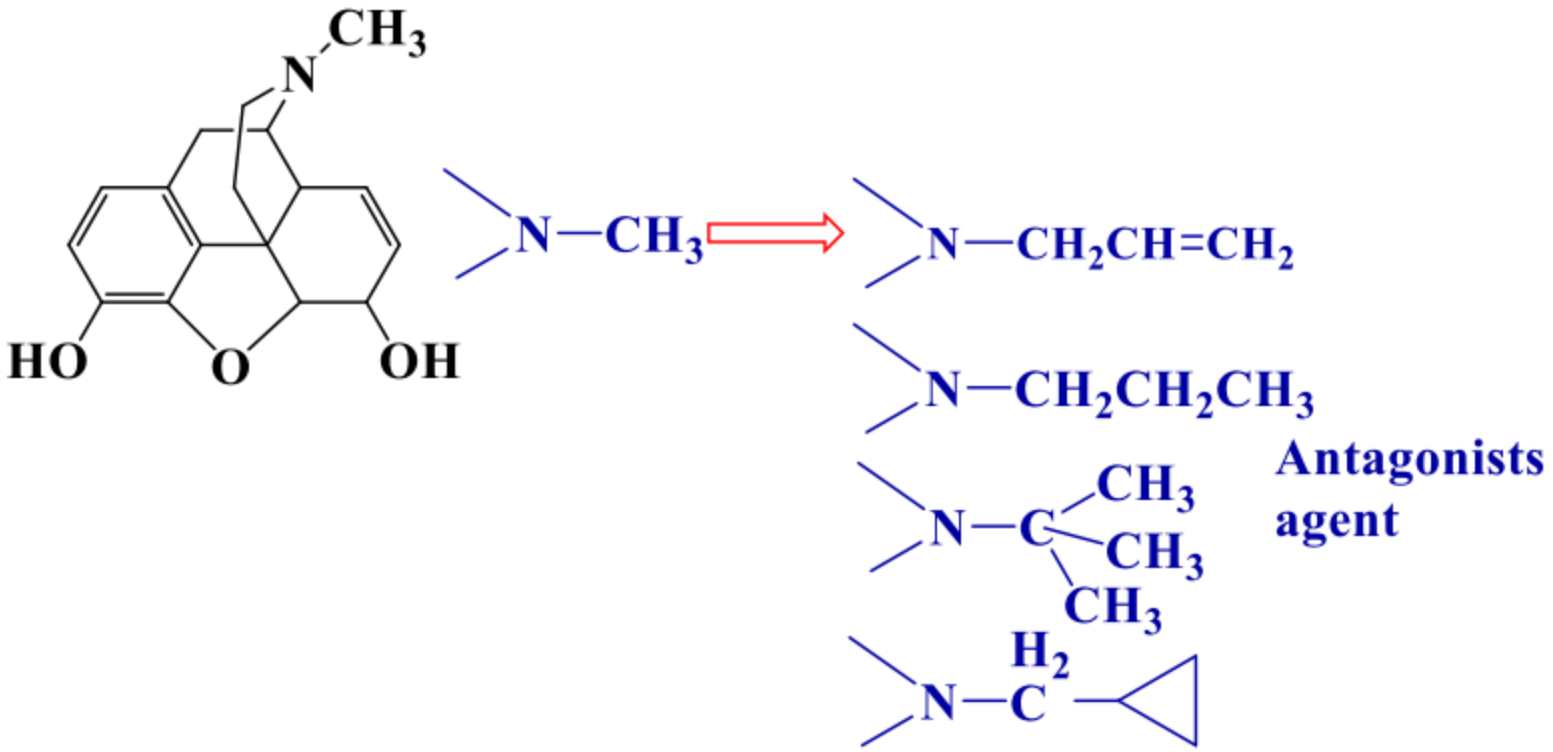
Organic Pharmaceutical Chemistry II

Analgesic Product

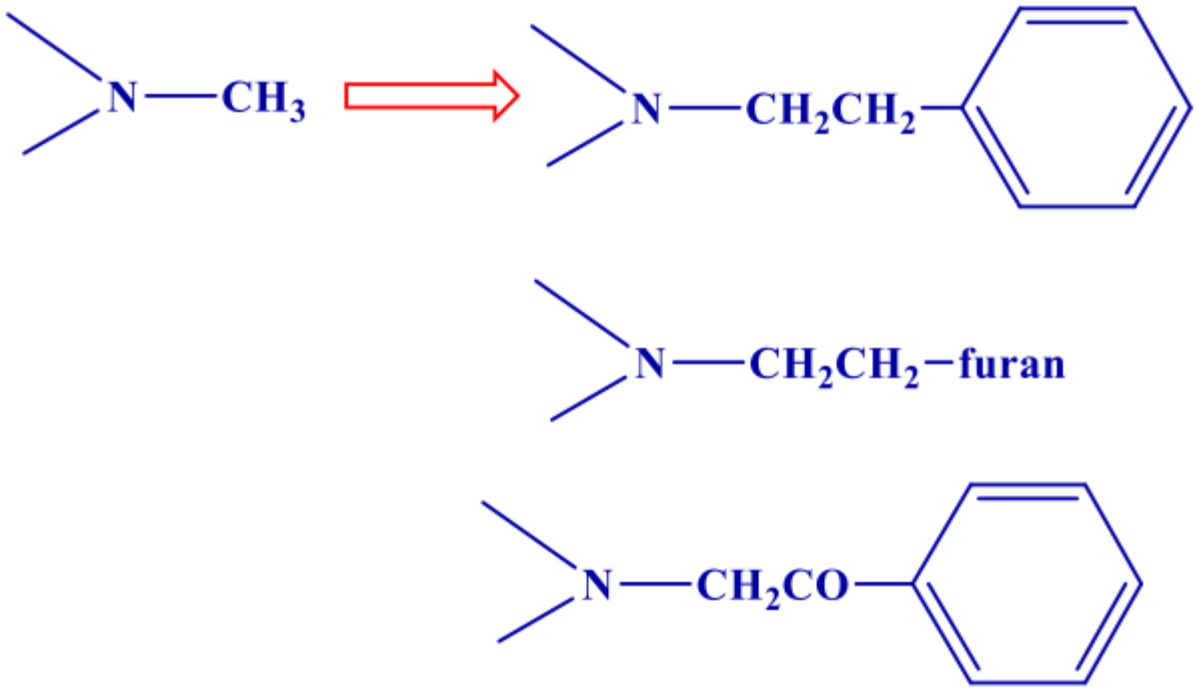
Lec. 11

- **Replacement of the N-methyl group in morphine by larger alkyl groups not only lowers analgesic activity, but also confers morphine-antagonistic properties on the molecule.**

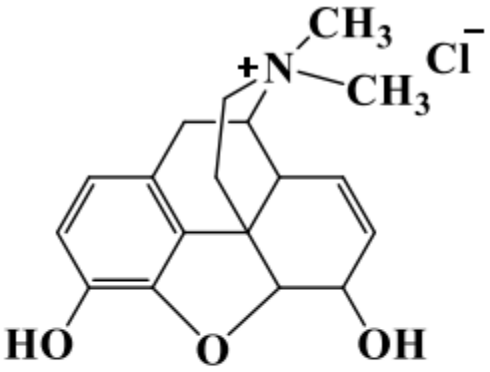
-1Replacement of methyl group at position 17 by $CH_2CH=CH_2$, CH_2-cyclopropyl groups, isobutyl, result compound that act as antagonists (reversal of activity.(

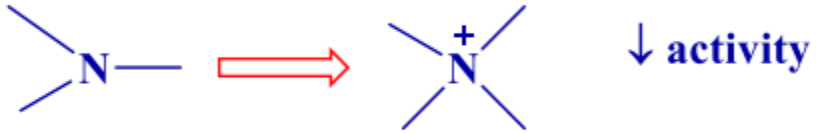


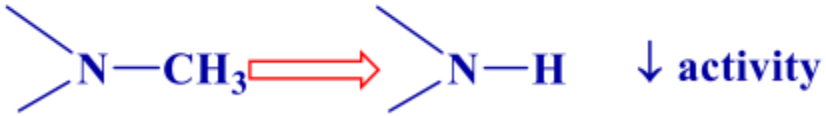
Replacement of methyl group at position 17 by phenyl ethyl• group, ethyl furane (CH_2CH_2 furan), and CH_2 C=O phenyl, result in increase in activity which is an exception to the above rule.



Quaternization of nitrogen or replacement of N-methyl group by • N-H group, result in decrease in activity.





