DRUGS EFFECTIVE ON THE RESPIRATORY SYSTEM

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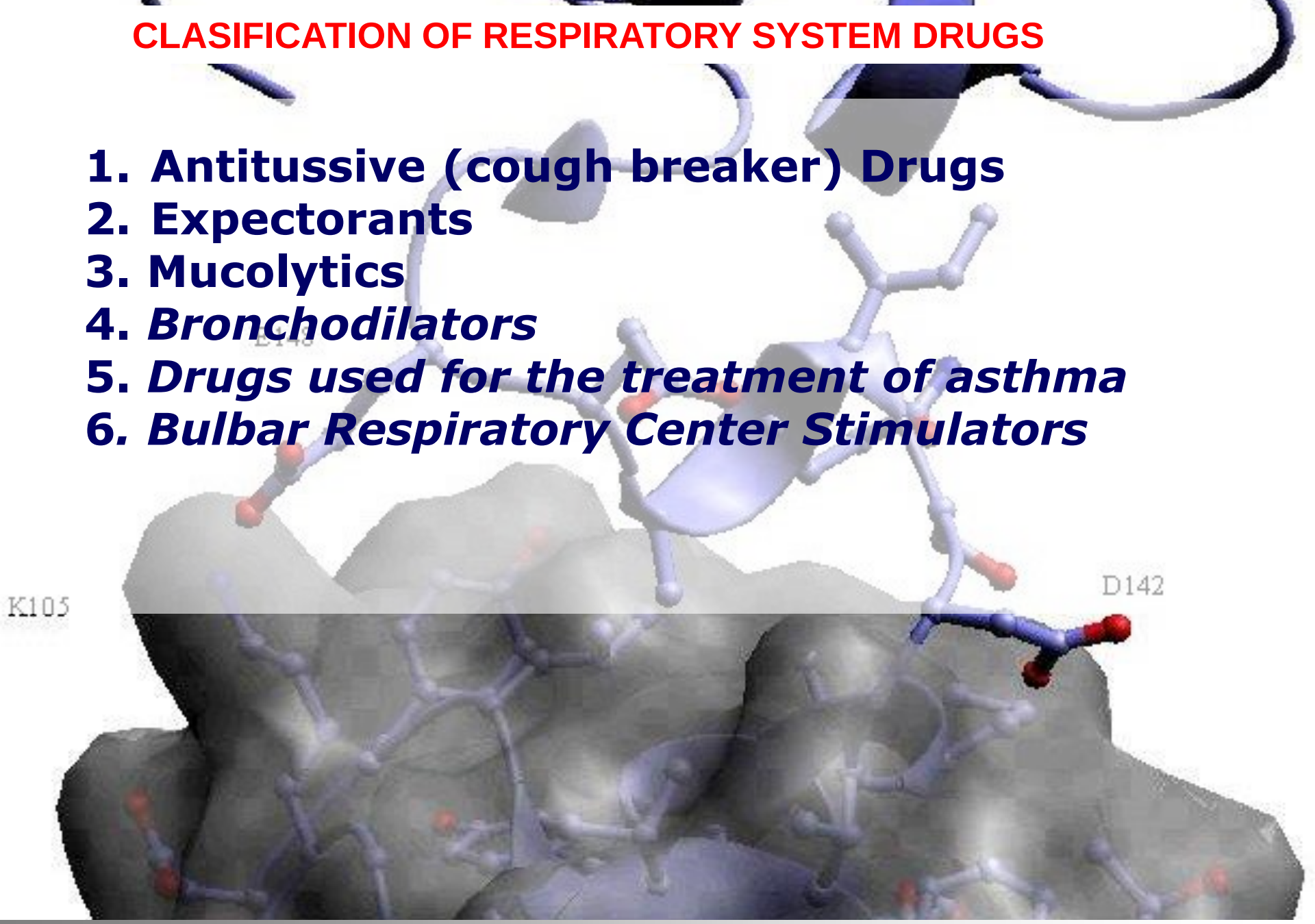
CLASIFICATION OF RESPIRATORY SYSTEM DRUGS

