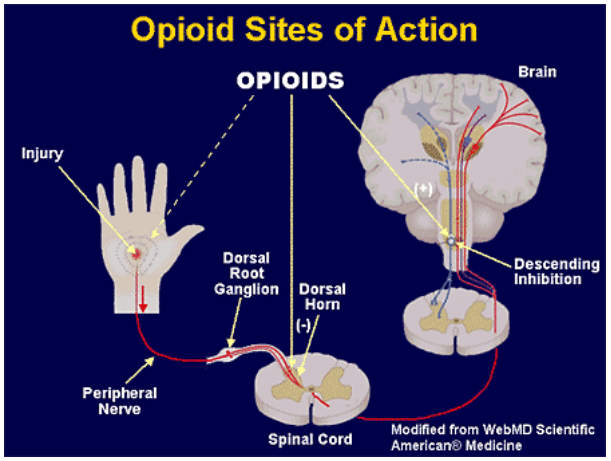


Narcotic (Opioid) Analgesics

NEPHAR 305
Pharmaceutical Chemistry I

Assist.Prof.Dr. Banu Keşanlı

Narcotic (Opioid) Analgesics

✓ **Analgesic** is a drug that reduces or eliminates pain.
✓ **Narcotic** (**Opioid) agents** are potent analgesics which are effective for the relief of severe pain.
✓ **Narcotic analgesics** are mainly centrally acting (brain and spinal cord) which are used for severe pain.
✓ The analgesic (painkiller) effects of opioids are due to decreased perception of pain, decreased reaction to pain as well as increased pain tolerance.
✓ These drugs are commonly prescribed to manage pain, but can also be prescribed to treat diarrhea (Lomotil) or severe cough (codeine).

Narcotic agents may be classified into four categories:

1) Morphine and codeine – natural alkaloids of opium.
2) Synthetic derivatives of morphine such as heroin.
3) Synthetic agents which resemble the morphine structure.
4) Narcotic antagonists which are used as antidotes for overdoses of narcotic analgesics

Examples of Narcotic Analgesics

Opioid Agonists
Morphine
Codeine
Heroin
Oxycodone (OXYCONTIN)
Buprenorphine (SUBUTEX)
Methadone (DOLOPHINE)
Meperidine (DEMEROL)
Loperamide (IMODIUM)
Fentanyl

Mixed Agonists-Antagonists
Nalbuphine (NUBAIN)
Butorphanol (STADOL)
Pentazocine (TALWIN)

Opioid Antagonists
Naloxone (short acting) NARCAN
Naltrexone (longer acting) TREXAN

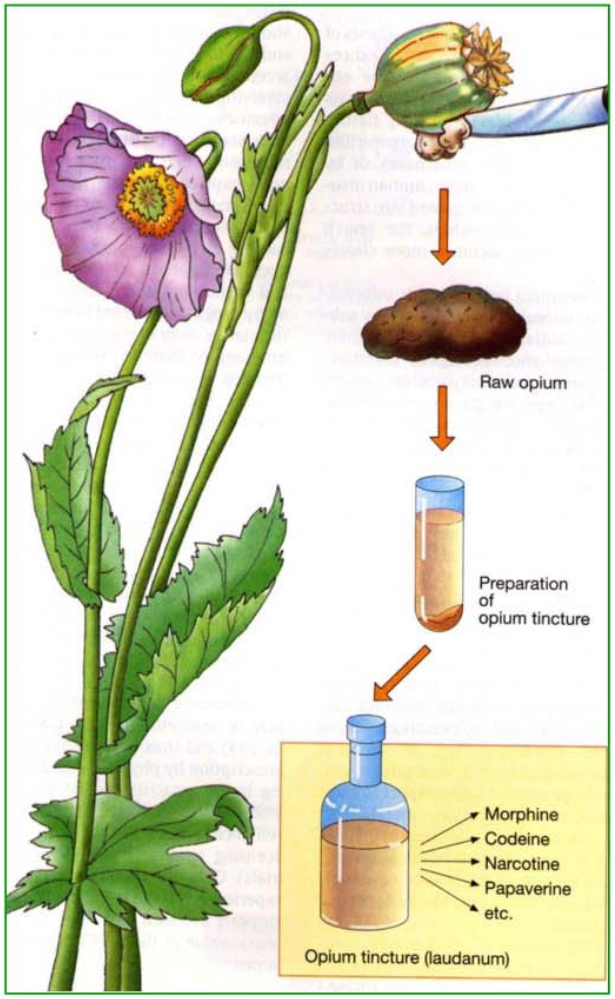
Opioid Agonists Analgesics

Mechanism of action

• Opioid agonists produce analgesia by binding to specific receptors, located primarily in the brain and spinal cord involved in the transmission and modulation of pain.

✓ **Morphine** is the prototypical opioid agonist
✓ The opium poppy is the source of crude opium
✓ Morphine was isolated from opium in the early 1800's and since then has been the most effective treatment for severe pain
✓ The analgesic actions of **codeine** are due to its conversion to morphine

✓ Narcotic analgesiscs isolated from opium



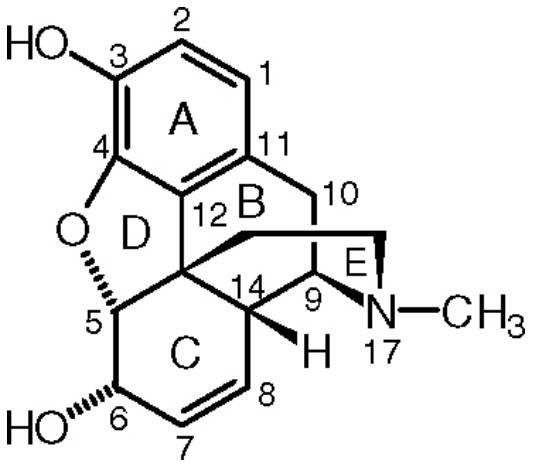
OPIOID ANALGESICS

Chemical Structure of Morphine

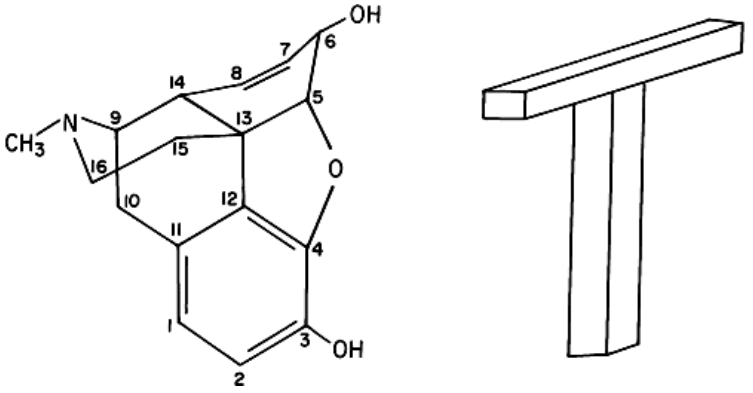
Morphine is a benzylisoquinoline alkaloid and is the most abundant opiate present in opium.

