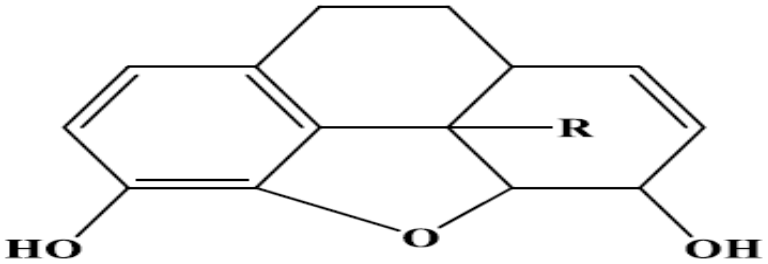
Organic Pharmaceutical Chemistry II

Analgesic Product

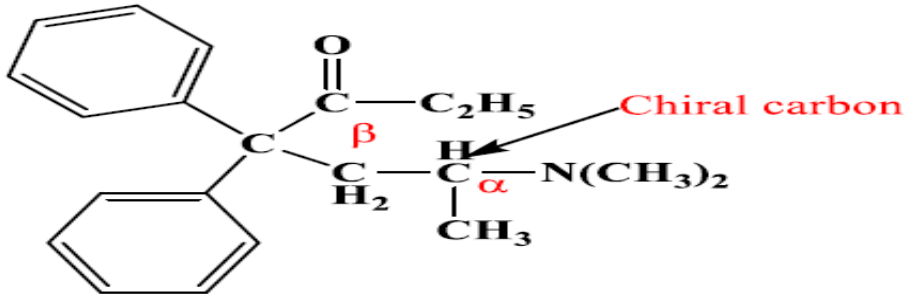
Lec. 12

Methadone and related compounds

On the basis, predicting whether a compound would or would not have activity without the nitrogen in a ring would favor a lack of activity or, at best, low activity. The first report indicating that this was a false assumption was based on the initial work of Bockmuehl and Ehrhart in which they claimed that the type of compound known as methadone possessed both analgesic and spasmolytic properties.

