LEC.3 4 STAGE

Chemistry II Organic Pharmaceutical

2020-2019

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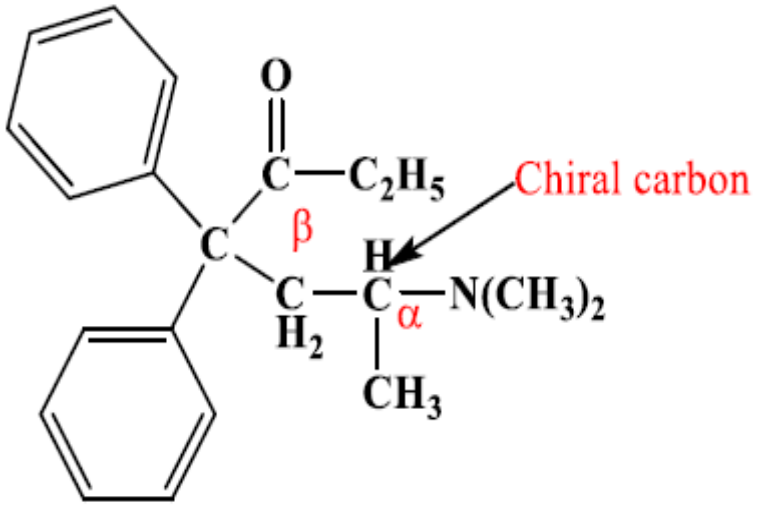
Diphenylheptanes

METHADONE

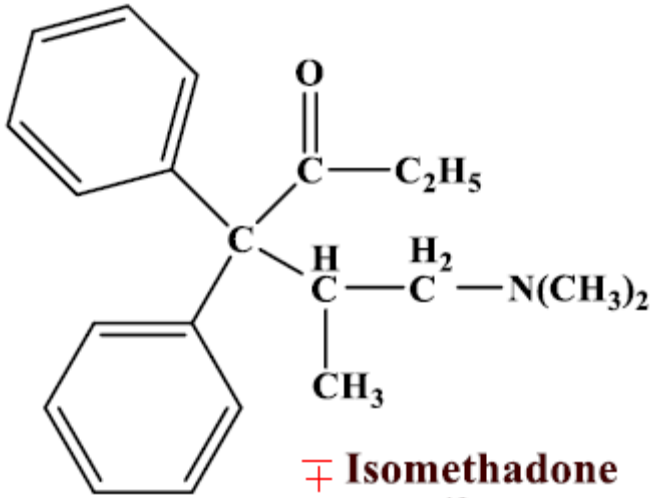
- is a synthetic opioid
- methadone possessed both analgesic and spasmolytic properties.

The general structure



(±) Methadone

accumulates in lipid tissue outside of the CNS, and thus has a **slow onset and long duration of action**



∓ Isomethadone

isomethadone

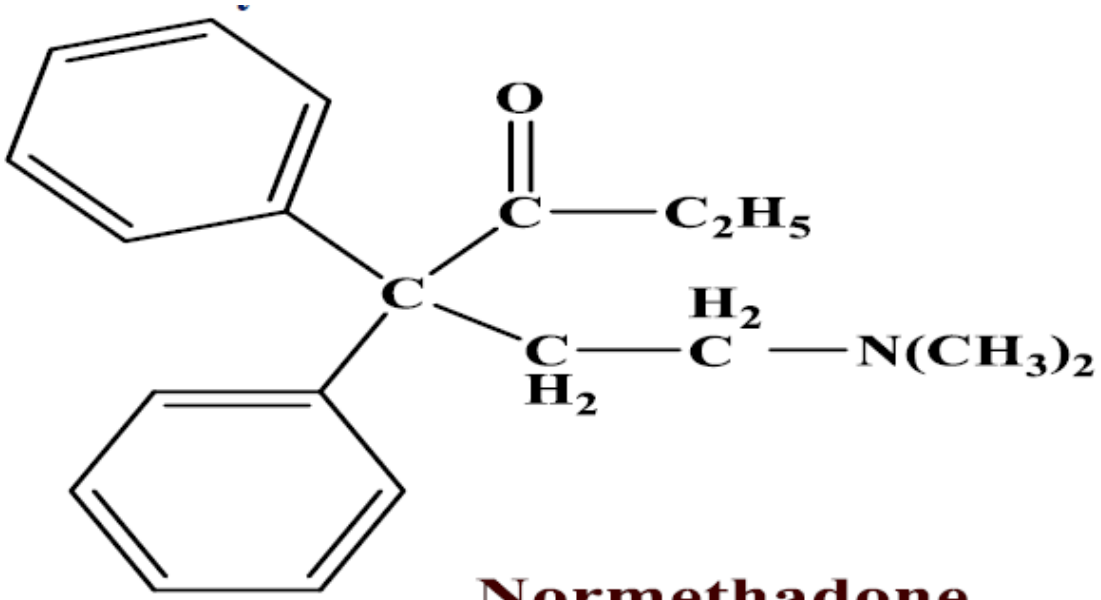
less active

less toxic

than methadone and all methadone derivatives r more active & more toxic than isomethadone grp.

