Lec 4 4th stage

Organic Pharmaceutical Chemistry II

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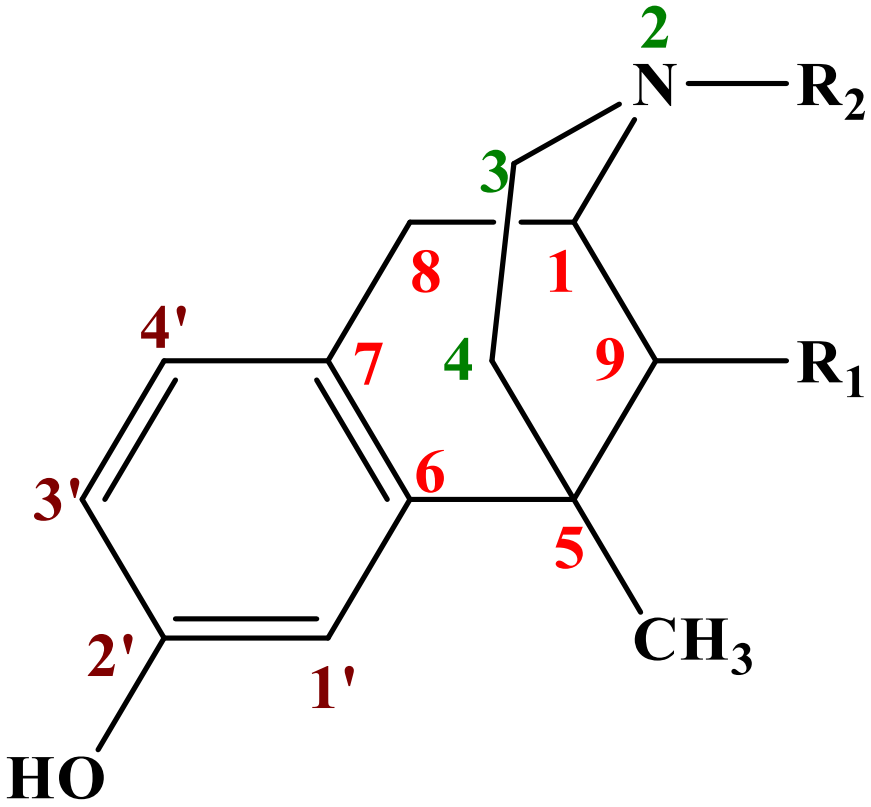
Assist prof. Dr.Rita Sabah Elias
College of Pharmacy, university of Basrah

Benzomorphan (benzazocines)

Removal of alicyclic ring

Since removal of the ether bridge and all the peripheral groups in the alicyclic ring in morphine did not destroy its analgesic action. May et al synthesized a series of compounds in which the alicyclic ring was replaced by one or two methyl groups. These are known as benzomorphan derivatives or more correctly benzazocines.