1. **Antitussive (cough breaker) Drugs**
2. **Expectorants**
3. **Mucolytics**
4. ***Bronchodilators***
5. ***Drugs used for the treatment of asthma***
6. ***Bulbar Respiratory Center Stimulators***



Cough

- **A protective physiological reflex.**
- **A weak syndrome**
- **It can also be observed in health status as in the case of disease.**
- **Cough reflexes are stimulated in some disease states or mechanical irritation of the respiratory tract (larynx, trachea, bronchial mucosa,..) or outside the respiratory tract (pleura, external ear canal, middle ear epithelium ..).**

Cough is accompanied by 2 reflexes.

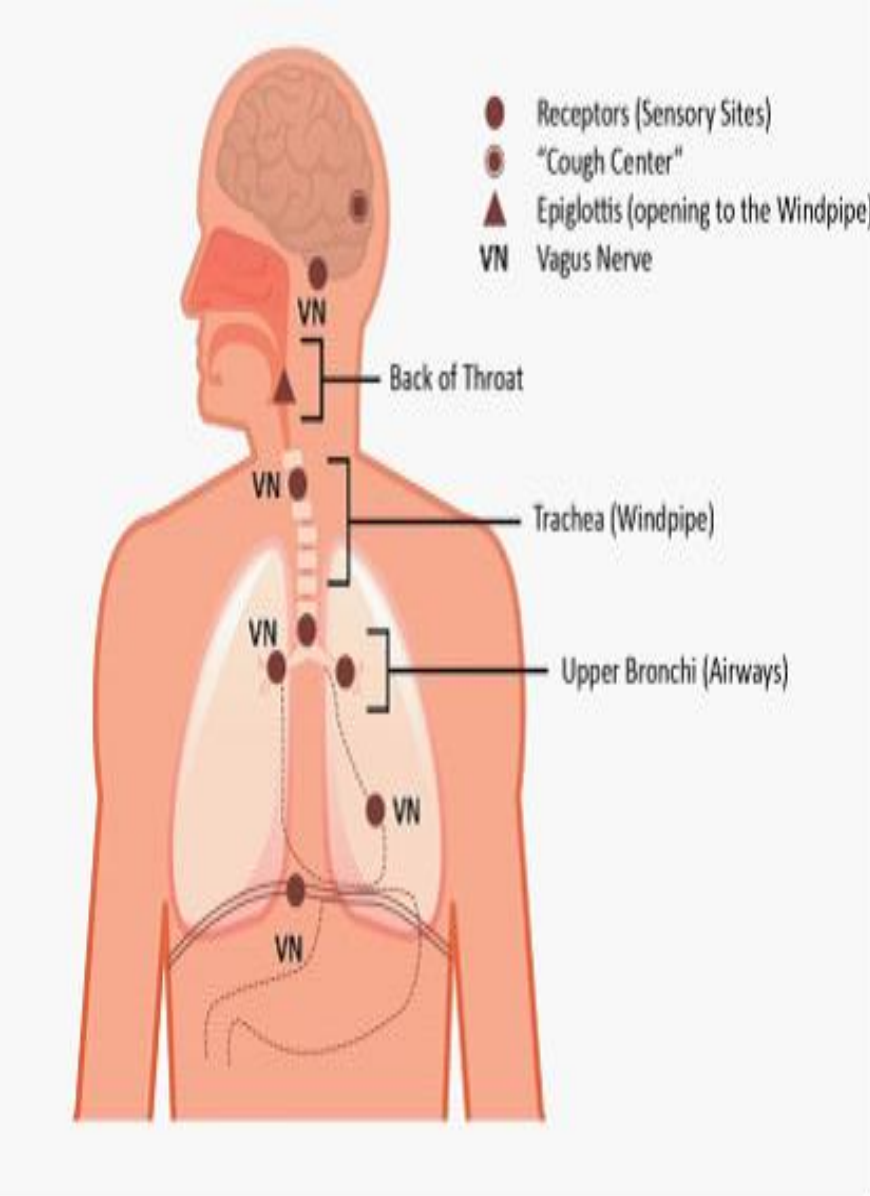
1. **Bronchoconstriction**
2. **Mucus secretion**