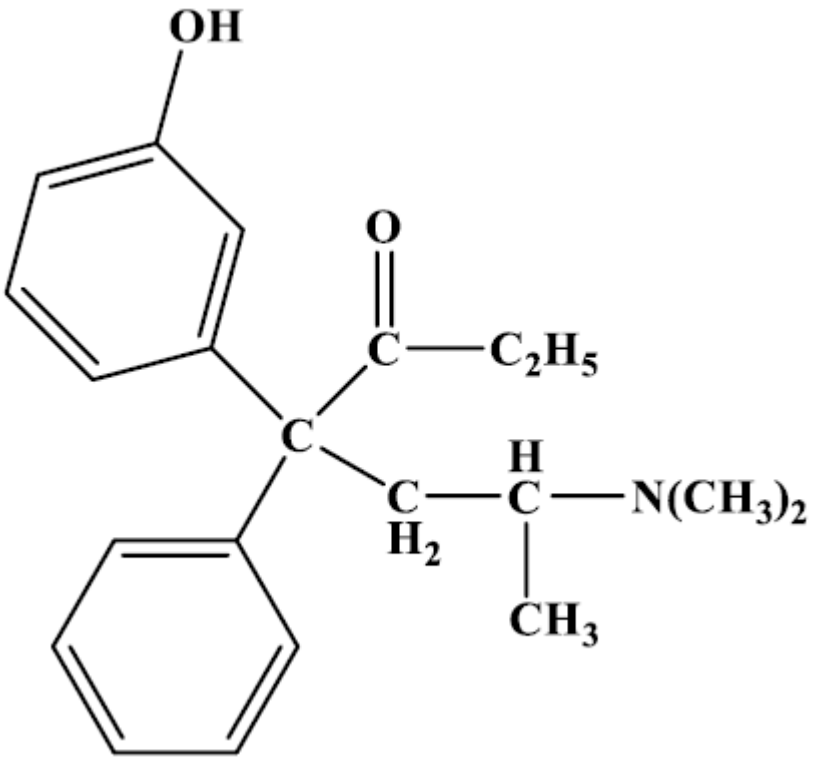
The levo isomer of methadone and isomethadone are twice as effective as their racemic mixture.

* **Removal of Me grp. at α-C →** ⬇ **activity.**

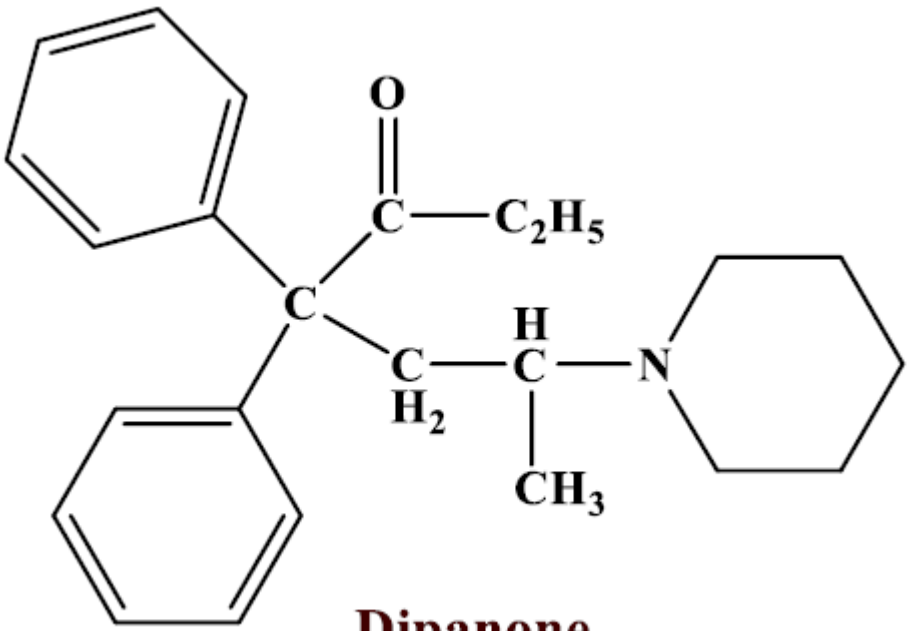


Normethadone
0.44

The insertion of an m-OH grp. on the one of the phenyl ring → ↓ analgesic activity.