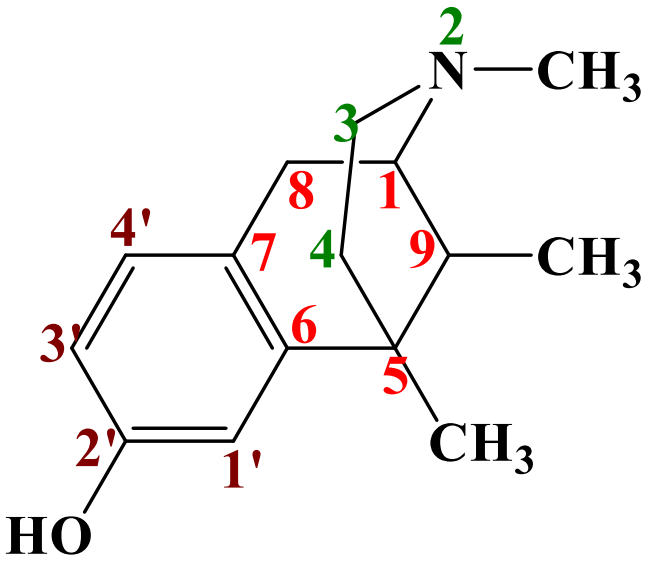


Derivative of morphine

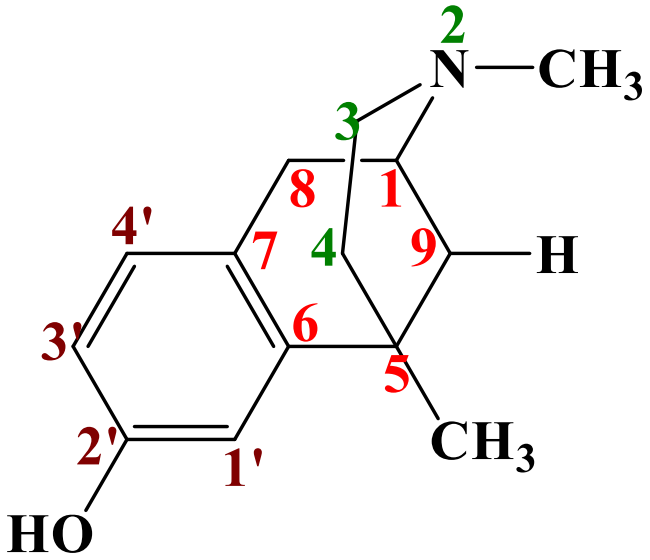
Does not contain ether bridge and alicyclic ring

SAR

1- The trimethyl compound (R1 = R2 = CH_3) is about 3 times more potent than the dimethyl (R1 = H, R2 = CH_3).