Its structure is: A rigid pentacyclic structure consisting of a benzene ring (A), two partially unsaturated cyclohexane rings (B and C), tetrahydrofuran ring (D) and a piperidine ring (E). Rings A, B and C are the phenanthrene ring system.

Of these five rings, three lie approximately in the same plane. The other nitrogen-containing ring and the remaining ring are at right angles to the other three. This ring system has little conformational flexibility. Its rigid pentacyclic structure conforms to a T-shape.



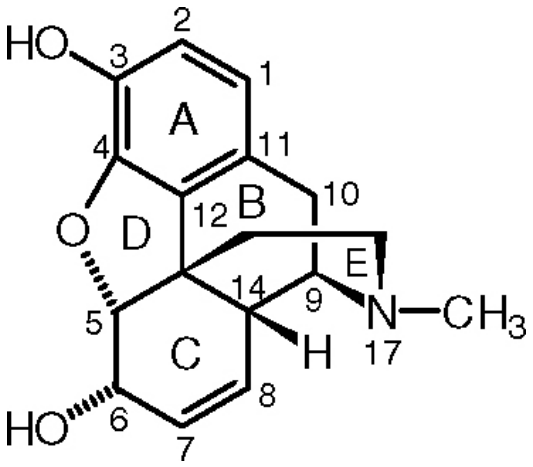
The T-shaped molecule of morphine

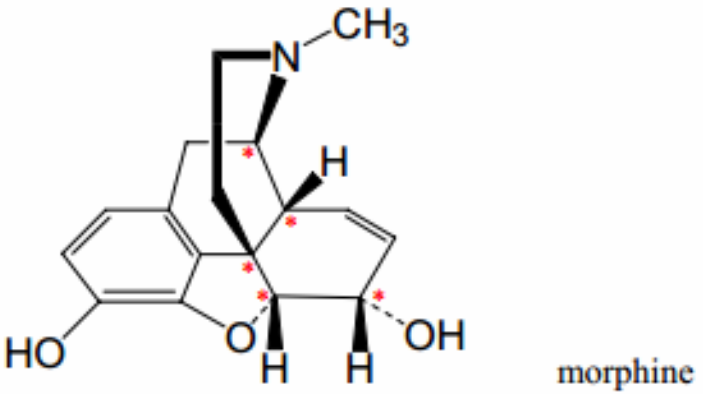


Chemical Structure of Morphine

All opioid analgesics have some similarities in their structure which include:

- ✓A tertiary nitrogen with a small alkyl substituent.
- ✓A quaternary carbon atom (C13 in morphine)
- ✓A phenyl group or its isosteric equivalent directly attached to the quaternary carbon.
- ✓A 2 carbon spacer ethane chain ($–CH_2$ -CH_2 -) between the quaternary carbon and the tertiary nitrogen.





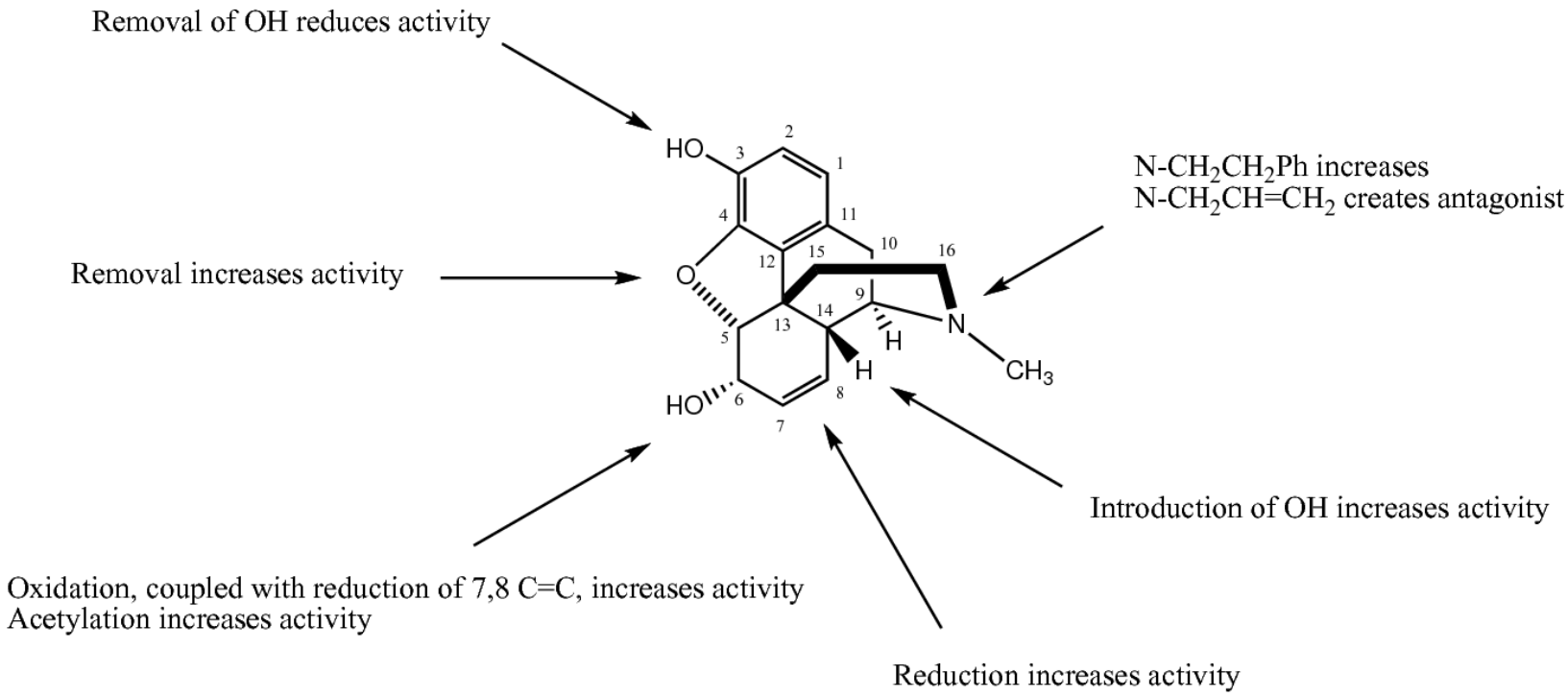
morphine

There are five chiralitv centers in morphine . It has 2^5 stereoisomers in principle.