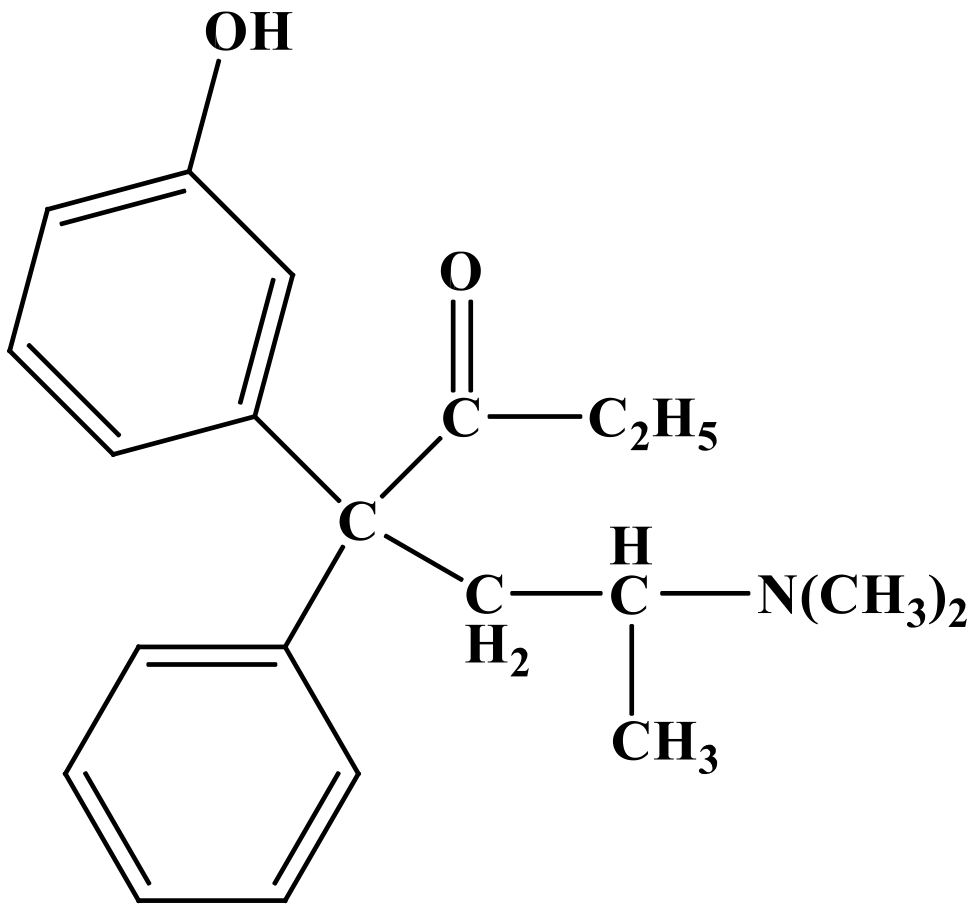


Morphimethine

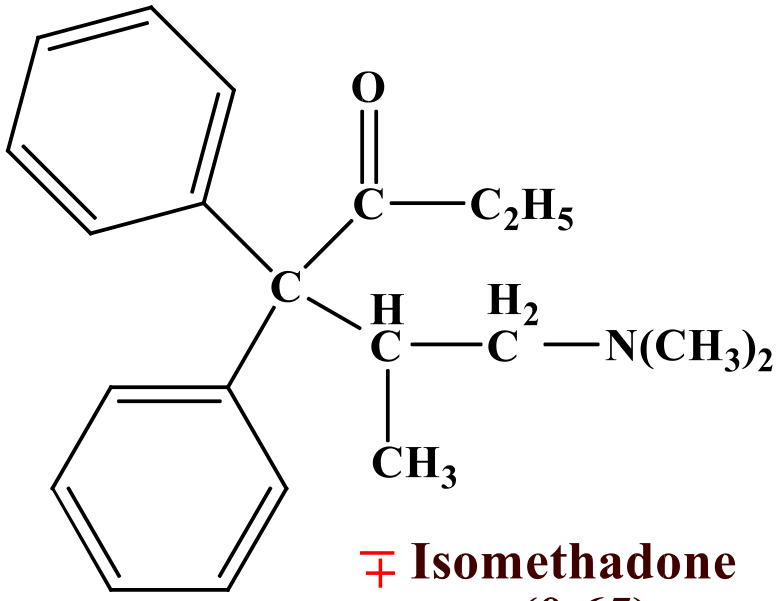


±Methadone
(1)

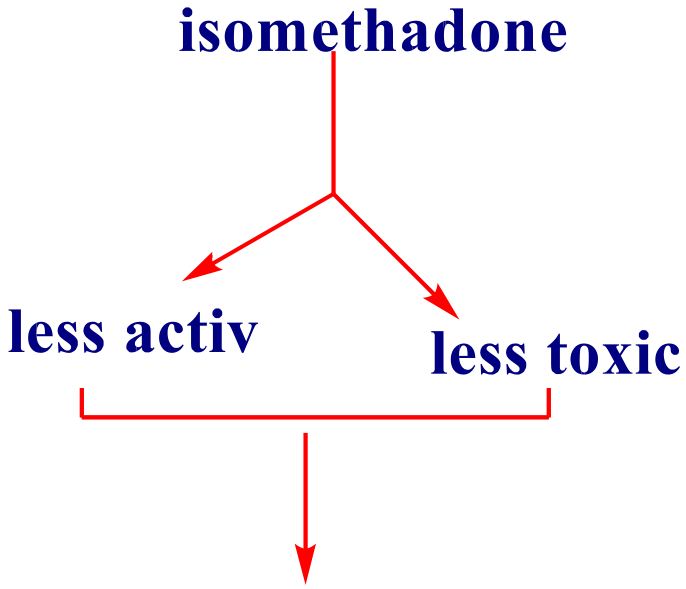
The insertion of an m-hydroxyl group on the one of the• phenyl ring →decrease analgesic activity.



• isomethadone is less active and less toxic than methadone (all methadone derivatives are more active and more toxic than isomethadone group.(