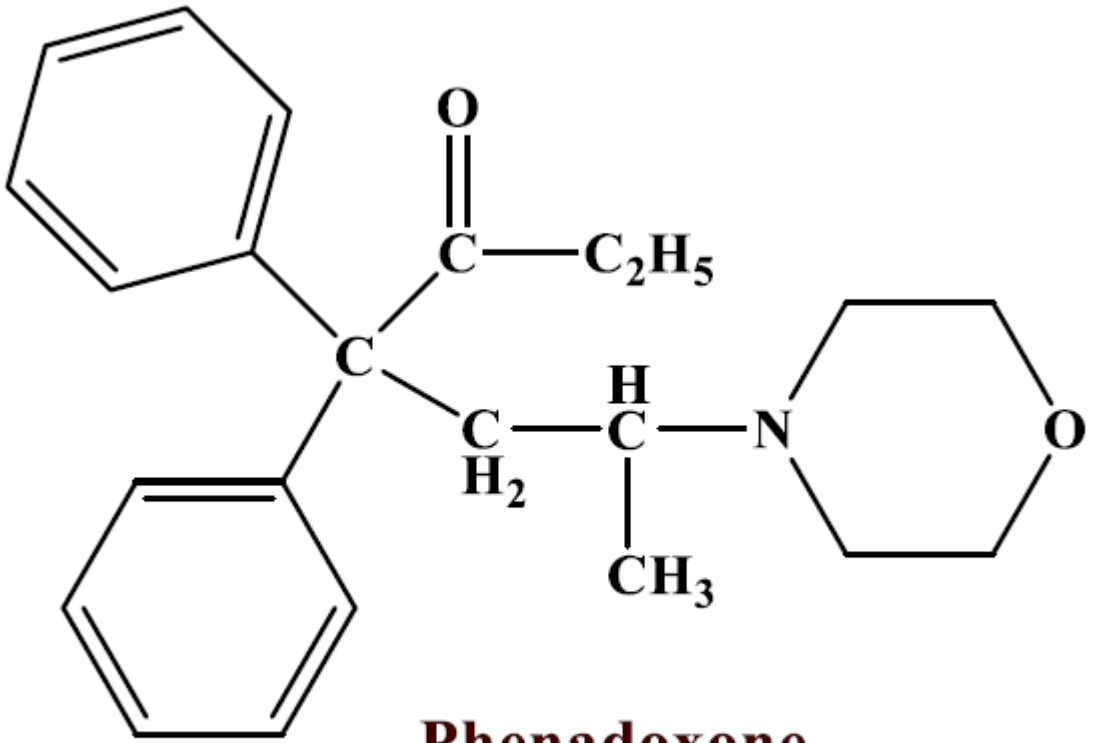


*-Replacement of $N(CH_3)_2$ (aliphatic amine) grp. to Alicycilic nitrogen → ⇩ the activity.



Dipanone
0.8

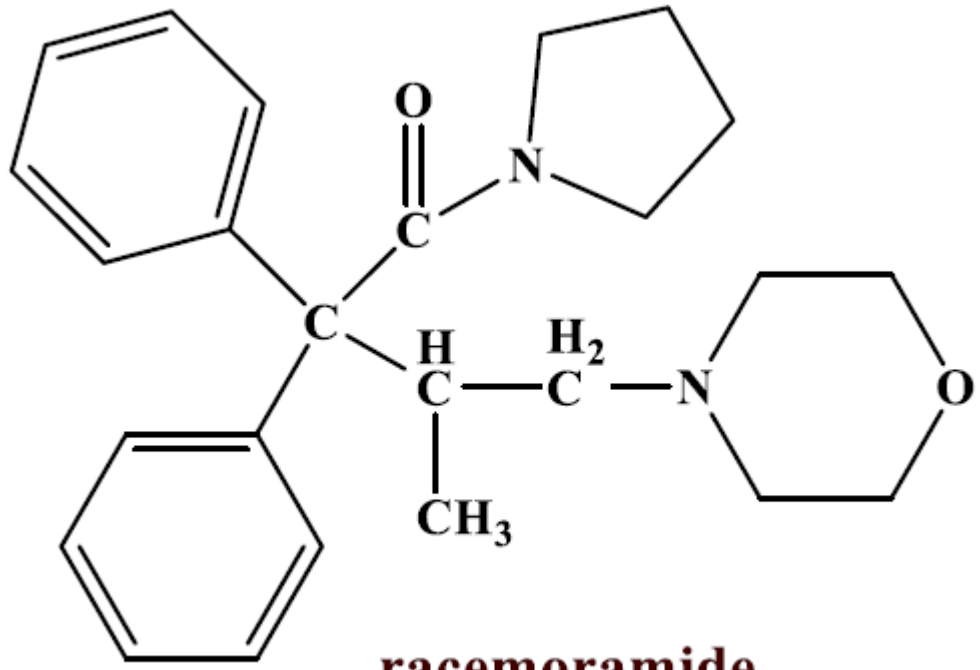
* Replacement of aliphatic amine to morpholine grp. ⬆ the activity.