Structure of Morphine

- ✓ Two **hydroxyl functional** groups: a C3-phenolic OH (pK_a 9.9) and a C6-allylic OH
- ✓ An **ether linkage** between C4 and C5
- ✓ **Unsaturation** between C7 and C8
- ✓ A basic, **3º-amine** function at position 17
- ✓ **5 centers of chirality** (C5, C6, C9, C13 and C14) with morphine exhibiting a high degree of stereoselectivity of analgesic action

Structure-Activity Relationships of Morphine Analogs



The most common changes to the morphine molecule involves:

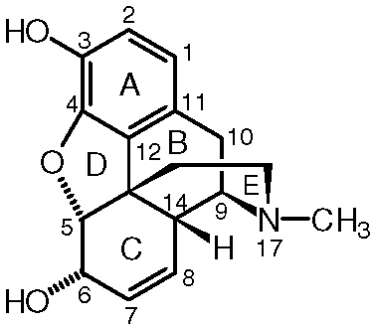
1. Changing substituents at **carbons 3 and 6**. In morphine these are alcohol (-OH) groups.

2. Reduction of the double bond between **carbons 7 and 8**.

3. Addition of an alcohol (-OH). group at **carbon 14**.

4. Addition or changes to the group bonded to the nitrogen. If this methyl group is replaced by a propenyl group, an antagonist of morphine called nalorphine is formed.

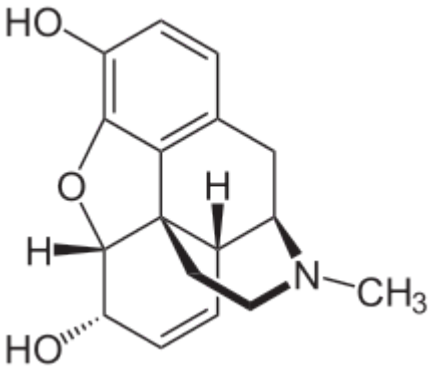
Morphine Analogs



Substituents				
Drug	**3**	**6**	**N**	**14**
Morphine	-OH	-OH	$-CH_3$	-H
Heroin	$-OCO.CH_3$	$-OCO.CH_3$	$-CH_3$	-H
Codeine	$-OCH_3$	-OH	$-CH_3$	-H
Levorphanol	-OH	-H	$-CH_3$	-H (no –O- at C_4-C_5)
Dihydrocodeine	$-OCH_3$	-OH	$-CH_3$	-H (no double bond C_7-C_8)
Nalorphine	-OH	-OH	$-CH_2CH=CH_2$	-H
Nalbuphine	-OH	-OH	$-CH_2$-cyclobutyl	-OH (no double bond C_7-C_8)
Butorphanol	-OH	-H	$-CH_2$-cyclobutyl	-H (no –O- at C_4-C_5 & double bond C_7-C_8)
Naloxone	-OH	=O	$-CH_2CH=CH_2$	-OH (no double bond C_7-C_8)

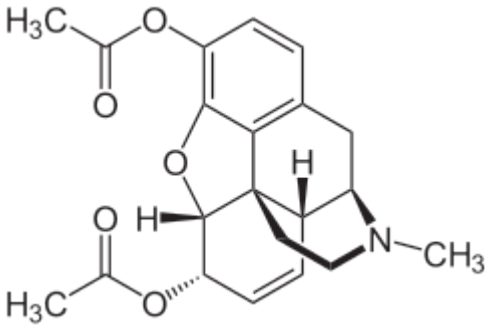
Examples of Opioid Agonists Analgesics

Morphine



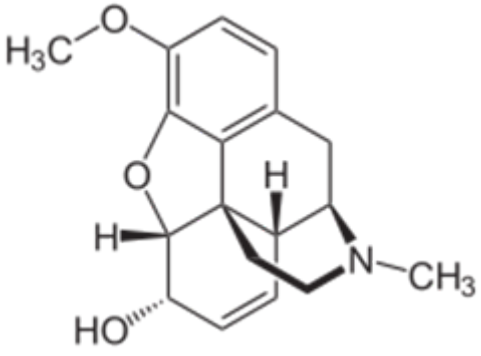
(5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol

Heroin



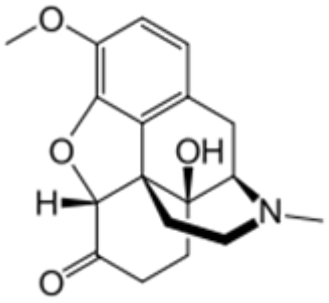
(5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol diacetate

Codeine



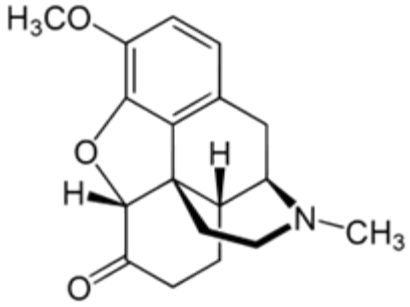
(5α,6α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol

Oxycodone



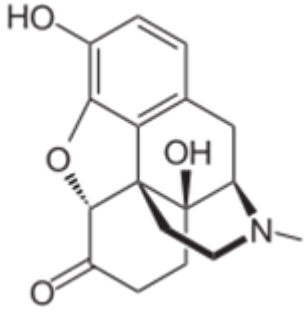
(5*R*,9*R*,13*S*,14*S*)-4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one

Hydrocodone



4,5a-Epoxy-3-methoxy-17-methylmorphinan-6-one

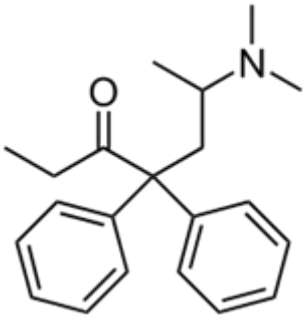
Oxymorphone



4,5α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one

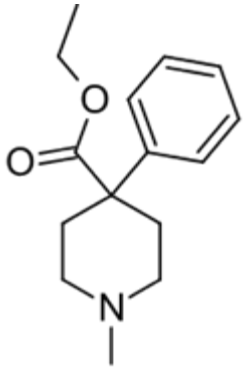
Examples of Opioid Agonists Analgesics

Methadone



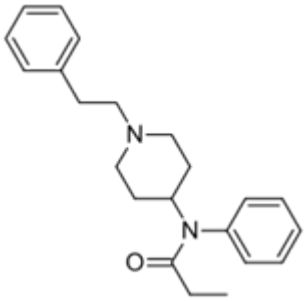
(*RS*)-6-(Dimethylamino)-4,4-diphenylheptan-3-one