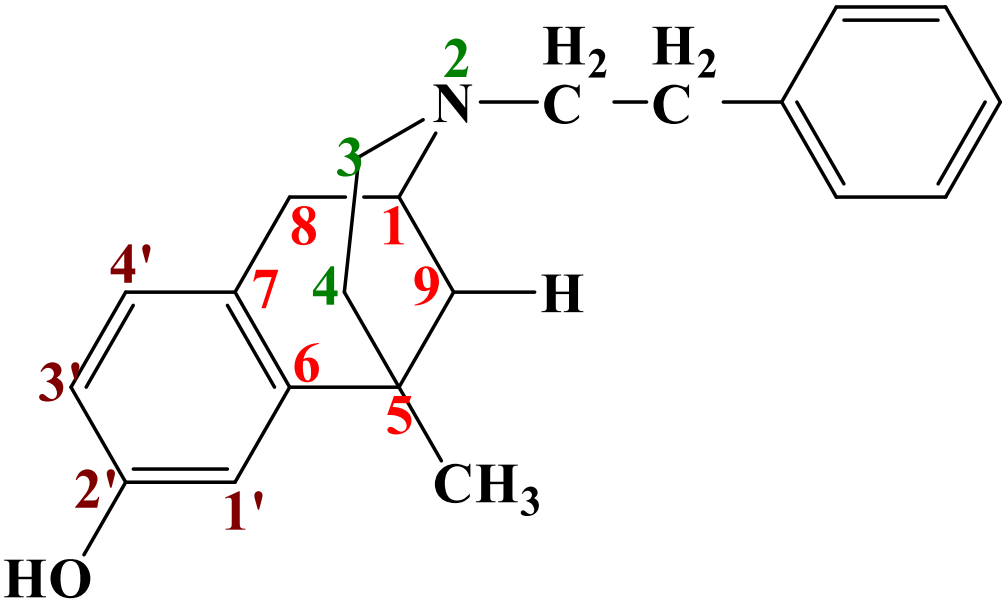


Trimethyl derivative
more potent than dimethyl derivative

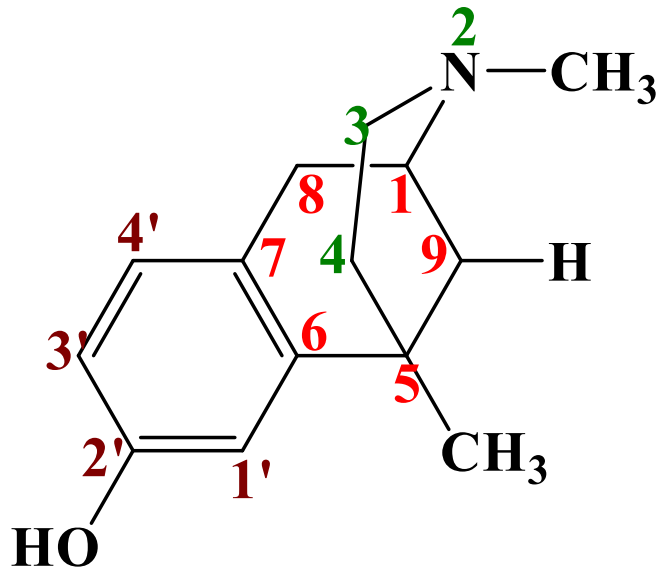


Dimethyl derivative
less potent than trimethyl derivative

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

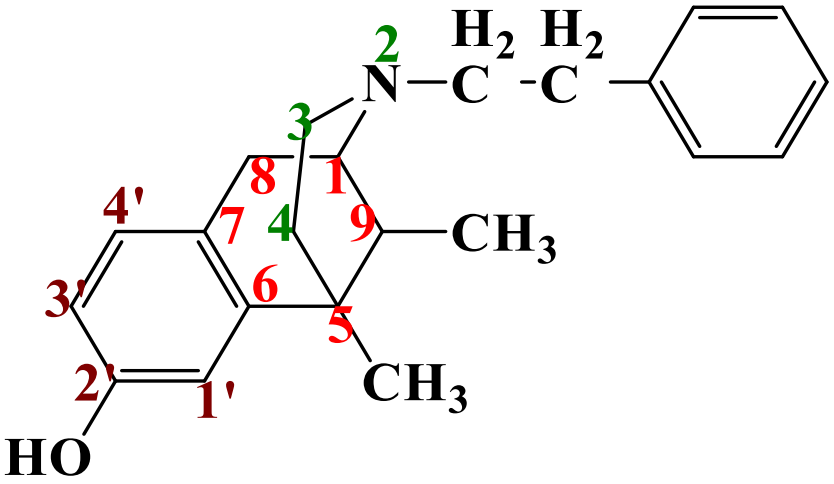


N-phenethyl derivative
more potent than N-methyl derivative

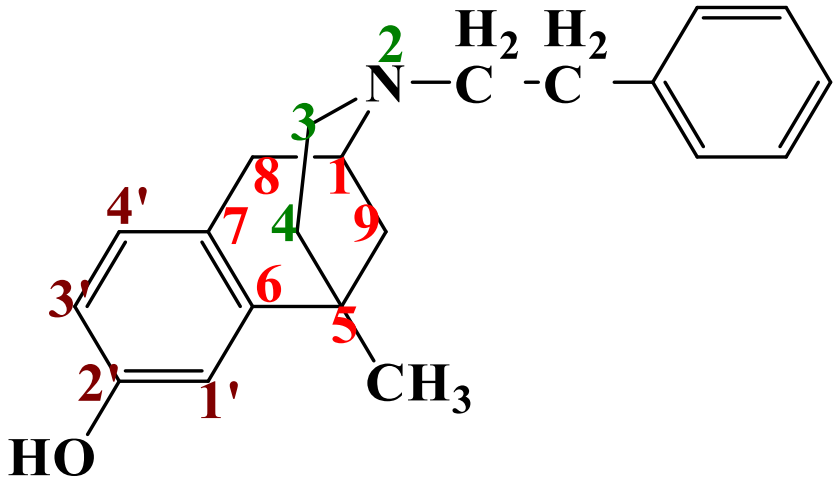


N-methy derivative less potent than N-phenethyl derivative

3- The more potent was the one containing the two ring methyls (ll, R1 = CH_3. R2 = CH_2-CH_2-C_6H_5).