Phenadoxone

1.4

*** Replacement of α-Me grp. & propionyl grp. of phenadoxone by β-methyl and amide grp. respectively results in ⇧ activity.**

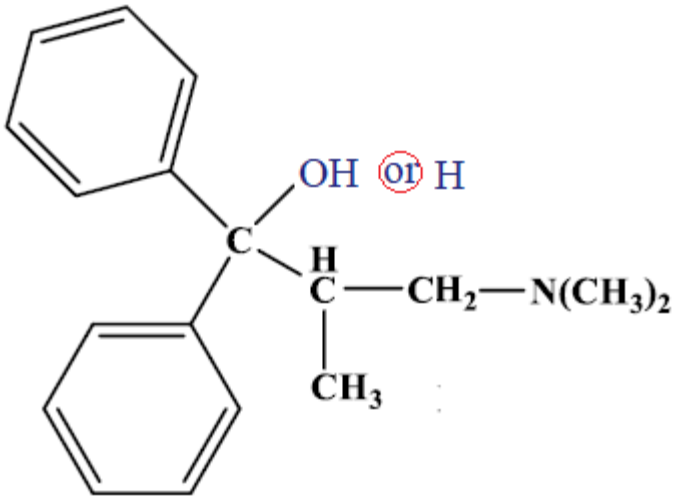


racemoramide

3.6

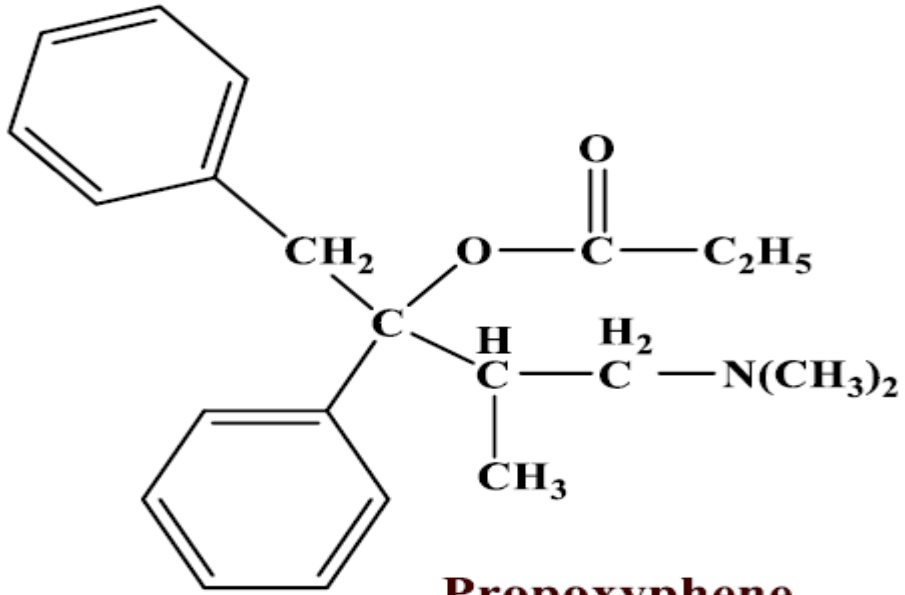
* Replacement of the propionyl group by H, OH, or acetoxyl, ↓ the activity

* Removal of any one of the phenyl ring, ↓ the activity.



* Replacement of one phenyl ring by benzyl grp. , propionyl grp. by propionoxy grp. and N-dimethyl α-methyl ethyl by N-dimethyl-β-methyl ethyl,

the activity.



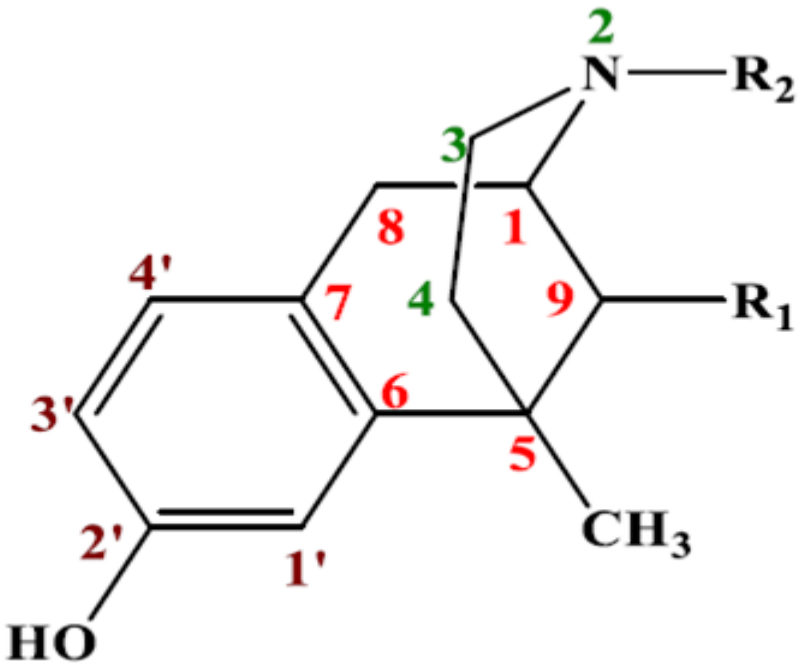
Propoxyphene
0.21

Benzomorphan(benzazocines)

Removal of alicyclic ring

_ Alicyclic ring was replaced by one or two methyl grps. These are known as benzomorphan derivatives or more correctly benzazocines.