Meperidine



Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate

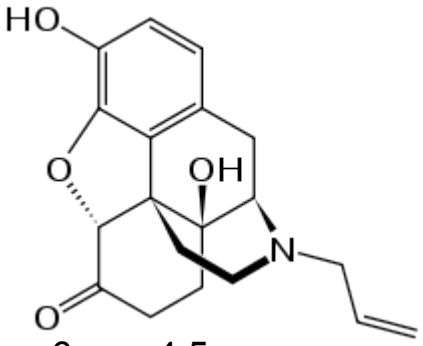
Fentanyl



N-(1-(2-phenylethyl)-4-piperidinyl)-*N*-phenylpropanamide

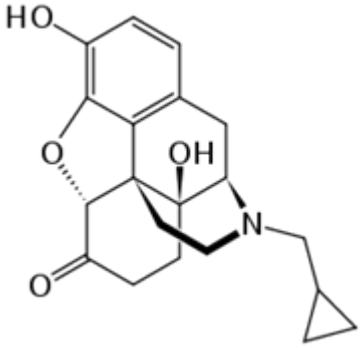
Examples of Opioid Antagonists Analgesics

Naloxone



Morphinan-6-one,4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride,

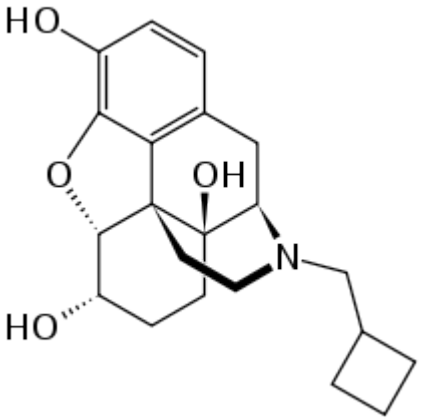
Naltrexone



17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one

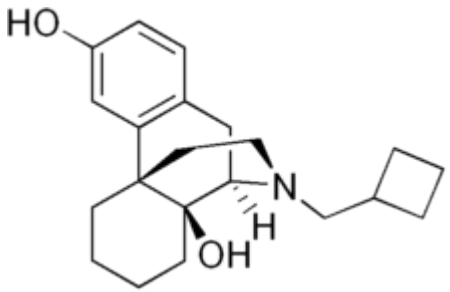
Examples of Mixed Agonists-Antagonists Analgesics

Nalbuphine



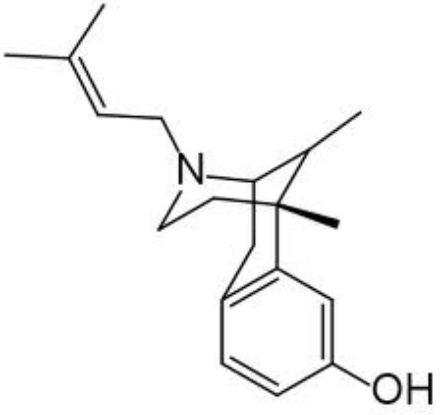
(–)-17-(cyclobutylmethyl)- 4,5α-epoxymorphinan- 3,6α,14-triol hydrochloride