Symptomatic (Palliative) Treatment

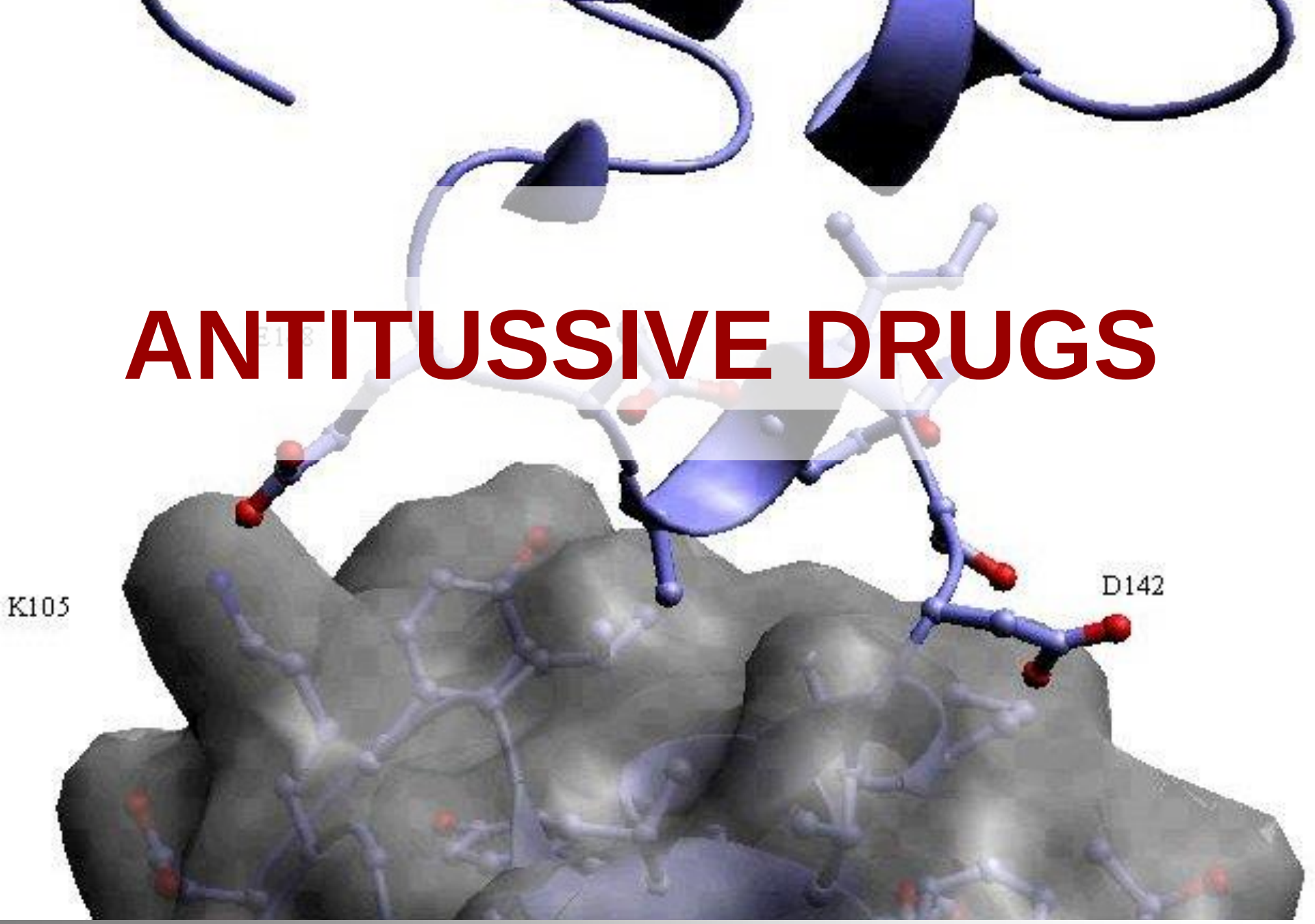
Antitussives; they reduce the intensity and frequency by suppressing the cough reflex.