_ Since removal of the ether bridge and all the peripheral grps in the alicyclic ring in morphine did not destroy its analgesic action.

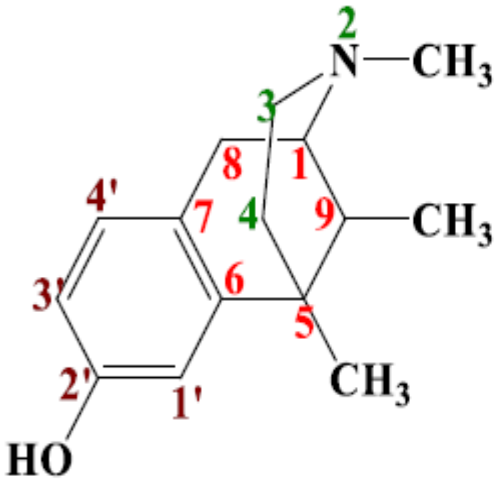


Derivative of morphine

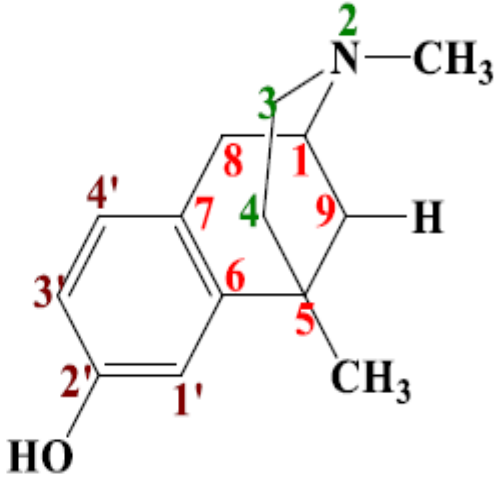
Does not contain ether bridge and alicyclic ring

SAR

1-The trimethyl cpd. ($R_1 = R_2 = CH_3$) is about 3 times more potent than the dimethyl ($R_1 = H$, $R_2 = CH_3$).



Trimethyl derivative

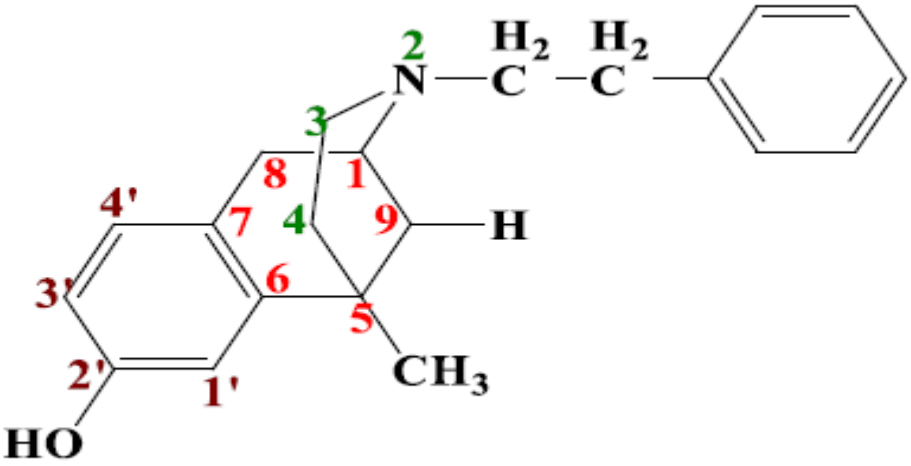


Dimethyl derivative

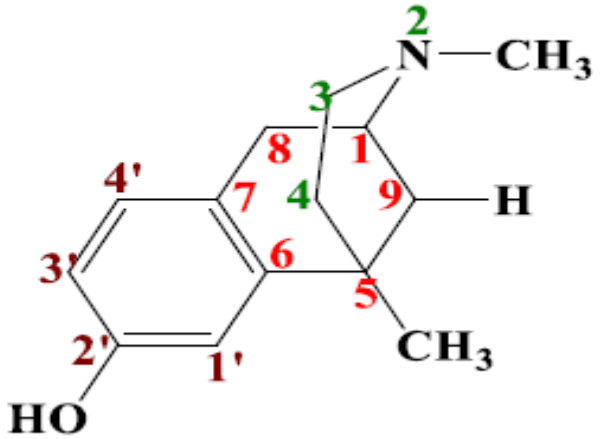
more potent than dimethyl derivative

less potent than trimethyl derivative

2-The N-phenethyl derivatives have 20 times the analgesic activity than N-methyl compounds.