Butorphanol



17-cyclobutylmethyl-morphinan-3,14-diol

Pentazocine

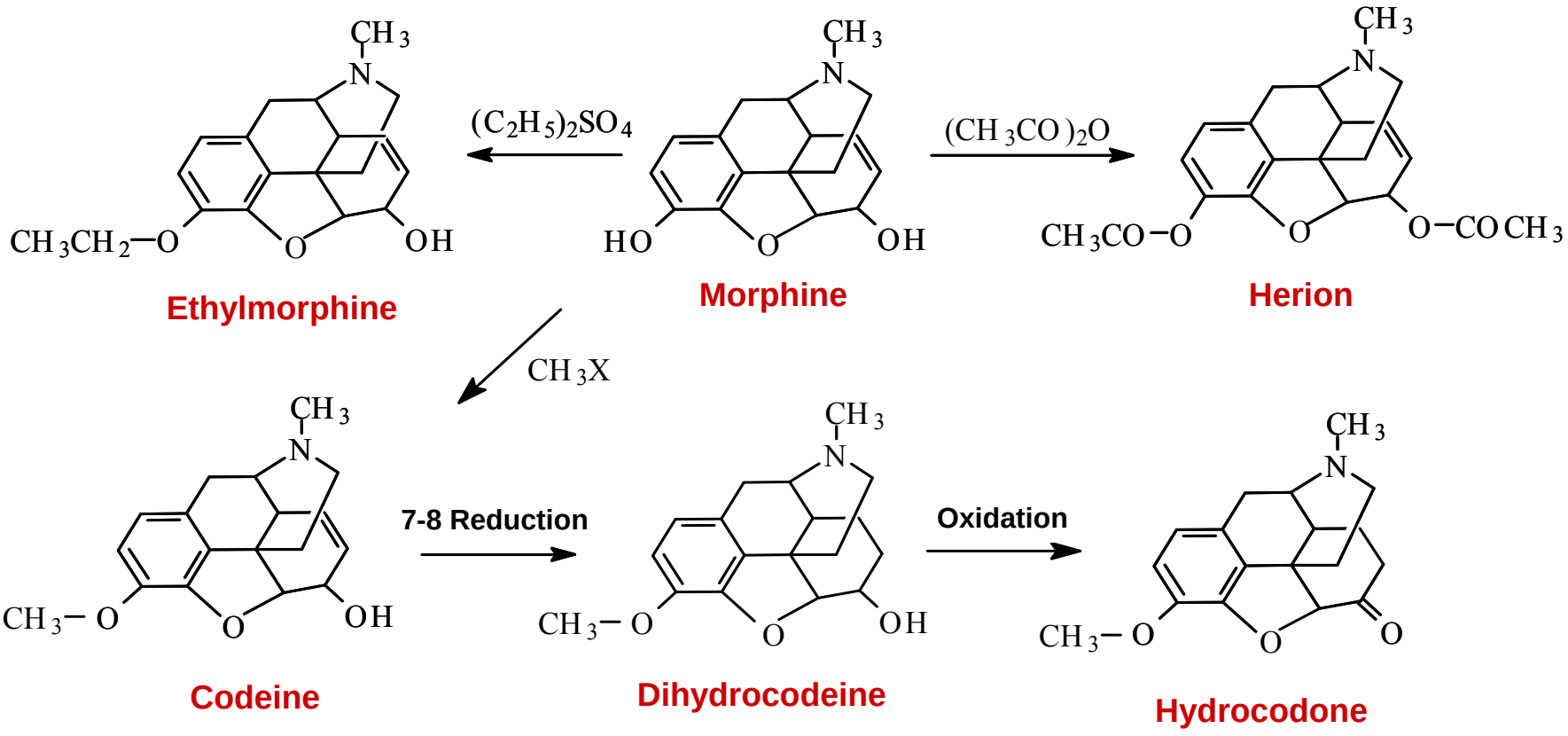


2-dimethylallyl-5,9-dimethyl-2'-hydroxybenzomorphan

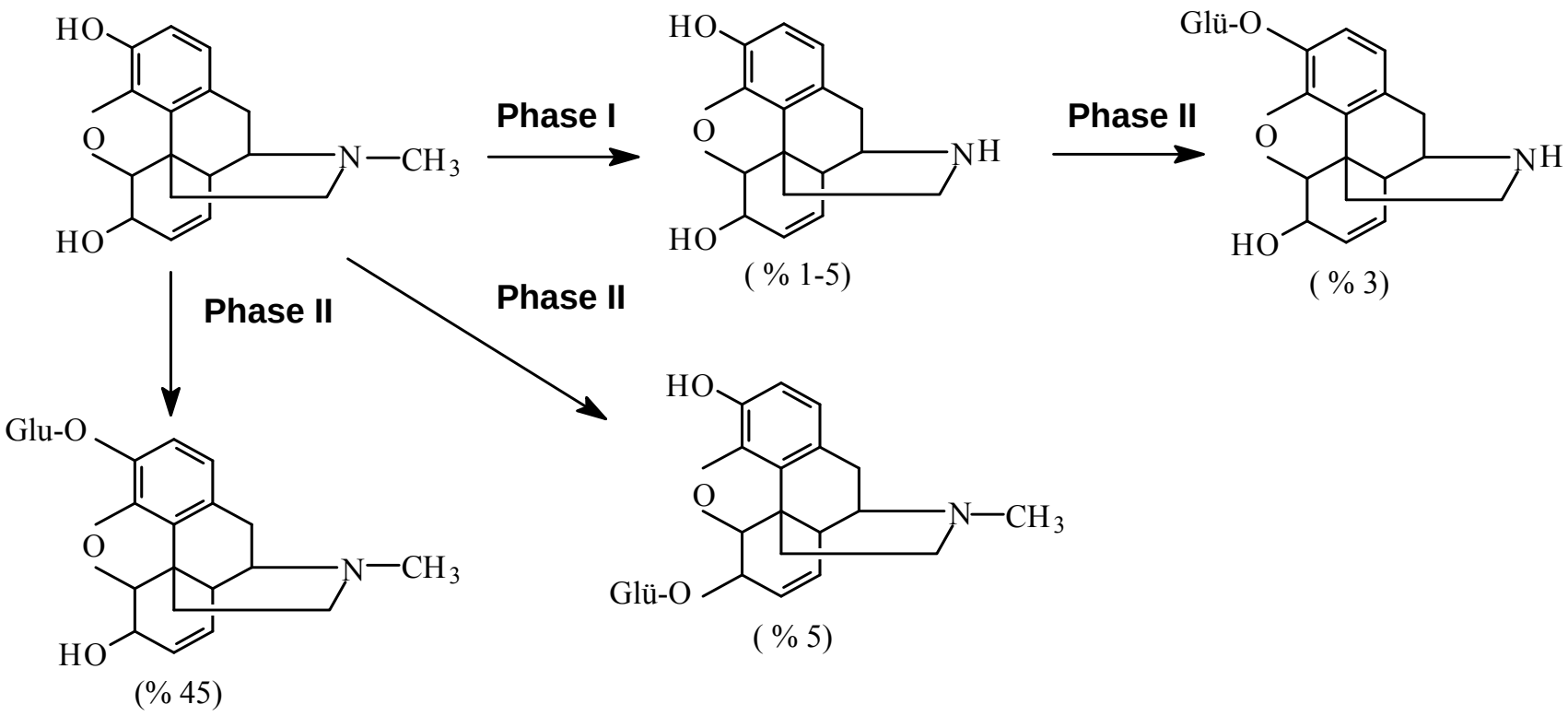
Synthesis of Morphine Analogs

✓ Total synthesis of morphine was done by Gates-Tschudi (1952-1956) and Elad-Ginsburg (1954). However this synthesis is expensive, it is more economical and easier to be obtained from opium as a natural product.