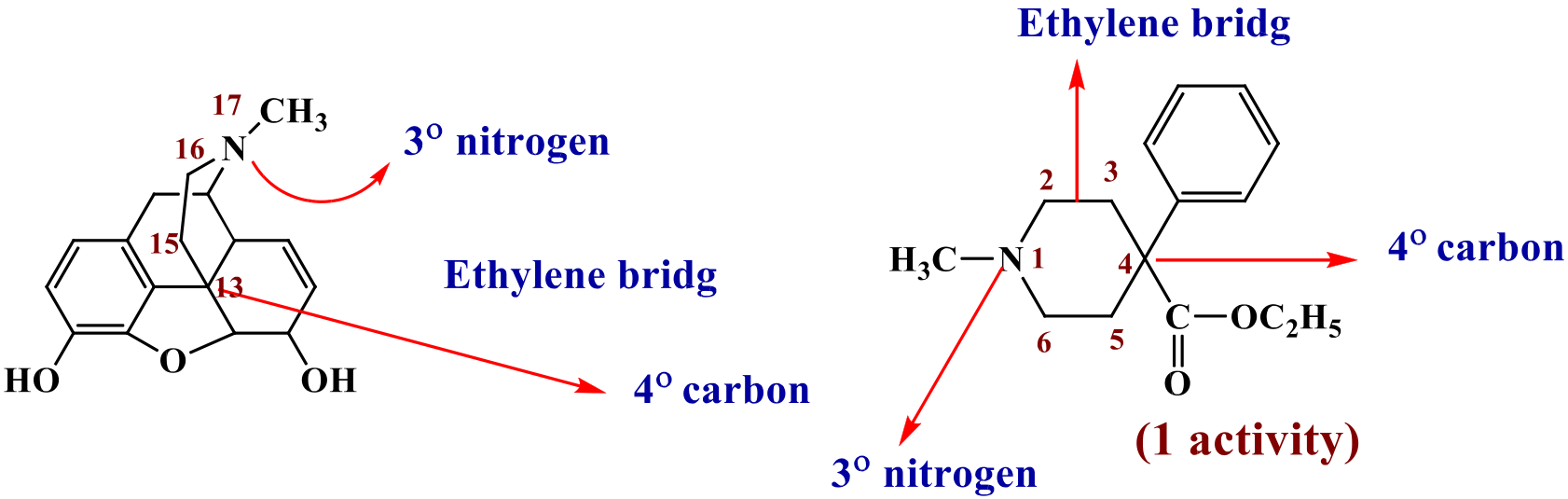


↓ Activty

Cl or Br substitution at position • 1
NH_2 substitution at position •2
result in decrease in activity•.

Meperidine and related compounds

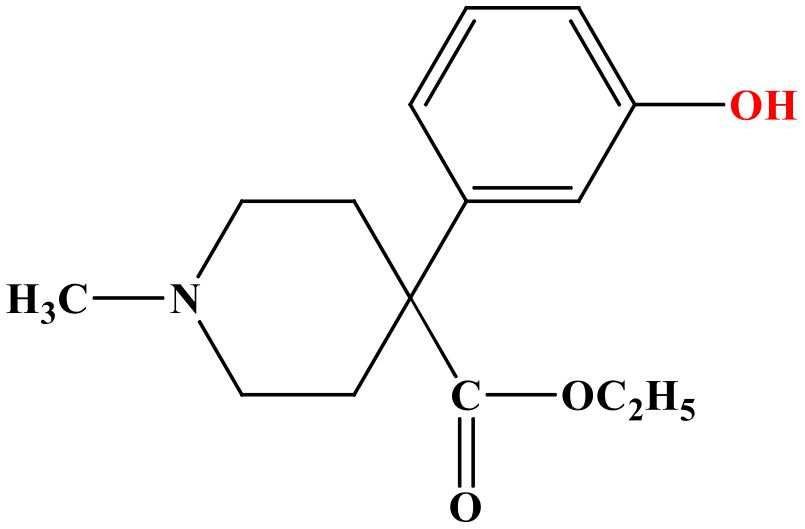
In 1938, Eisleb and Schaumann discovery that a simple piperidine derivative, now known as meperidine, possessed analgesic activity, and found to be about one fifth as active as morphine.it was prepared as an antispasmodic.



SAR

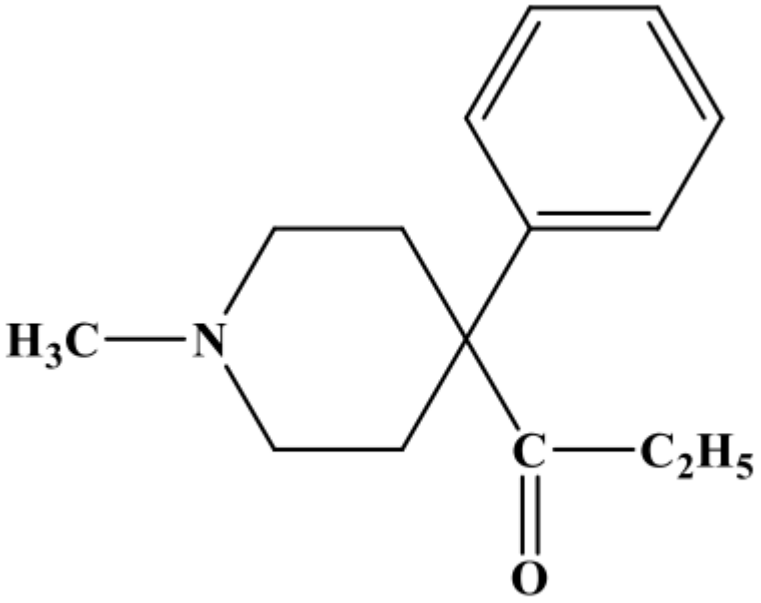
-1Placement of the phenyl and ester groups at the 4 position of 1-methylpiperidine gave optimum activity. It was found that replacement of the 4-phenyl group by hydrogen , alkyl, aralkyl and heterocyclic group groups reduced analgesic activity.

-2The insertion of an m-hydroxyl group on the phenyl ring increase analgesic activity.