COUGH STIMULATION

It is initiated by chemoreceptors or mechanoreceptors in the lungs.
Stimulus is transmitted to the COUGH CENTER where the afferent nerve fibers in the vagus nerve are located in the brain stem in the Medulla.

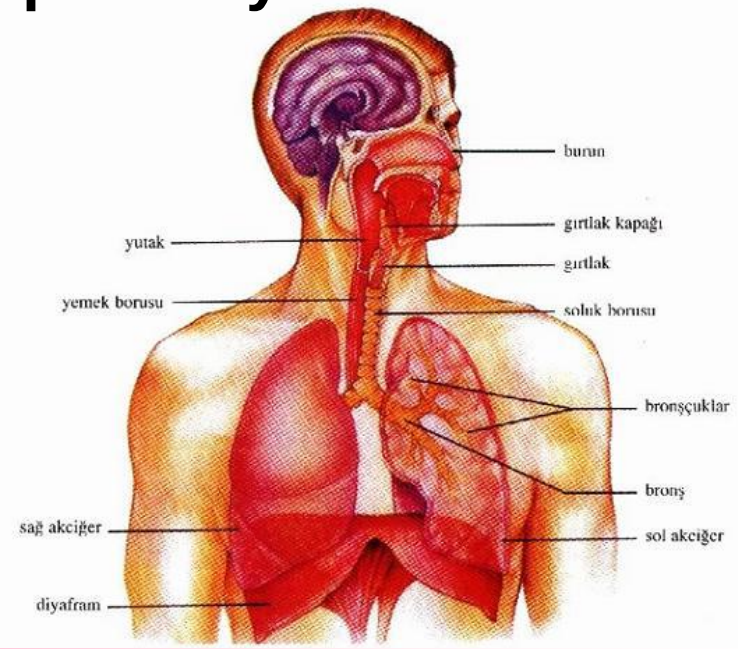


ANTITUSSIVE DRUGS



Mechanisms of Action of Antitussives

- ***Central effect:*** **Inhibition of cough center**
- ***Peripheral effect:*** **Depression of nerve endings in the lung and other peripheral areas**
- ***Spasmolytic effect:*** **Reducing the sensitivity of cough receptors in the lungs due to spasmolytic effect**



ANTITUSSIVE DRUGS

1. ***Opioid derivatives***

2. ***Synthetic Antitussives***

I. Methadone Type Antitussives
II. Antitussives with Basic Ester Group
III. Local Anesthetic Effective Antitussives
IV. Other Antitussives Not Classified by Chemical Structures

OPIOID DERIVATIVES

- **Morphine and similar drugs**
- **Inhibitory effect on cough center**

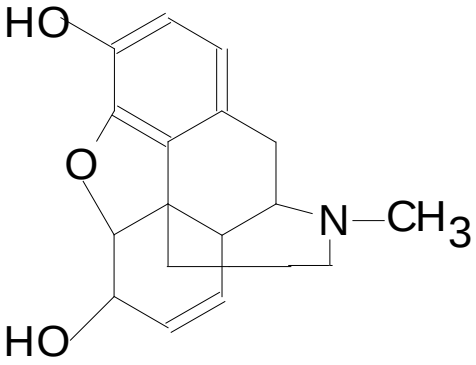
Affected Receptors:

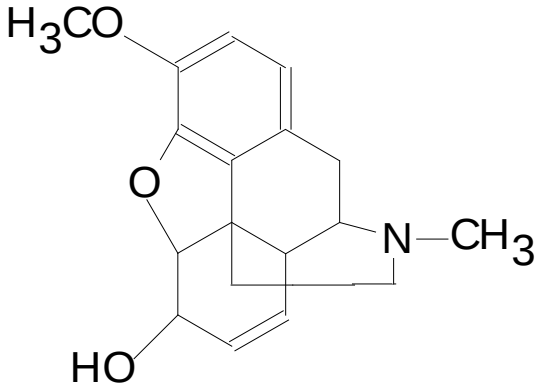
1. Opioit receptors

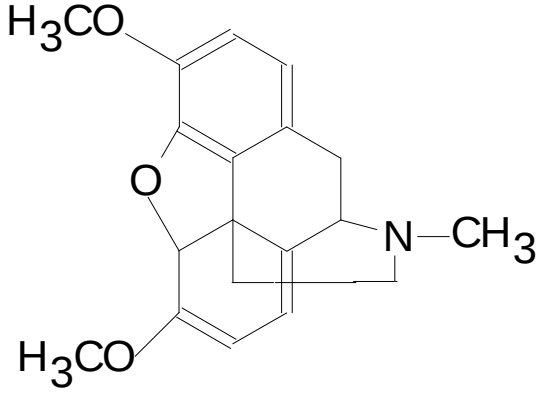
2. Cough inhibitory receptors

Although these compounds are effective, their use is limited due to their intolerance and dependence and toxic effects.

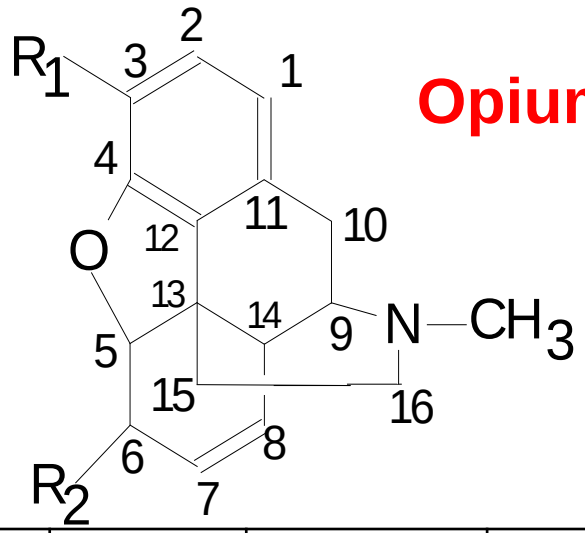
OPIOID DERIVATIVES



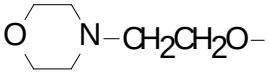




Morphine	*Codeine*	Thebaine
(Narcotic analgesic)	**(Prototype antitussive)**	(very toxic)
3,6-dihydroxy-7,8-didehydro-4,5-epoxy-17-methylmorphinan	**7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol**	(Synthesis of starting compound)