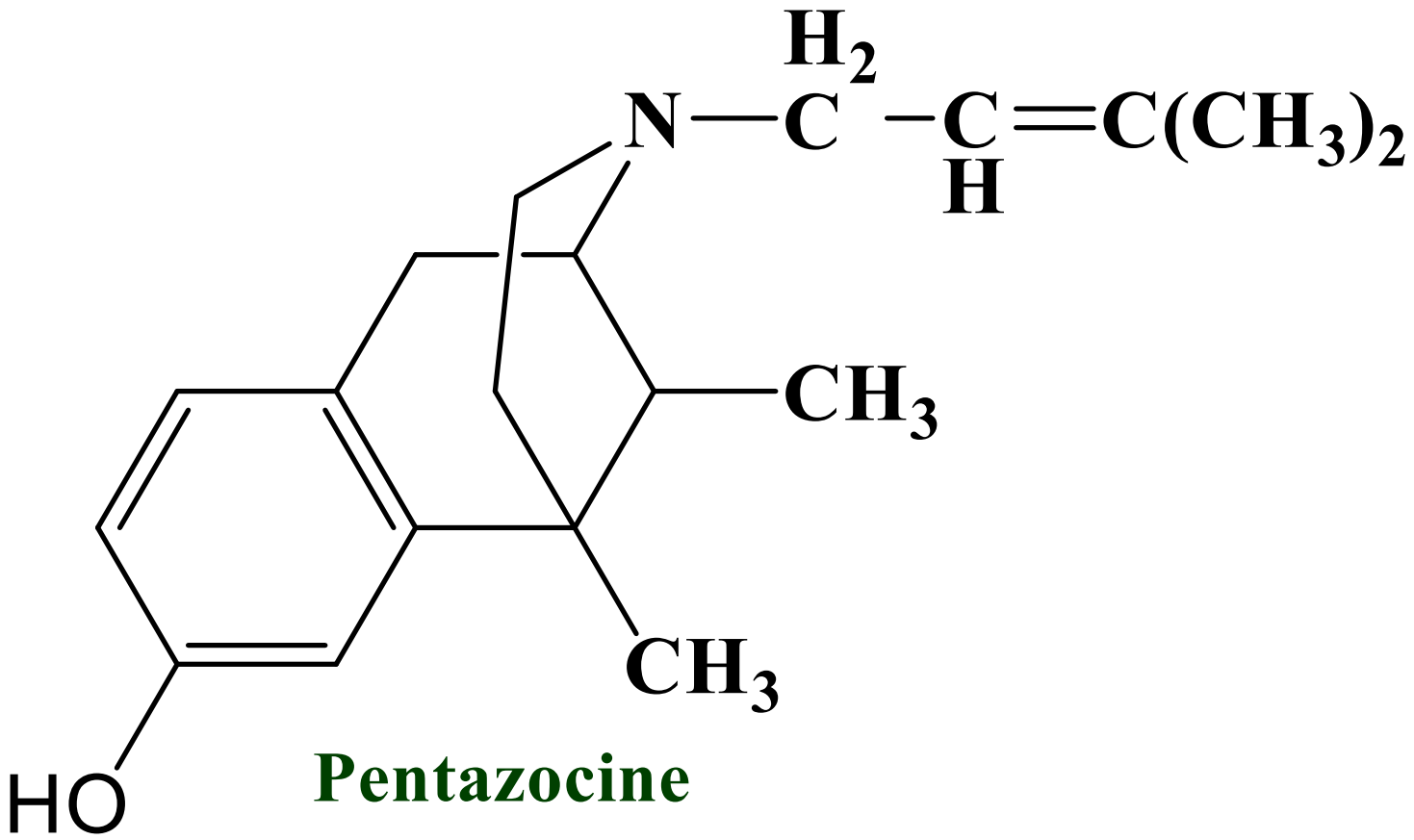
∓ **Phenazocine**
more potent
contain two ring methyls