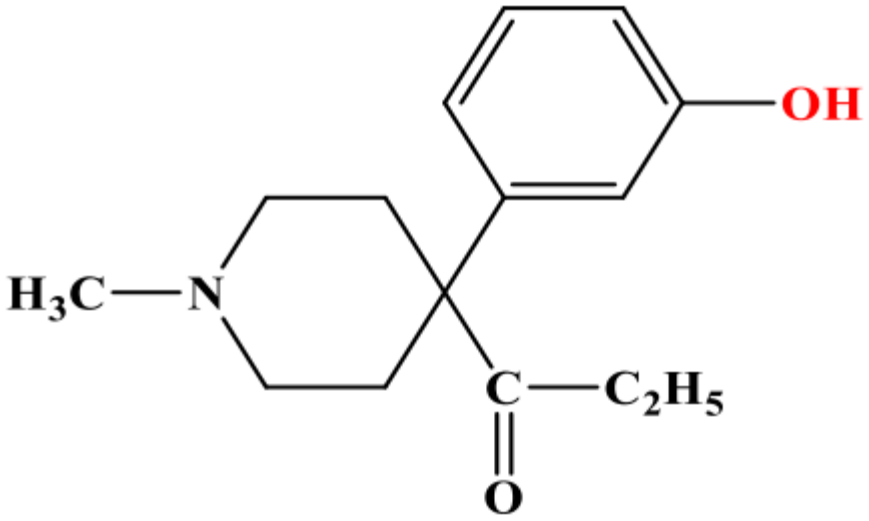
Bemidone(1.5)

-3Replacement of the 4-ester group by ketone of meperidine• , decrease analgesic activity.



(0.5)

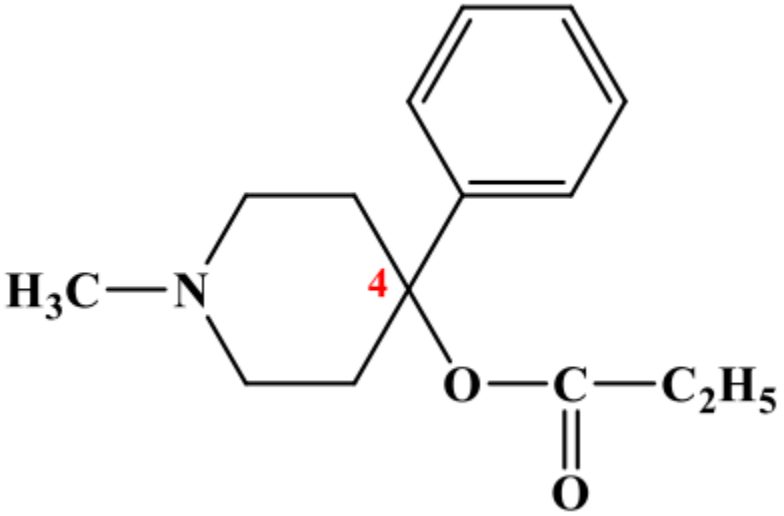
-4Replacement of the 4-ester group by ketone of bemidone• , increase analgesic activity.



Ketobemidone (6.2)

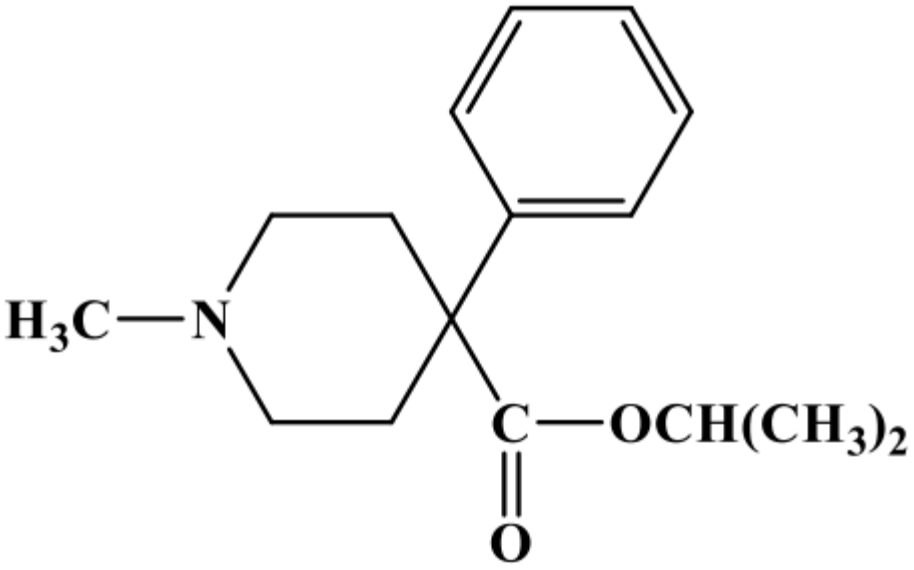
its equivalent to morphine in activity and was once widely used

-5Replacement of the carbethoxyl group in meperidine by• acyloxyl groups gave better analgesic, as well as spasmolytic, activity.