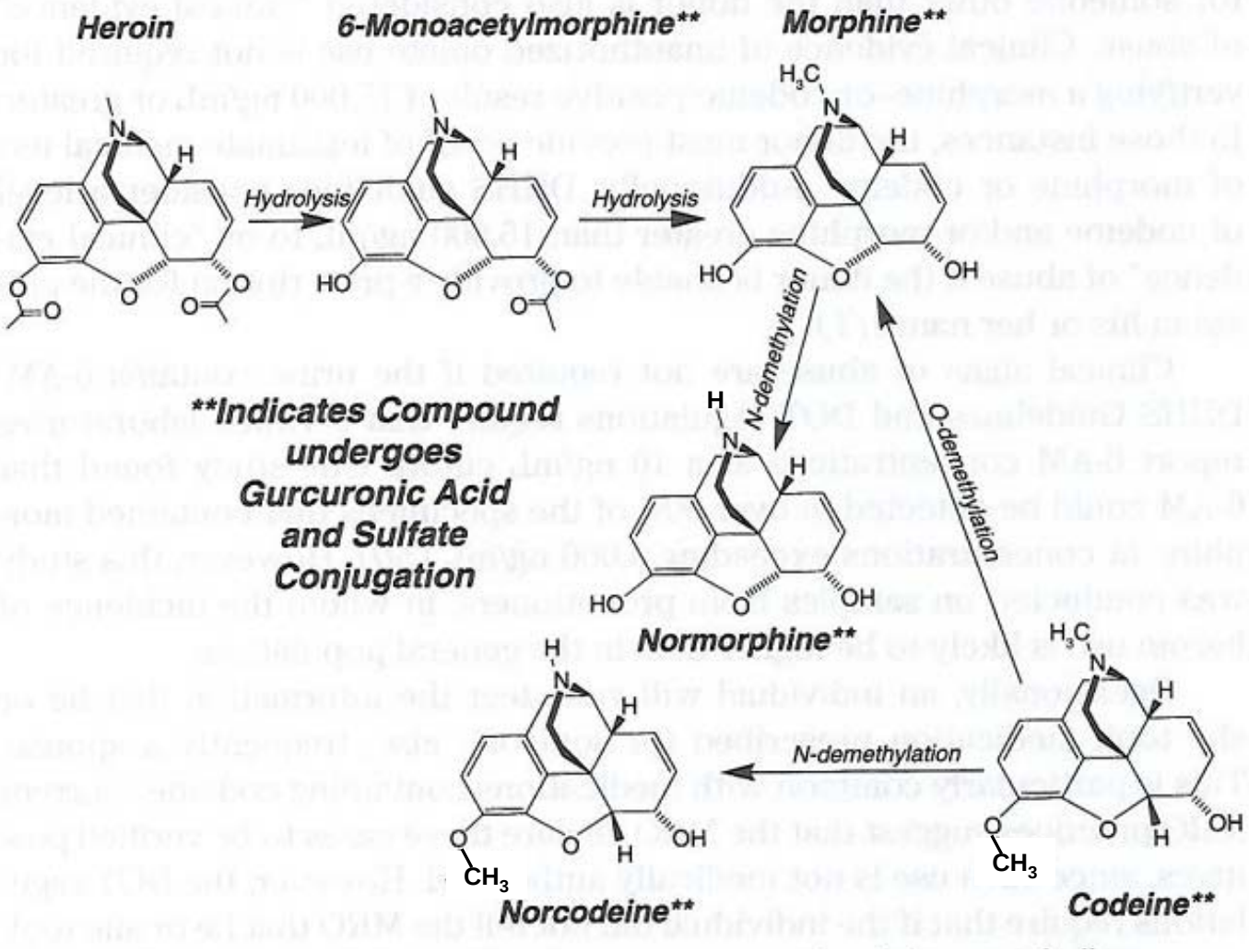
Synthesis of morphine analogs from morphine is outlined below:



Metabolism of Morphine



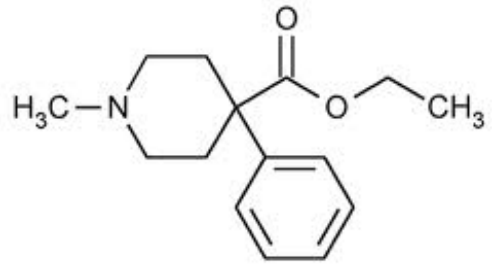
Hereoin, Morphine and Codeine Metabolism



Narcotic Analgesics - Meperidine

Meperidine (Pethidine, Demerol) is a narcotic analgesics used to relieve moderate to severe pain.

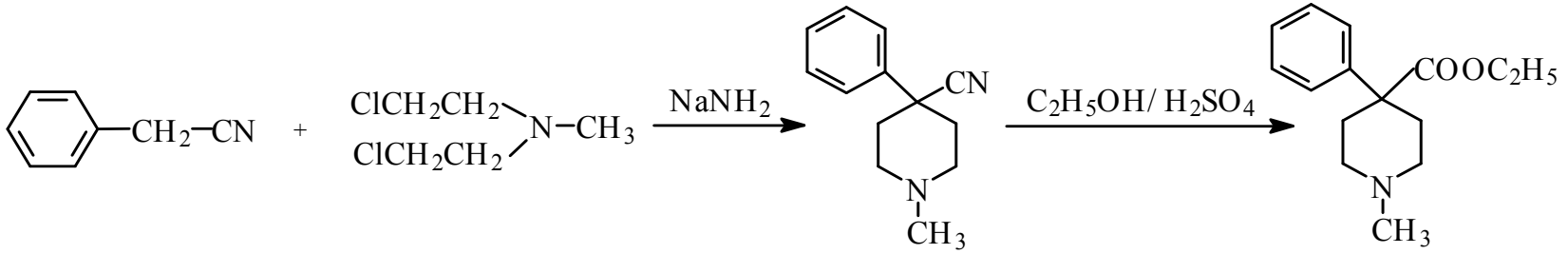
- ✓ Meperidine acts on the central nervous system (CNS) to relieve pain.
- ✓ It was the **first synthetic opioid** synthesized in 1932 by the chemist Otto Eislib.
- ✓ Meperidine is the most common subsitute for morphine.



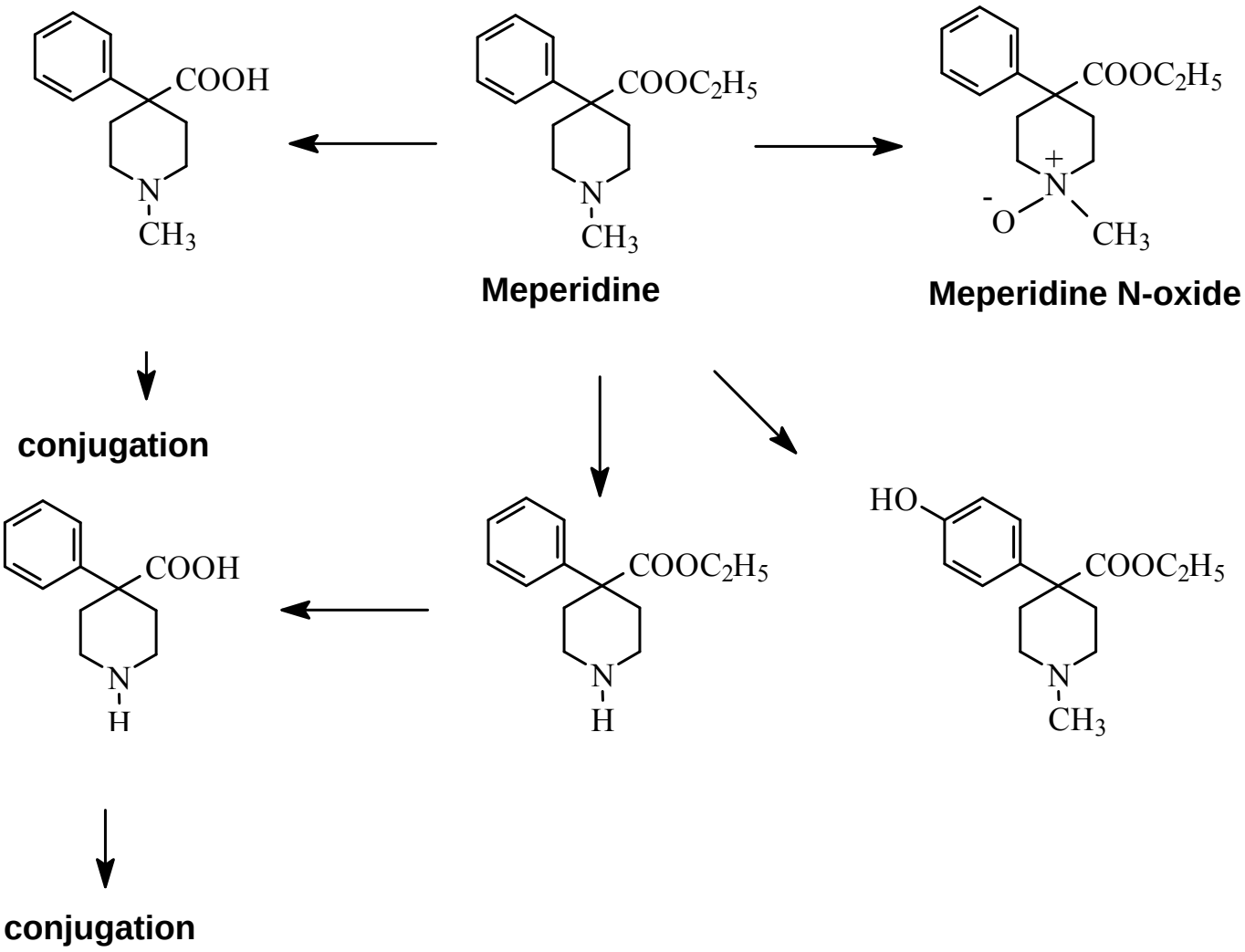
Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate