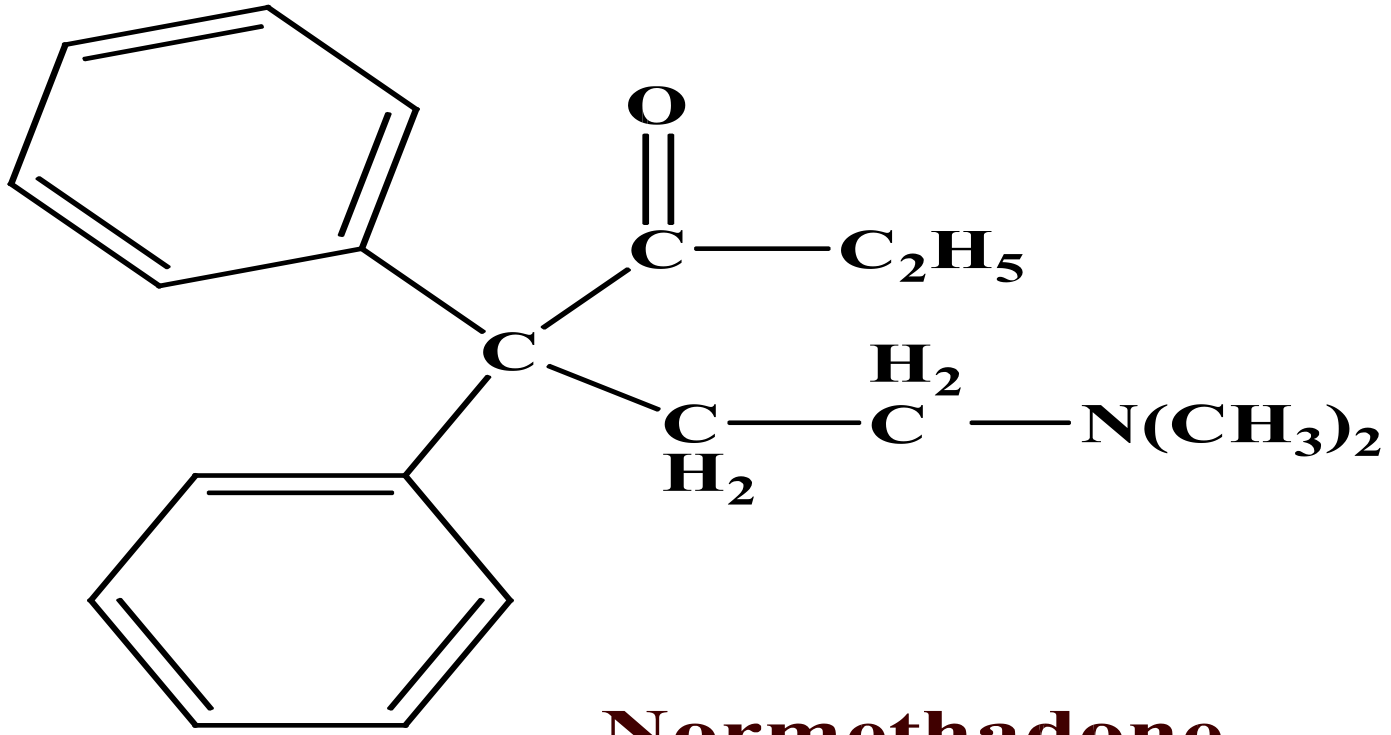
∓ Isomethadone
(0.65)



than methadone and all methadone derivatives

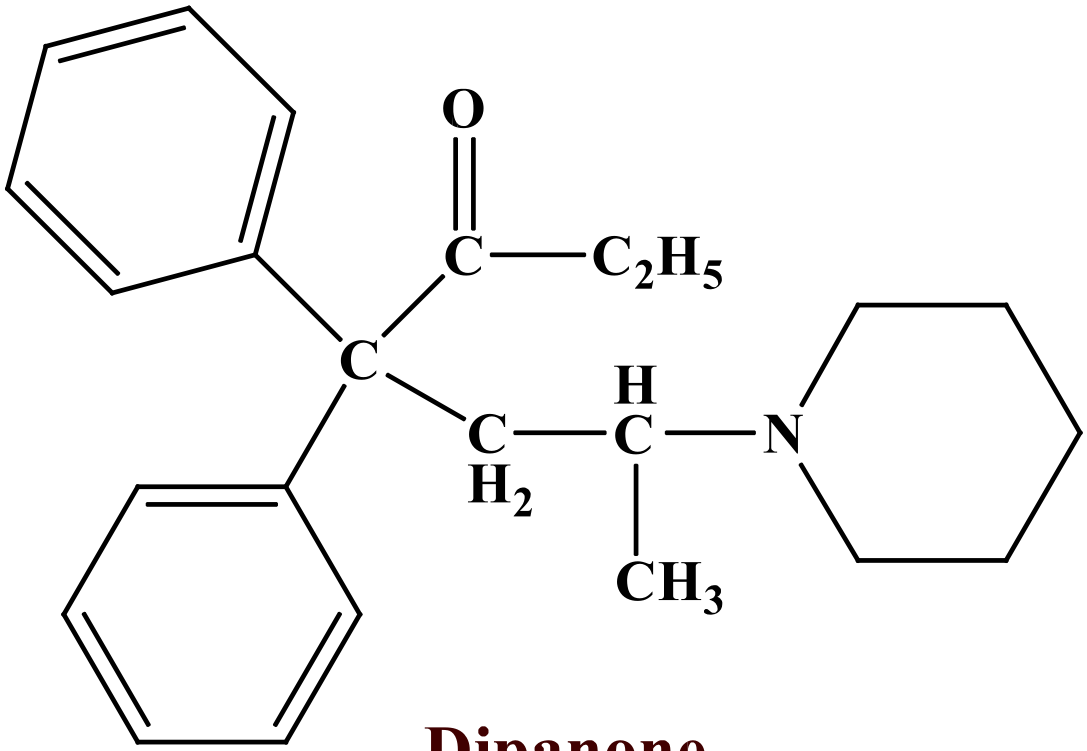
C- The levo isomer of methadone and isomethadone are twice as effective as their racemic mixture.