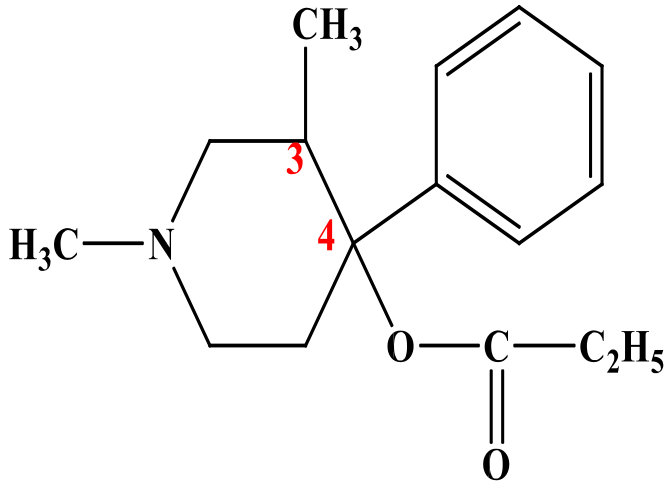
(5) Propionoxy
the reverse ester of meperidine
5 times as active as meperidine

-6Replacement of the carbethoxyl group in meperidine by• carboxy isopropyl group results in increase in activity.



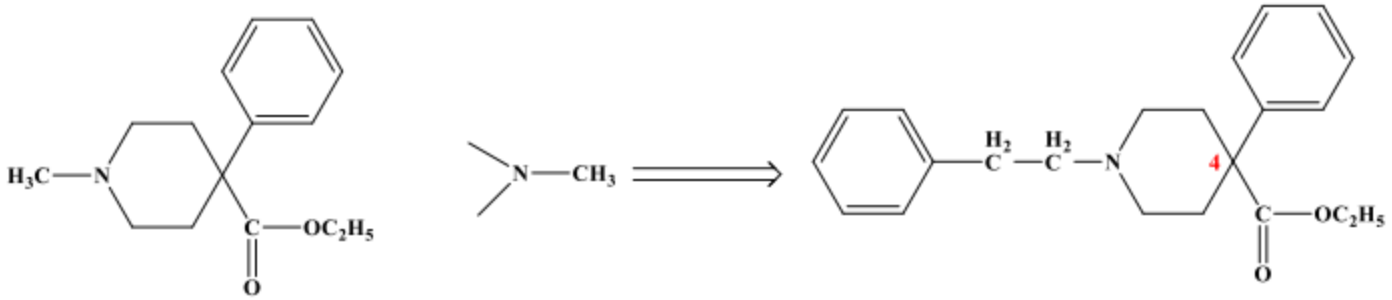
Properidine (15)

-7The introduction of a methyl group into position 3 of the• piperidine ring in the propionoxy compound would yield two isomers, one with activity approximating that of desomorphine and the other with less activity.

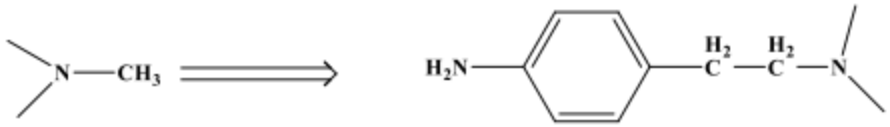


Alphaprodine[trans (methyl/phenyl)]less the activity of desomorphine (5)
Betaprodine[*cis*(methyl/phenyl)] with activity approximating that of desomorphine(14)

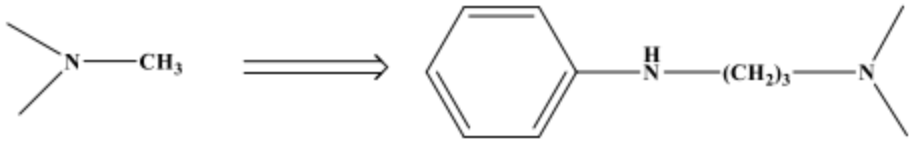
-8Replacement of the N- methyl group by various arylalkyl• groups can increase activity•.