less potent
contain one ring methyl

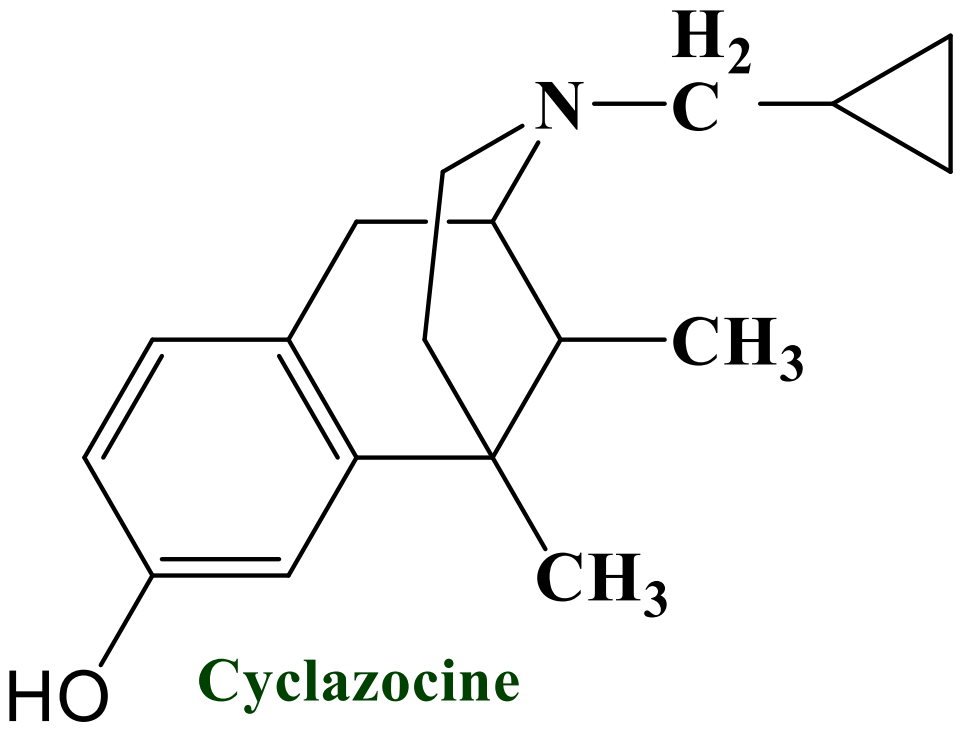
Antagonist

1. When N-methyl group replacement by N-$CH_2CH=C(CH_3)_2$ (pentazocine) has about half the analgesic activity of morphine, with lower addiction liability.



Pentazocine

2- When N-CH_3 replacement by N-CH_2— cyclopropyl Cyclazocine, which is 10 times more potent than morphine, but its hallucination side effect limited its uses.

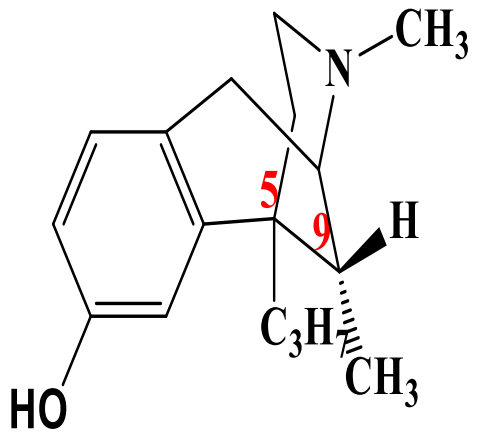


Cyclazocine

10 times more potent than morphine

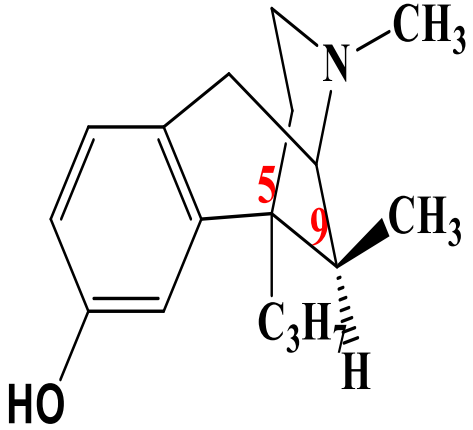
S/E hallucination→no longer used

3-There are two isomer of N-methyl benzomorphans in which the alkyl in the 5 position is n-propyl (R1) and the alkyl in the 9 position is methyl (R2). 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. **A tertiary nitrogen, with the group on the nitrogen should be relatively small.**