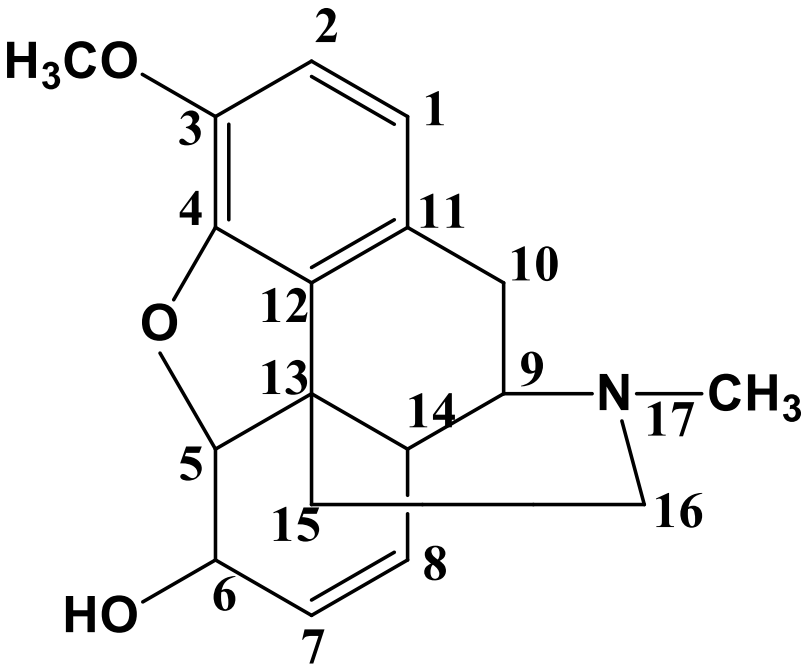
Opium Alkaloids and Derivatives:

R_1	R_2	Position of ethylenic bond	Other	Name	Salt
CH_3O -	- OH	Δ^7	—	**Codeine**	HCI, phosphate
C_2H_5O -	- OH	Δ^7	—	**Ethylmorphine** (Dionine)	HCI
	- OH	Δ^7	—	**Pholcodine**	—
CH_3O -	- OH	Saturated	—	**Dihydrocodeine** (Paracodin)	Hydrogen Tartrate
CH_3O -	=O	Saturated	—	**Hydrocodone** (Dicodid)	Hydrogen Tartrate
CH_3O -	=O	Saturated	14-OH	**Oxycodone** (Eucodal)	HCI
CH_3O -	$-OCOCH_3$	Δ^6	—	**Tebacon** (Acedicon)	HCI

CODEINE

It is still used today.

Phenolic OH —> Ether : analgesic effect decreases, antitussive effect increases, side effect decreases



Levo and dextro isomer effective

levo = 6 x dekstro

- The compound inhibits gastrointestinal motility and fluid secretion of the intestinal mucosa.

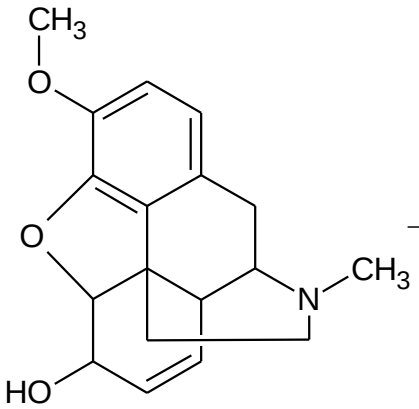
- Side Effects: Sedation, Drowsiness, Constipation (antidiarrheal)

Rarely; Euphoric and addiction

Used as base or sulfate salt

Polystyrene salt is long effective.