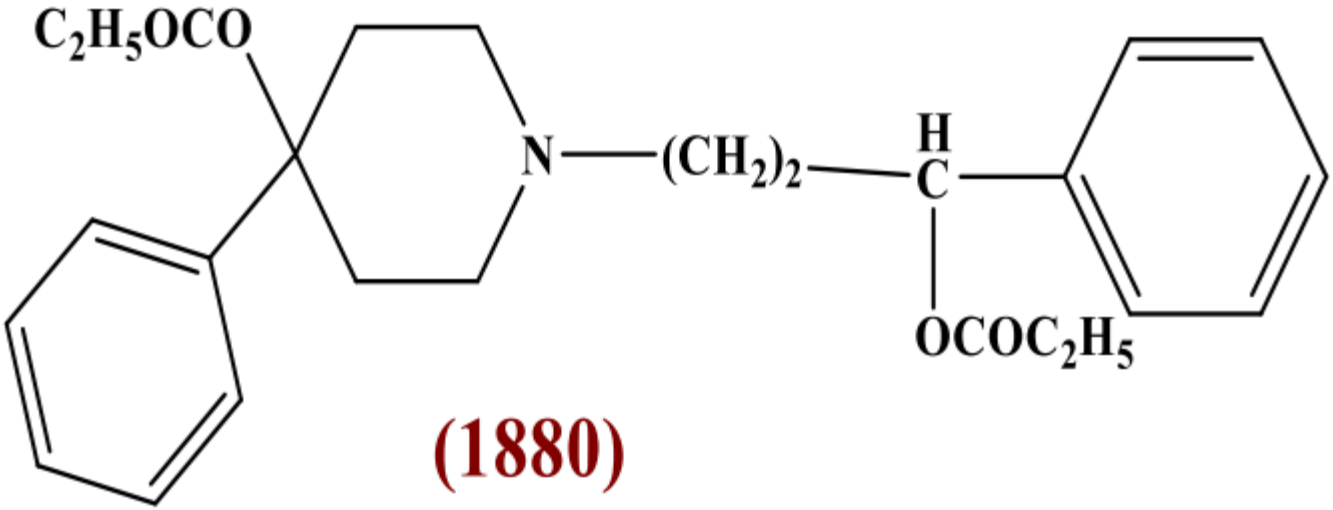
Pheneridine(2.6)
N-Phenylethyl derivative of meperidine
3 times more potent than meperidine



Anilieridine(3.5)



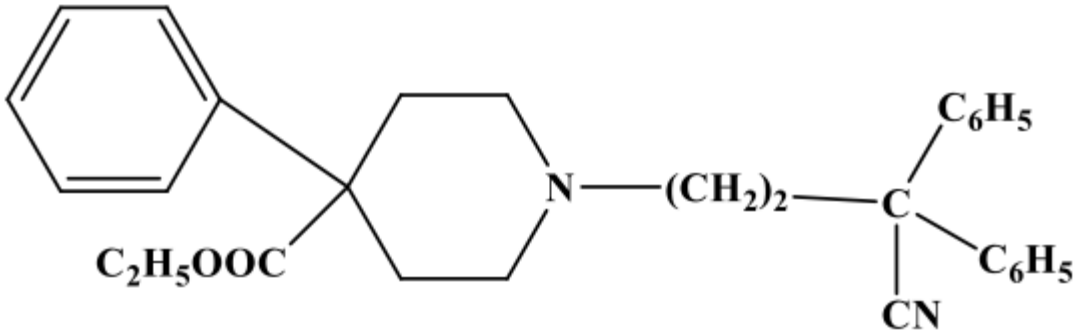
Piminodine(55)
N-Phenylaminopropyl derivative of mepridine



(1880)

(1880)

N-Phenylpropionoxy derivative of mepridine the most active meperidine type of compound 2000 times as active as meperidine