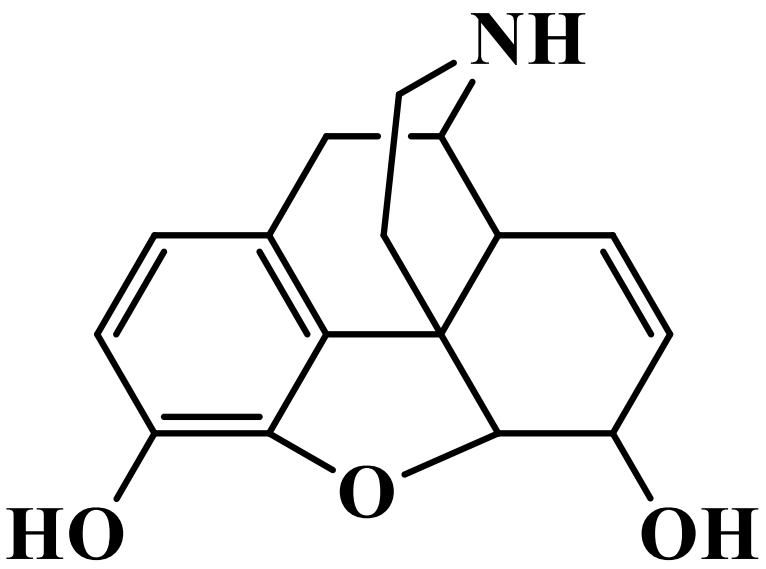
1. **A central carbon atom, which is 4° (i.e., not connected to hydrogen).**

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

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

Exception for SAR

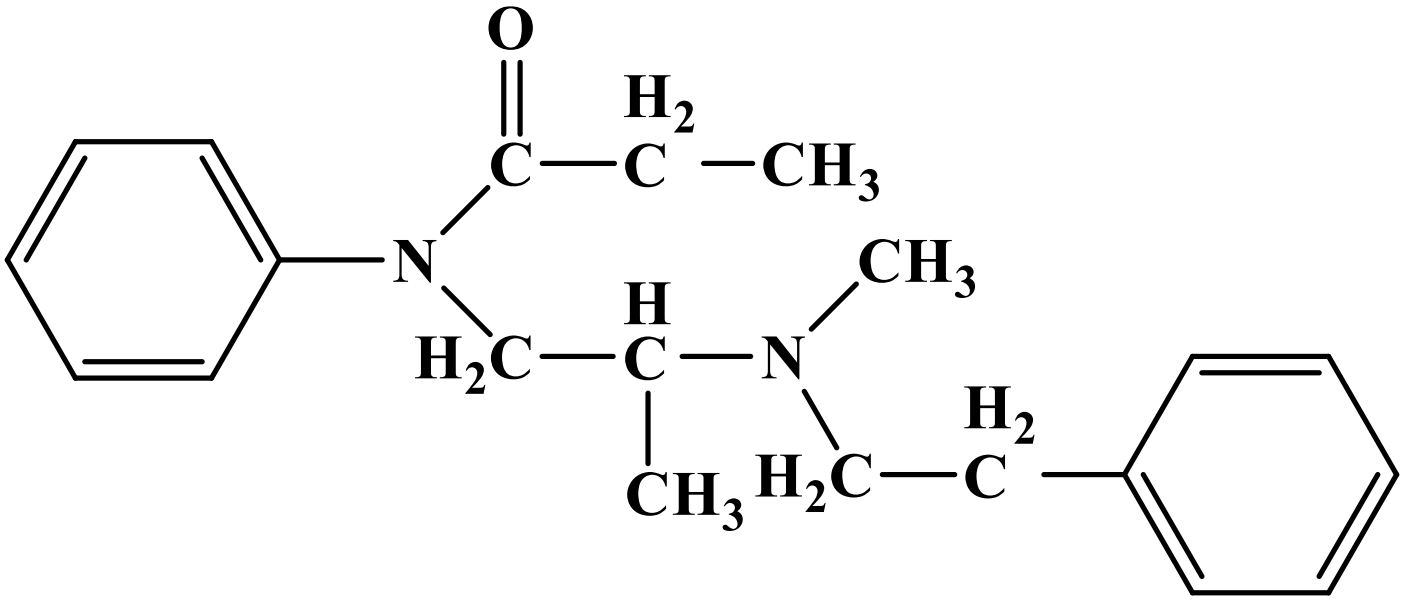
1- Tertiary nitrogen is not necessary for analgesic activity, where normorphine (product of N-dealkylation in the brain) is also possesses analgesic activity.