D- Removal of methyl group at alpha carbon→ decrease the activity.



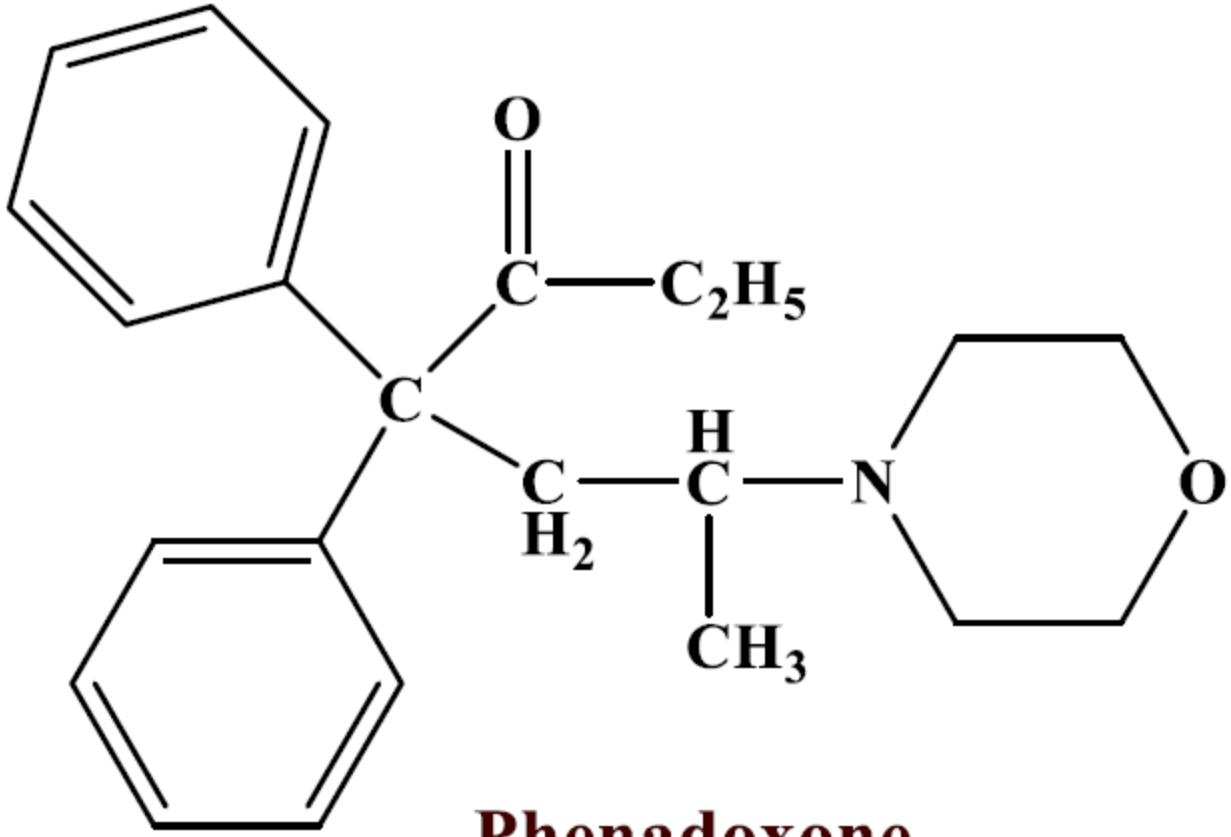
Normethadone
0.44

E- Replacement of dimethylamino (aliphatic amine• (group to alicycilic nitrogen →decreases the activity.