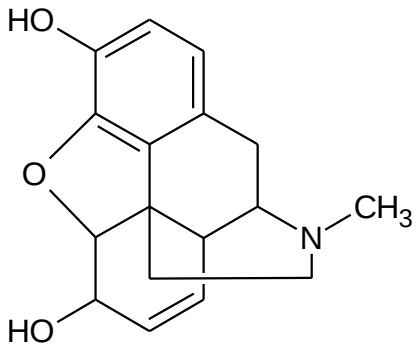
Codeine Metabolism



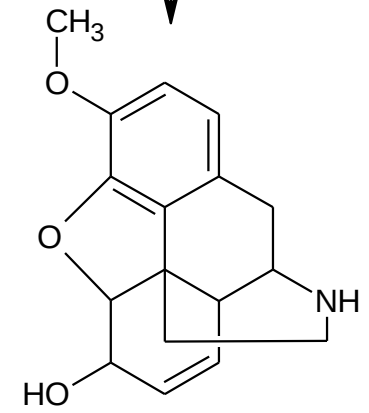
Codein

O-demethylation

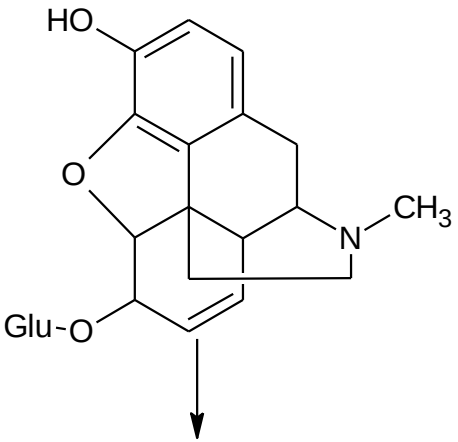
N-demethylation



Morphine (%5-15)



Norcodein (%10-20)