Synthesis of Meperidine

Phenylacetonitrile reacts with di(β-chloroethyl)methyl amine in the presence of sodium amide resulting in a piperidine ring. Acid hydrolysis in the presence of ethanol changes nitrile into ester group.



Metabolism of Meperidine

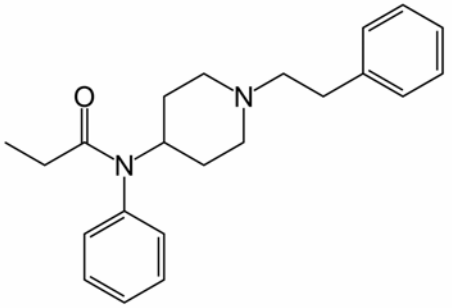


Narcotic Analgesics - Fentanyl

✓ **Fentanyl (**Actiq, Duragesic) acts upon specific receptors in your brain and spinal cord to decrease the feeling of pain and to reduce emotional response to pain.

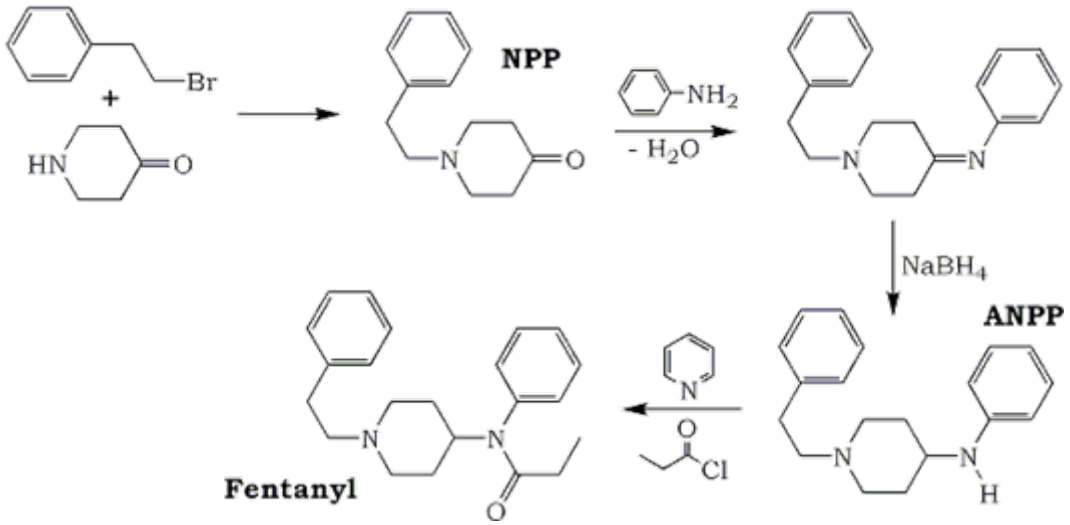
✓ It is a synthetic opioid analgesic with a rapid onset and short duration of action

✓ It is 100 times more potent than morphine



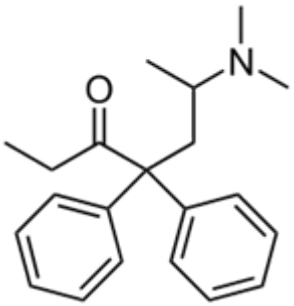
N-(1-(2-phenylethyl)-4-piperidinyl) -*N*-phenylpropanamide

Synthesis: N-Phenethyl-piperidone (NPP) which can be easily synthesized from piperidone andphenethyl-tosylate or phenethyl-bromide through a simple S_N2 mechanism.The NPP is reacting with aniline giving the imine derivative which is reduced to the 4-anilino-N-phenethyl-piperidine (4-ANPP). The 4-ANPP is then reacted with propionyl chloride giving **Fentanyl**.