Dipanone
0.8

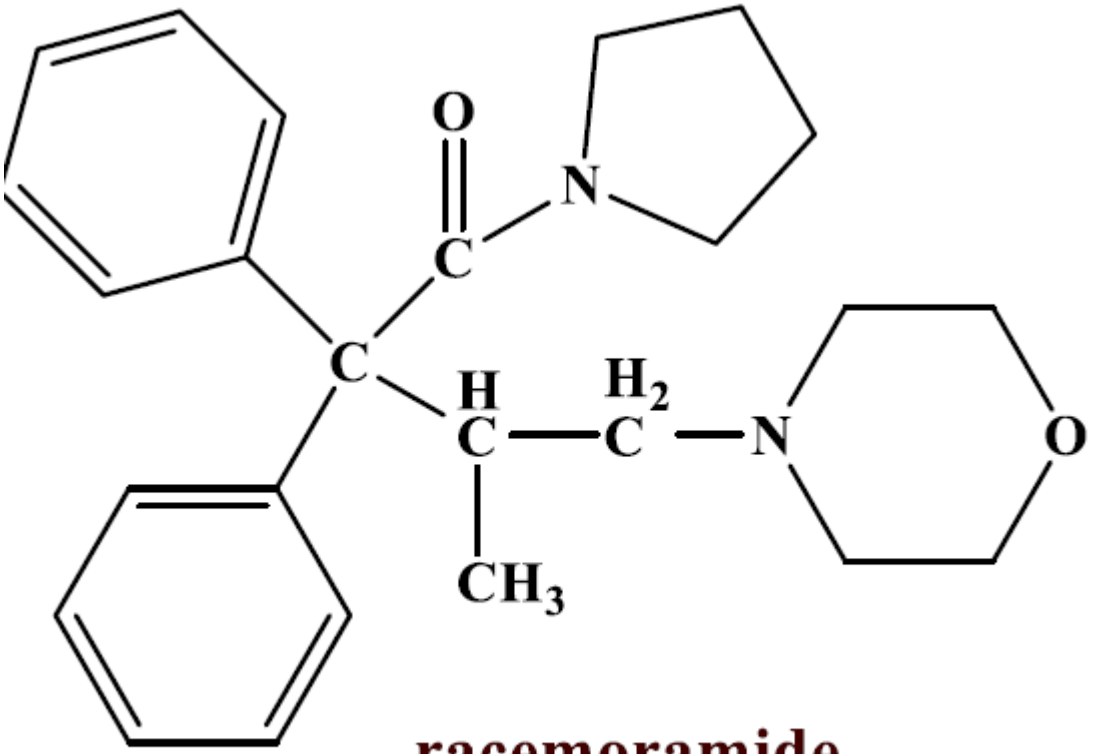
F- Replacement of aliphatic amine to morpholine group• increases the activity.



Phenadoxone

1.4

G- Replacement of α-methyl group and propionyl group• of phenadoxone by β- methyl and amide group respectively results in increase the activity.



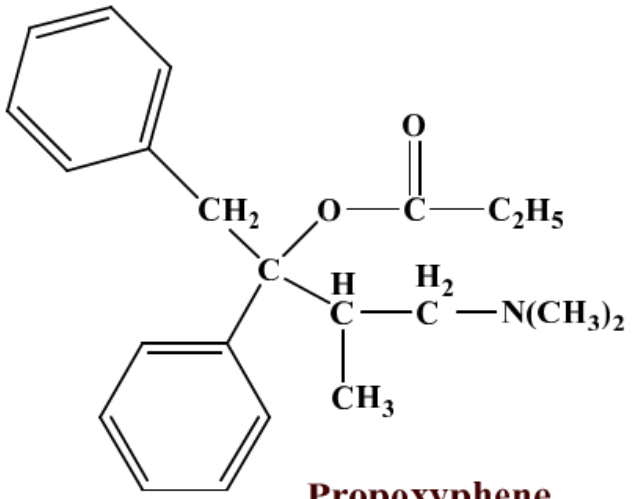
racemoramide

3.6

H- Replacement of the propionyl group by H, OH• , or acetoxyl, decreases the activity.

i- Removal of any one of the phenyl ring, decrease the activity.