Normorphine

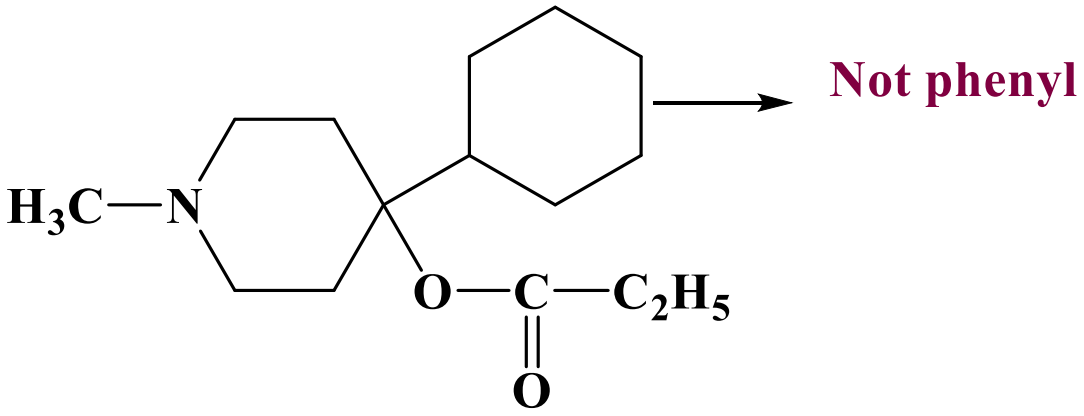
2- A small group on the 3°N is not necessary and N-CH_3 can be replaced by aralkyl group, (i.e., N-CH_2CH_2-C_6H_5).

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.

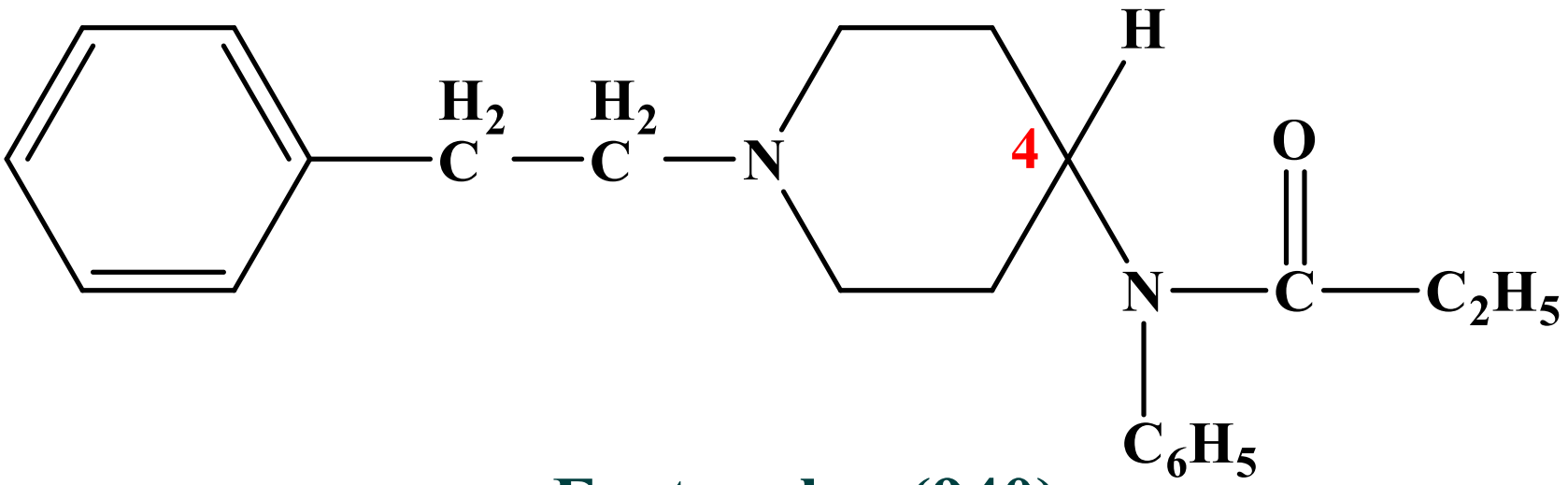


Diampromide

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 (940)

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

Write the chemical (structure and name) of morphine and then discuses the influence of modifications on it is activity. In each case write the chemical structure and generic name for the resultant compounds.

1- Replacement 3-OH by OCH3

2- replacement of methyl group at position 17 by Phenylethyl group.