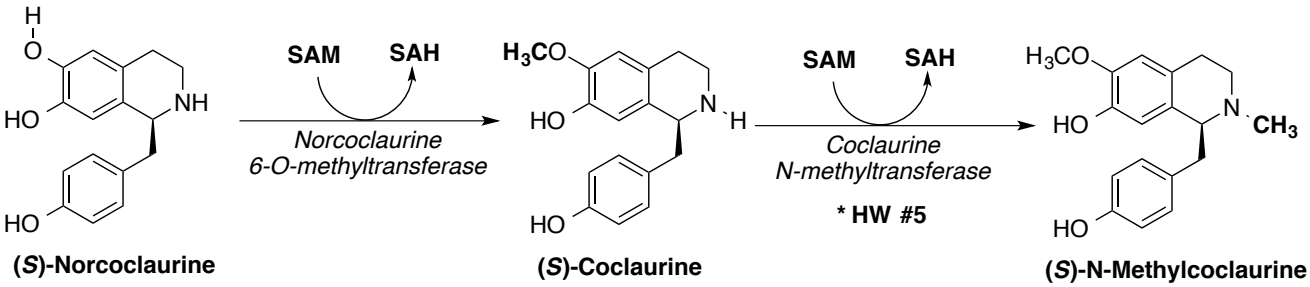


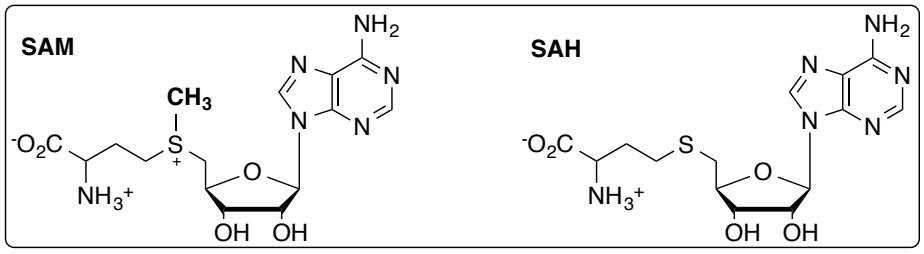
Biosynthesis of Morphine – *select reactions*

Two Tyrosine derivatives combine for first cyclization step in a process similar to **reductive amination** and **EArS** on the aromatic ring.