J- Replacement of one phenyl ring by benzyl group• , propionyl group by propionoxy group and N- dimethyl α-methylethyl by N- dimethyl- β-methyl ethyl, decreases the activity.

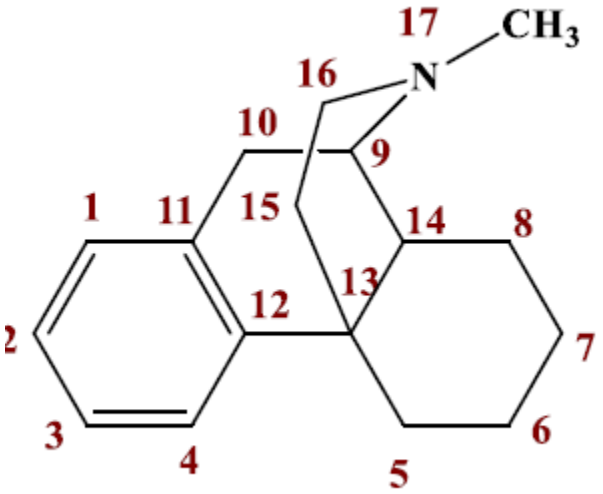


Propoxyphene
0.21

Morphine modification initiated by Grewe

Structural modification on morphine ring

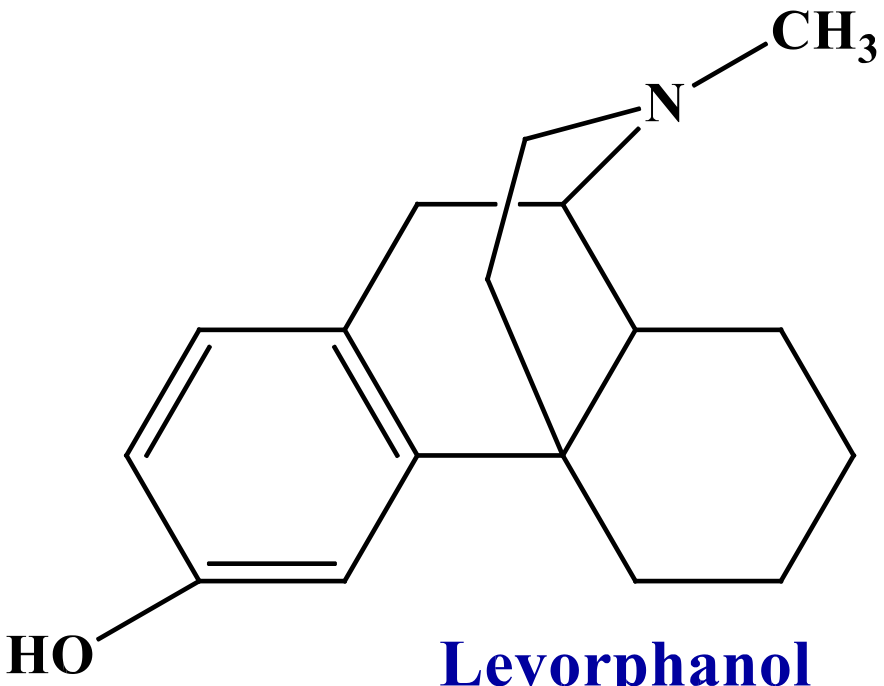
Grewe in 1946 approached the problem of synthetic analgesics from another direction when he synthesized the tetracyclic compound that he first named morphan and then revised to N-methylmorphinan.