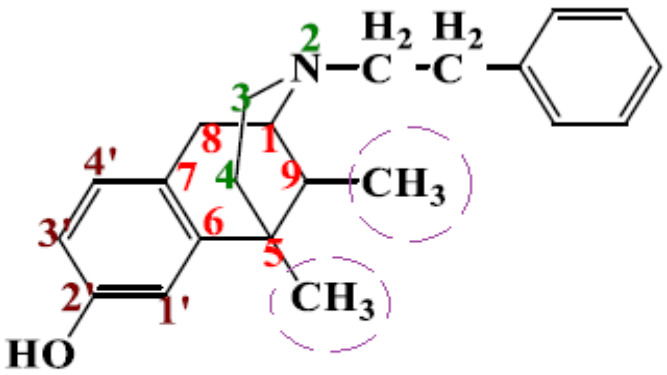


N-phenethyl derivative
more potent than N-methyl derivative

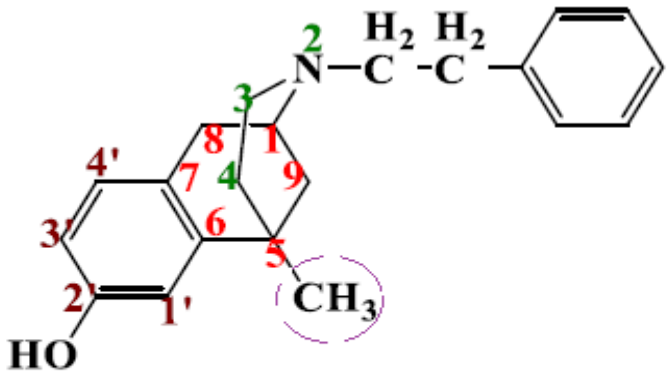


N-methy derivative less potent
than N-phenethyl derivative

3-The more potent was the one containing the two methyls at the same ring ($R_1 = CH_3$, $R_2 = CH_2\text{-}CH_2\text{-}C_6H_5$).



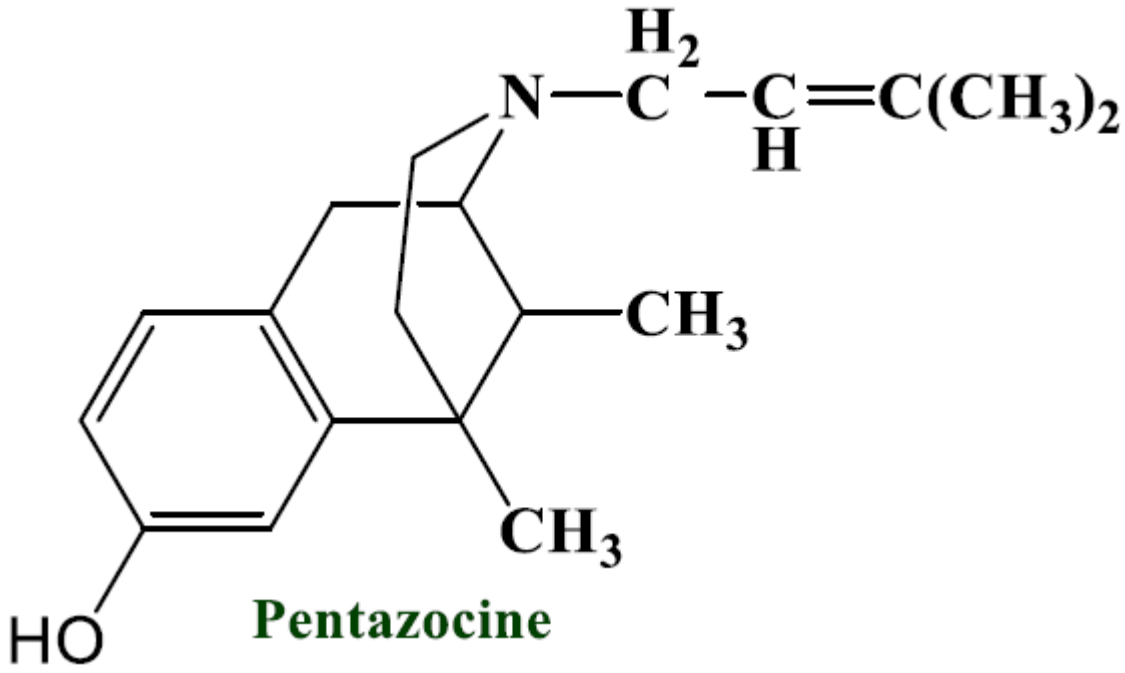
∓ Phenazocine
more potent
contain two ring methyls



less potent
contain one ring methyl

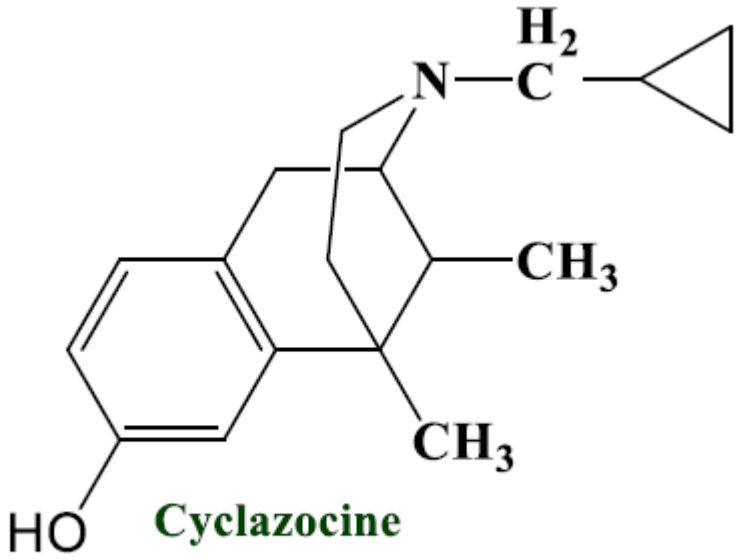
1.Wn N-Me grp. replacement by N-$CH_2CH=C(CH_3)_2$

give about half the analgesic activity of morphine, with lower addiction liability.