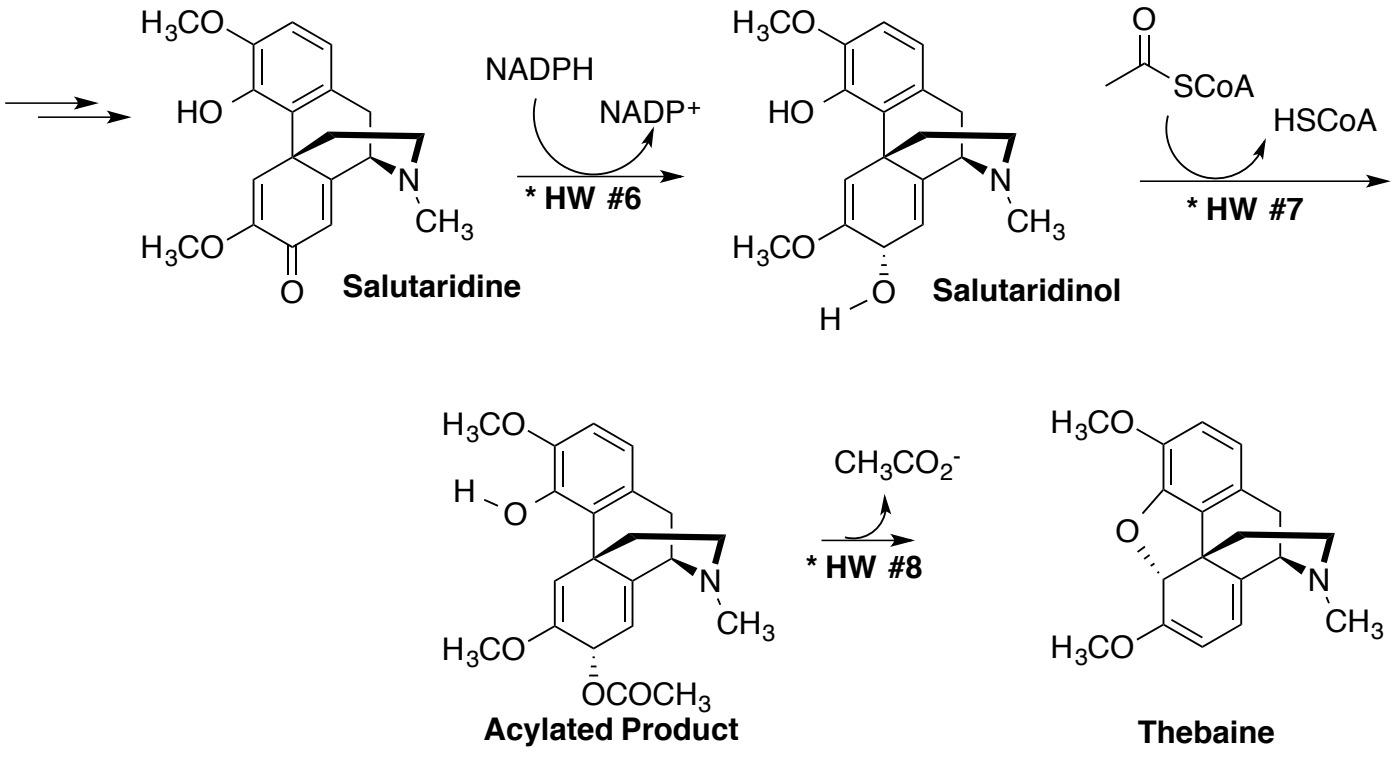


Two consecutive **methylations** are carried out using ***S*-Adenosylmethionine (SAM)**

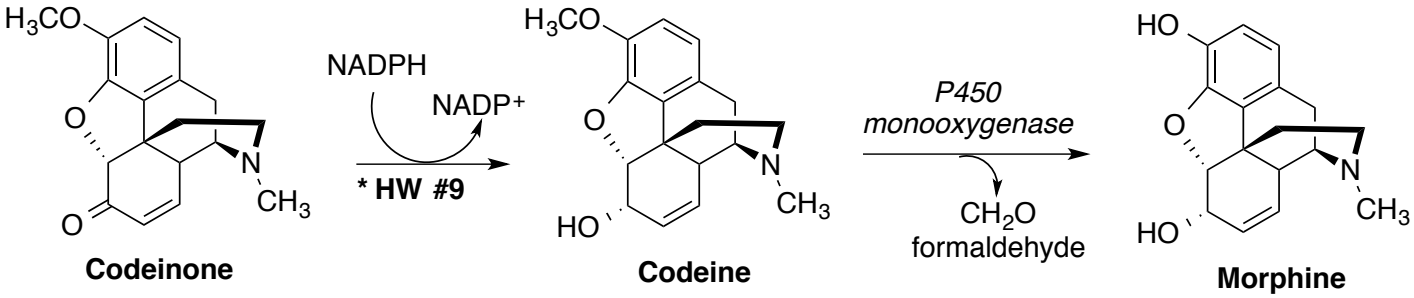




(*S*)-*N*-Methylcoclaurine is converted into **Salutaridine**, which is **reduced**, **acylated**, and **cyclized** to form **Thebaine**.



Thebaine undergoes demethylation and reduction to form **Codeinone**, which is subsequently **reduced** to **Codeine** and **demethylation** to produce **Morphine**.



CHEM 109 – What have we learned?...
- **Acid-base** chemistry
- Intuitive **arrow-pushing** (*not* memorizing mechanisms!)
- **Amino acid, carbohydrate, lipid** metabolism and/or catabolism
- **Enzymes**, the perfect synthetic organic chemists!
- Structural characteristics of **DNA & RNA**; **mutations**
- Introduction to **Medicinal Chemistry**

Next time…Q&A – not a review session (BYOQ)

Course evals help me be a better teacher – Please complete soon!
- Constructive feedback – course materials, organization, etc.