N-Methylmorphinan

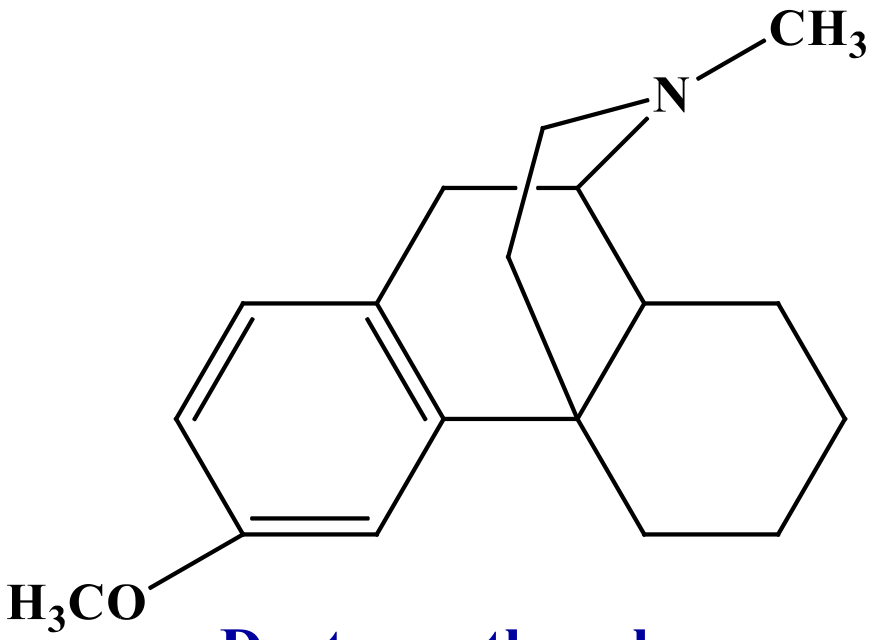
1 - Removal of epoxy group (Ether bridge). Epoxy group is not essential for activity, because N-methylmorphinan is potent analgesic.

A- The levo rotatery isomer of the 3-OH derivative of N•-methylmorphinan called levorphanol which is very potent analgesic.



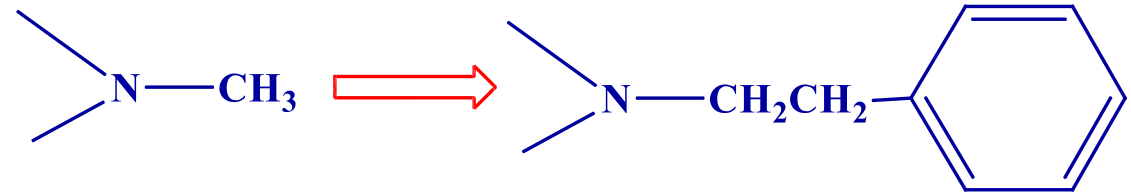
Levorphanol
(-)-3-hydroxy-N-methylmorphinan

B- the dextro isomer of the 3-OCH_3 derivative of• N-methylmorphinan called Dextromethorphan which is only antitussive.

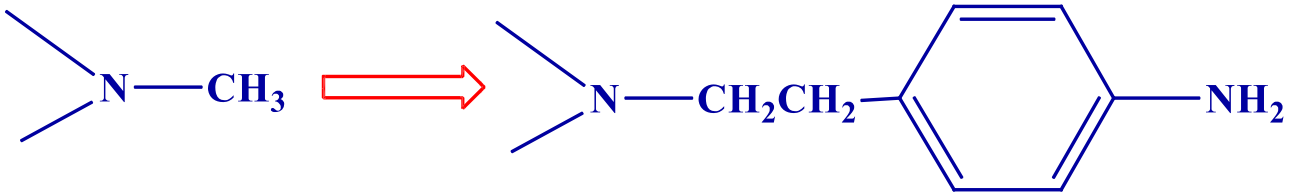


Dextromethorphan
(+)-3-methoxy-N-methylmorphinan

e- Replacement of CH_3 at position 17 of levorphanol by N•-phenyethyl and N-aminophenethyl groups, are about 3 and 18 times more active respectively than levorphanol. The most potent member of the series was the N-β-furylethyl analogue, which was nearly 30 times as active as levorphanol or 160 times as active as morphine.