Pentazocine

2-Wn N-CH_3 replacement by N-CH2—cyclopropyl



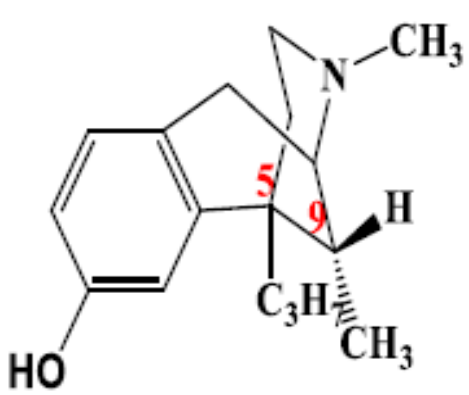
Cyclazocine

10 times more potent than morphine

S/E hallucination→no longer used

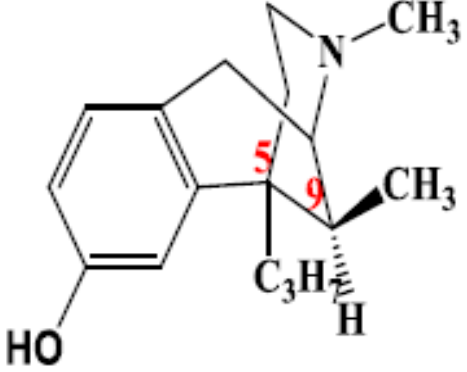
Cyclazocine, which is 10 times more potent than morphine, but its hallucination side effect limited its uses.

3-There are two isomer of N-methyl benzomorphansin which the alkyl in the 5 position is n-propyl (R_1) and the alkyl in the 9 position is methyl (R_2). These have been termed the α isomer and β isomer.



α-isomer (*cis*)

posses analgesic activity equal to morphine but has little or no capacity to suppress morphine withdrawal symptoms



β-isomer (*trans*)

has one of the highest analgesic potencics among the benzomorphans. but its quite able to suppress morphine withdrawal symptoms

The(-) isomer is a stronger analgesic without the dependence capacity and possesses antagonistic activity

(+) isomer has weak analgesic activity but a high physical dependence capacity

This demonstrated that it is possible to divorce analgesic activity comparable with morphine from addiction potential

SAR exception

We can summarize the SAR of morphine and related compounds by:-

1- 3 ° N >N-R

with the grp. (R)on the N should be relatively small.

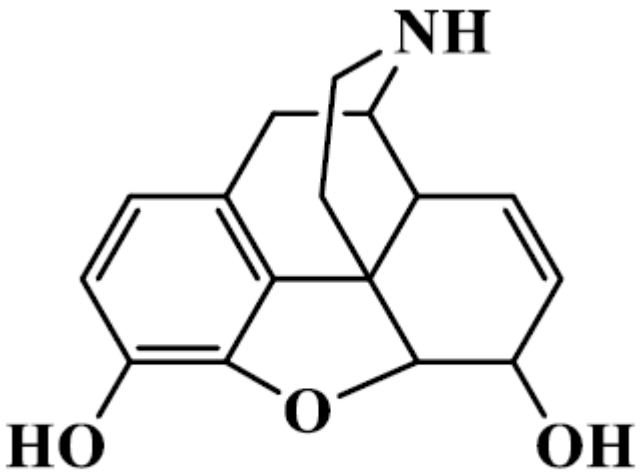
2.A central carbon atom, which is 4◦(i.e., not connected to H).