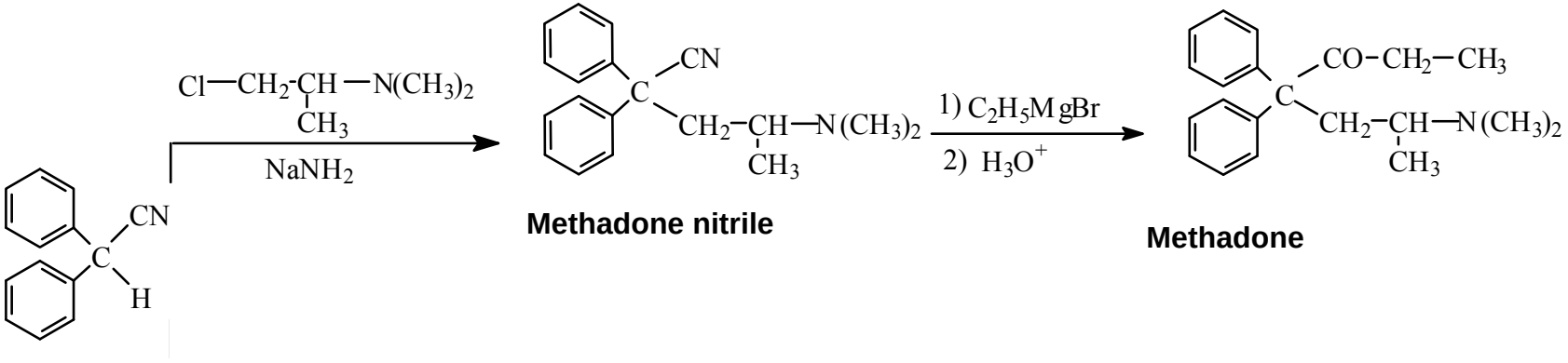
Narcotic Analgesics - Methadone

- ✓ **Methadone** (**Symoron**) is a synthetic opioid.
- ✓ It is used medically as an analgesic and also it works on parts of the brain and spinal cord to block the "high" caused by using opiates (such as heroin).
- ✓ It also helps reduce cravings and withdrawal symptoms caused by opiate use.
- ✓ Methadone is more active and more toxic than morphine



(*RS*)-6-(Dimethylamino)-4,4-diphenylheptan-3-one

Synthesis of Methadone

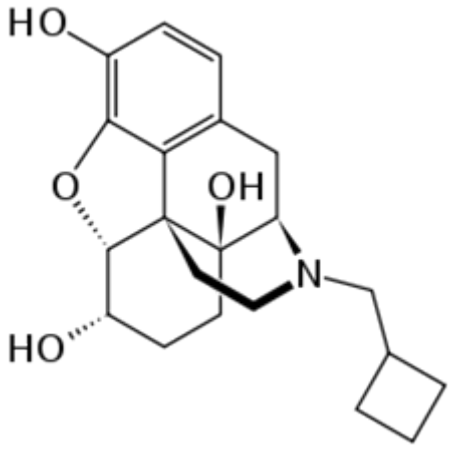


Methadone nitrile

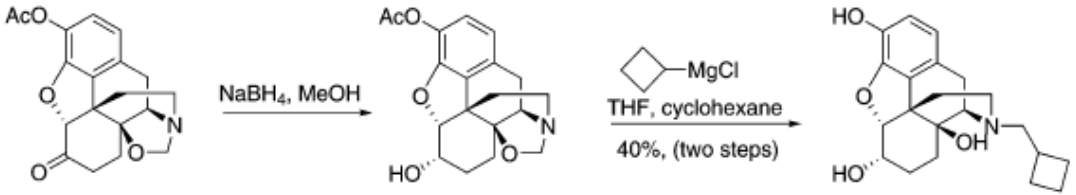
Methadone

Opioid Agonist-Antagonist - Nalbuphine

Nalbuphine (Nubain) is a semi-synthetic opioid agonist-antagonist used commercially as an analgesic.
Less abuse potential than pure agonist opioids
Structrually similar to oxymorphone and opioid antagonist naloxone



(–)-17-(cyclobutylmethyl)- 4,5α-epoxymorphinan- 3,6α,14-triol hydrochloride

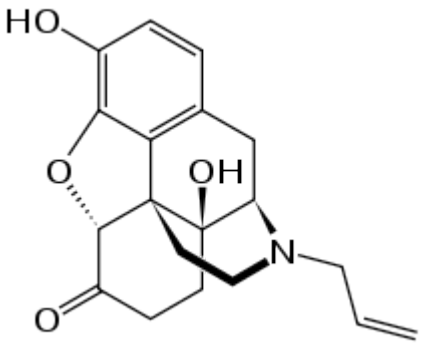


oxazolidine

nalbuphine

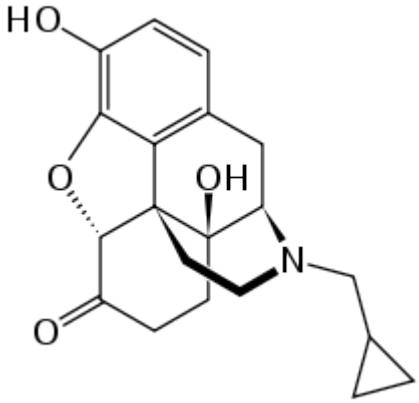
Opioid Antagonists

✓ **Naloxone** is an opioid antagonist drug in the 1960s. and is used to counter the effects of opiate overdose, for example heroin or morphine overdose.



✓ **Naltrexone** is an opioid receptor antagonist used primarily in the management of alcohol dependence and opioid dependence.

✓ Naltrexone should not be confused with naloxone (which is used in emergency cases of opioid overdose)



http://www.elmhurst.edu/~chm/vchembook/674narcotic.html

Müstahzarlar:

Difenoksilat hidroklorür: Lomotil (Ali Raif)

Dionin: Codeinal (Zambo), Dicoben (Vita), Fenokodin (Adeka), Neocodin (Şanlı)

Fentanil: Durogesic (Janssen-Cilag), Fentanyl (Janssen-Cilag), Fentanyl Citrate (Abbott), Fentanil Citrate BP Antigen (Filiz).

Kodein: A-Ferin (Hüsnü Arsan), A.P.C. (Dermancı), Apex (Biokem), Codasel (Akdeniz), Codeinal (Zambo), Dicoben (Vita), Doladomon P (İ.E.Ulagay), Dolviran (Bayer), Fenokodin (Adeka), Geralgine-K (Münir Şahin), Neocodin (Şanlı), Pacofen (İ.E.Ulagay), Pirosal (Saba), Plevron (Sano), Temsaljin (Biosel), Theraflu (Novartis), Tussifed (Glaxo Smith Kleine).

Loperamit hidroklorür: Diadef (Şanlı), Lopermid (Saba)

Meperidin hidroklorür : Alodan Gerot Ampul (Liba), Dolantin (Hoechst)

Metadon hidroklorür : Dolofin Hidroklorür (Lilly, A.B.D.) Cuticura (Lokman), Gastroguanil (Lokman), Undo Talk (İlsan).

Morfin hidroklorür: Morfin HCl (Anonim), Vendal Retard (Liba).

Morfin sülfat: M-Esion (Nobel).

Noskapin: Coldex (Deva), Tusifon (Mulda).

Papaverin hidroklorür: Asthmadol (Bozok), Atropa (Solmaz), Papaverin (Biosel).

Tramadol hidroklorür: Contramal (Abdi İbrahim).