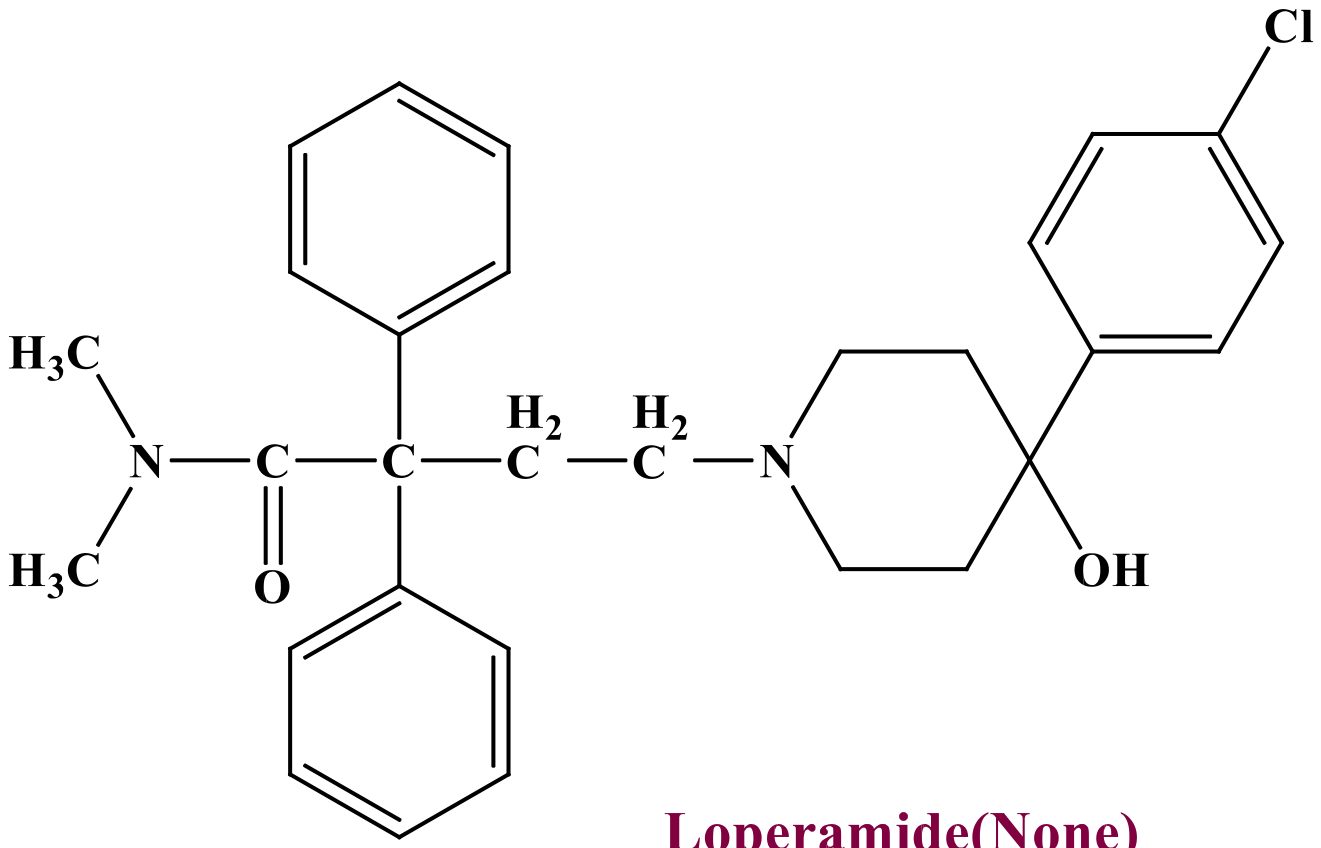
Diphenoxylate

has hybrid structure between meperidine and methadone

have no analgesic activity

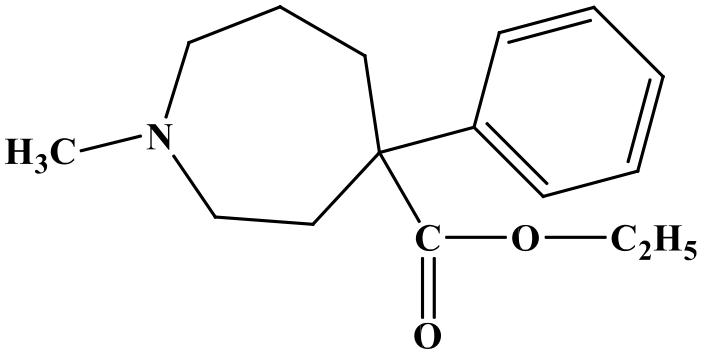
used as intestinal spasmolytic and used for the treatment of diarrhea

Replacement of the 4-phenyl group by P-chlorophenyl• group, ester group at position 4 by (OH), and N- methyl group by $-CH_2CH_2C(C_6H_5)_2C{=}ON(CH_3)_2$ to give loperamide , which is bind to the opiate receptor in the brain but does not penetrate BBB enough to produce analgesic(have no analgesic activity) so used only as antispasmodic.

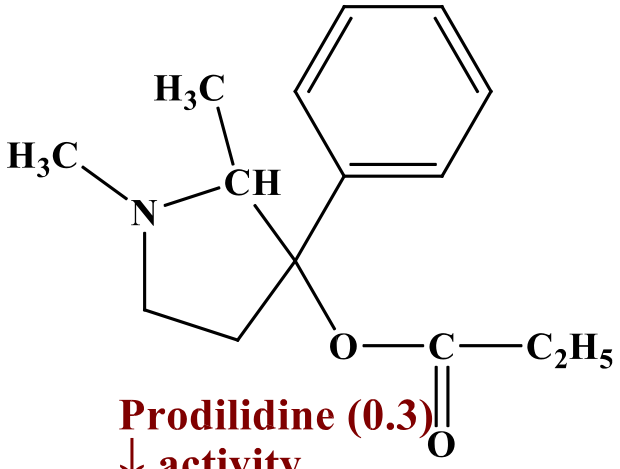


Loperamide(None)

Enlargement of the ring to 7- member ring (i,e: R= -CH_2-CH •-$_2$ CH_2), or reduce its size to 5-member ring (i,e: R= -CH_2-) lead to decrease the activity.