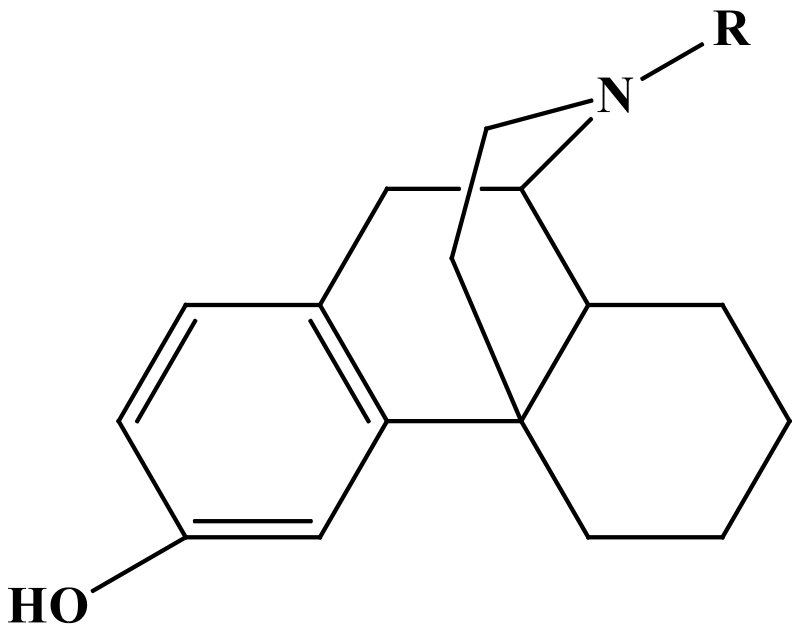


3 times more potent than levorphanol

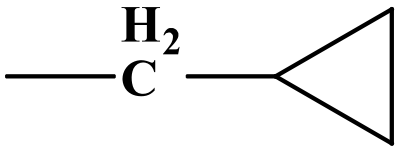


18 times more potent than levorphanol

D-Replacement of CH_3 at position 17 of levorphanol by• allyl and cyclopropylmethyl groups give potent antagonist.

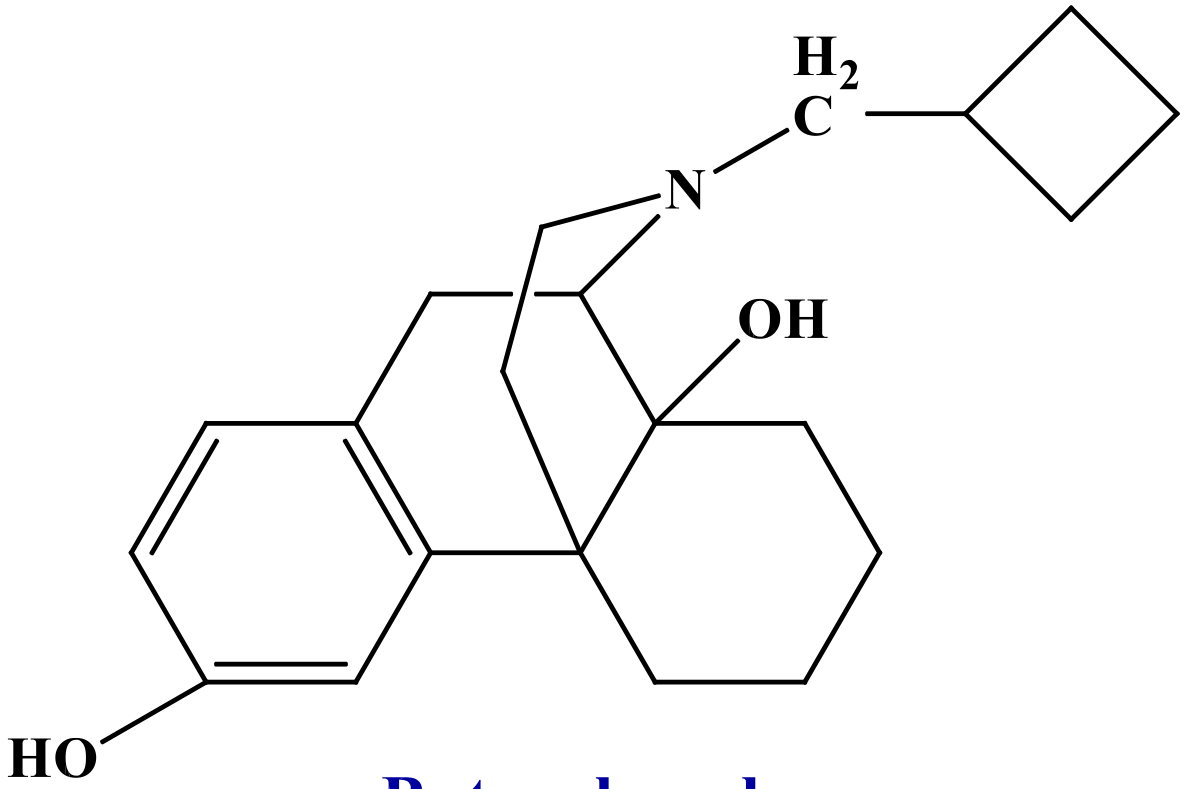


R= —CH_2—C(H)=CH_2 Levallorphan

R= —CH_2—  Cyclorphan

Antagonist

E- Replacement of CH_3 at position 17 of levorphanol by• methylcyclobutyl group (butorphanol) groups give potent analgesic with mixed agonist and antagonist activity.



Butorphanol
mixed agonist and antagonist