3. A phenyl grp. or a group isosteric with phenyl, which is connected to the central carbon atom.

4. A two carbon chain separating the central carbon atom from the nitrogen for maximal activity.

Exception for SAR

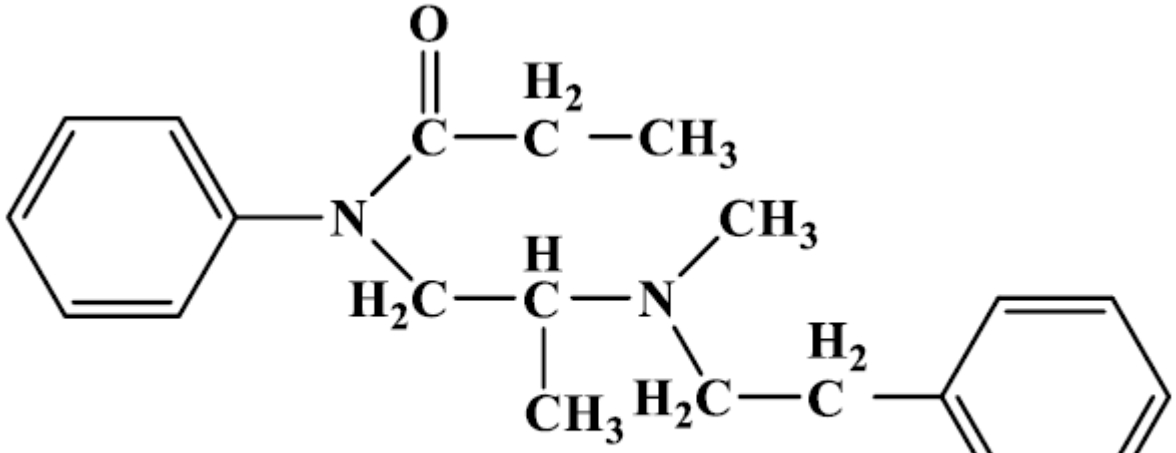
1- 3◦N , is not necessary for analgesic activity, where normorphine(product of N-dealkylation in the brain) is also possesses analgesic activity.



Normorphine

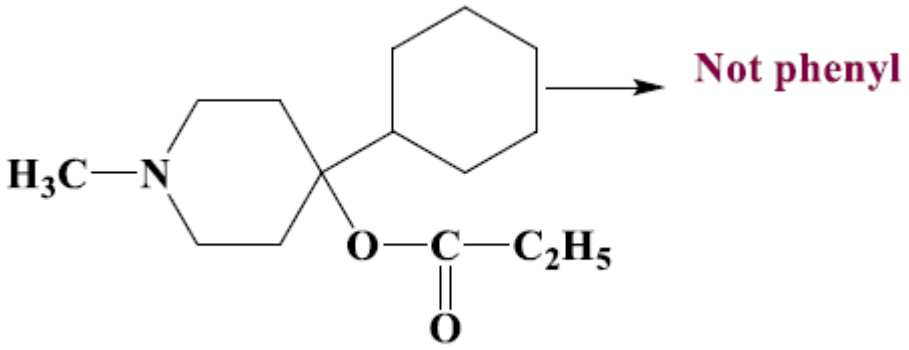
2-A small grp. on the 3◦N is not necessary and N-CH_3 can be replaced by aralkyl grp, (i.e., N-CH_2CH_2-C_6H_5).

3-Central carbon is not necessary for analgesic activity and can be replaced by 3◦N, like Diampromide(methadone derivative) which have comparable potency to morphine, but its not appeared on the marked, because it has shown addiction liability.

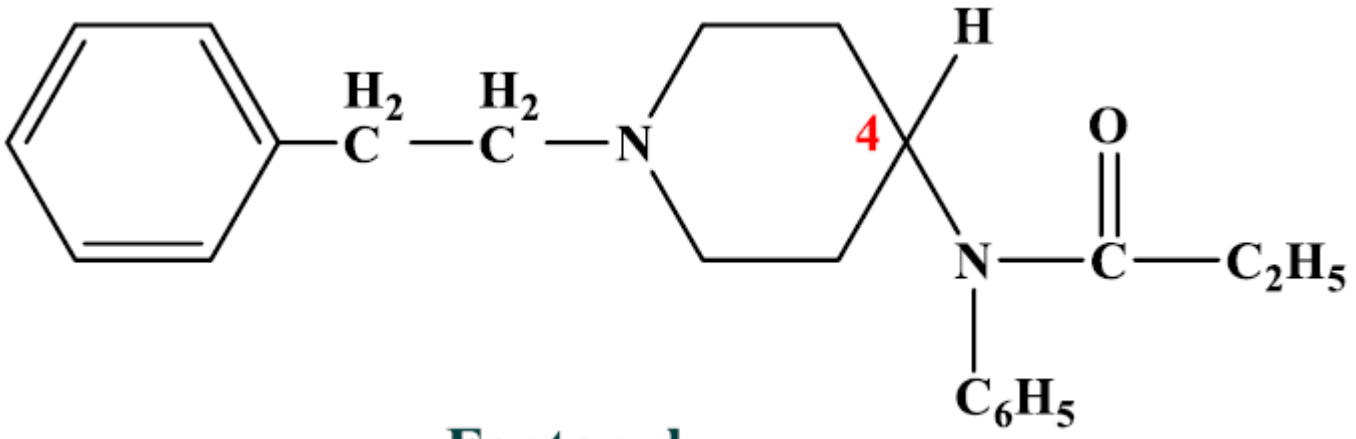


Diampromide

4-Phenyl ring is not necessary for analgesic activity, where the cyclohexyl analogue of meperidine is also active.



5-The two carbon chain separating 3◦N and central carbon is not necessary, like fentanyl.



Fentanyl

So the activity was associated not only with certain structural features but also with thesize and the shape of the molecule.