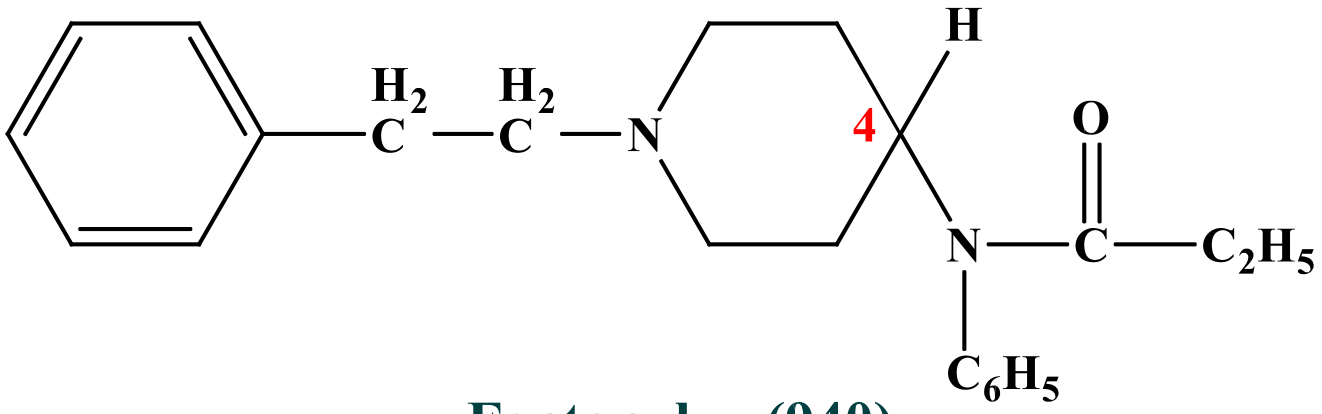


Ethoheptazine(1)
↓ activity

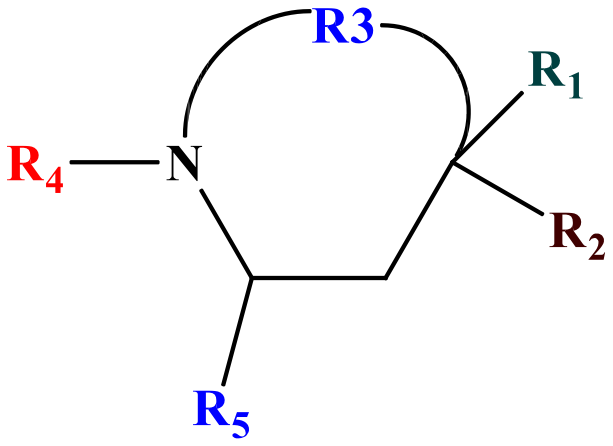


Prodilidine (0.3)
↓ activity

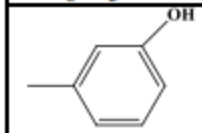
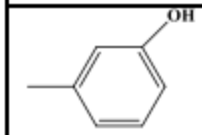
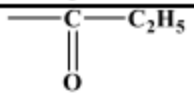
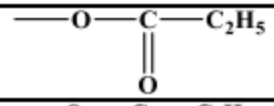
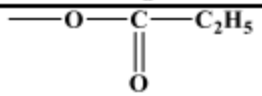
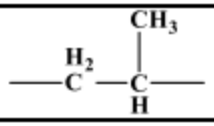
fentanyl in which the phenyl and the acyl groups are• separated from the ring by a nitrogen. It is a powerful analgesic, 50 times stronger than morphine in humans, with minimal side effects.

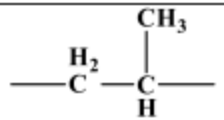
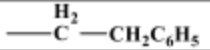
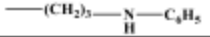
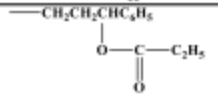
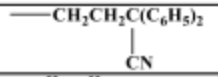
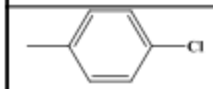
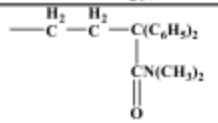
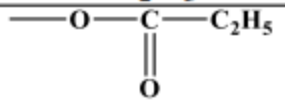
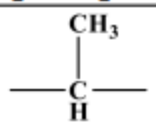
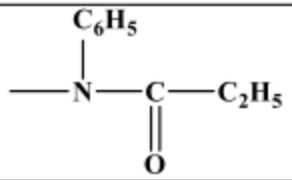
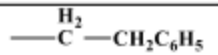


Fentanyl (940)



Meperidine

R1	R2	R3	R4	Name	Activity relation to meperidine
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-$	$-CH_3$	Meperidine	1
	$-COOC_2H_5$	$-CH_2-CH_2-$	$-CH_3$	Bemidone	1.5 ↑
$-C_6H_5$	$-COOCH(CH_3)_2$	$-CH_2-CH_2-$	$-CH_3$	Properidine	15↑
$-C_6H_5$		$-CH_2-CH_2-$	$-CH_3$		0.5↓
		$-CH_2-CH_2-$	$-CH_3$	Ketobemidone	6.5↑
$-C_6H_5$		$-CH_2-CH_2-$	$-CH_3$		5↑
$-C_6H_5$			$-CH_3$	Alphaprodine Betaprodine	5↑ 14↑

$-C_6H_5$			$-CH_3$ ($R5=CH_3$)	Trimepridine	7.5↑
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-$		Pheneridine	2.6↑
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-$		Anileridine	3.5↑
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-$		Piminodine	55↑
$-C_6H_5$		$-CH_2-CH_2-$			1880
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-$		Diphenoxylate	None
	-OH	$-CH_2-CH_2-$		Loperamide	None
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-CH_2-$	$-CH_3$	Ethoheptazine	1
$-C_6H_5$			$-CH_3$	Prodilidine	0.3
H		$-CH_2-CH_2-$		Fentanyl	940