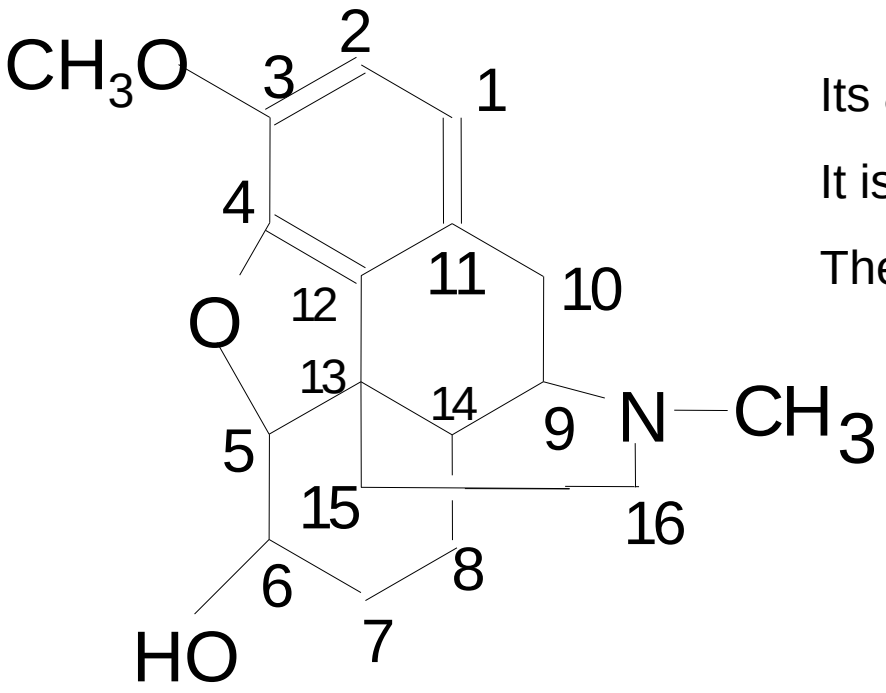
6-Glucuronate

Glucuronate conjugates

excretion

Glucuronate conjugates

Dihydrocodeine

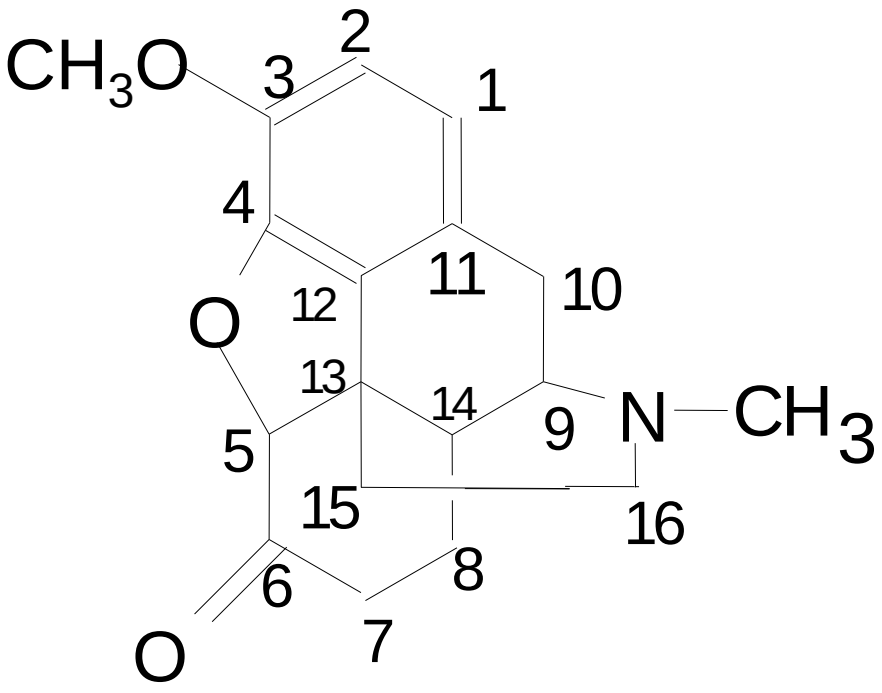


Its antitussive effect is more than codeine.

It is addictive like morphine.

Therefore it is used only in severe cases.

Dihydrocodeinone



- Potent analgesic
- Antitussive
- Addictive effect is more than codeine

Effect and Usage of General Opioid Derivatives:

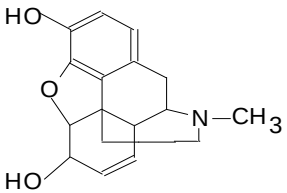
Reduction of mucosal secretion in the respiratory tract —> sense of dryness

They expose histamine —> It should not be used in bronchial asthma.

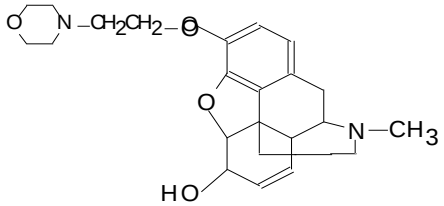
Pholcodine —> less addictive than codeine, equally effective
Dionine —> less addictive than codeine, equally effective
Paracodin —> more addictive than codeine
Dicodid —> more addictive than codeine, stronger effect
Oxycodone —> more addictive than codeine, stronger effect

7-8 Saturated bond is more addictive

Synthesis



MORFIN

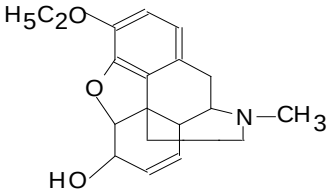


PHOLCODİNE

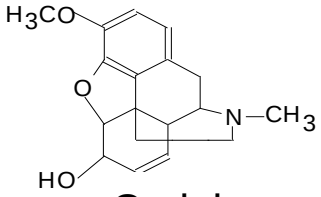
ethylation

+ CH_3Cl

methylation

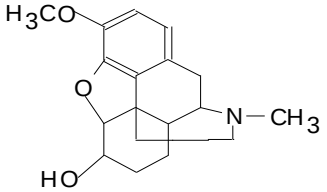


DIONINE

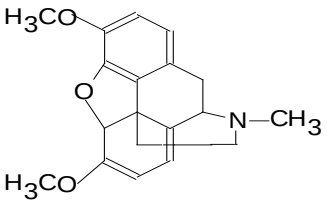


Codein

Red.



PARACODINE



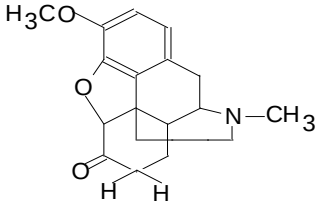
THEBAIN

1) Red.

2) demethylation

(HBr)

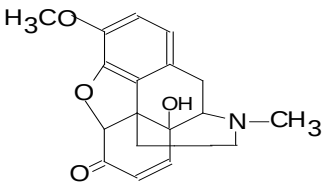
Red. ⇄ Oks.



DICODID
Dihidrokodeinon
(HYDROCODON)

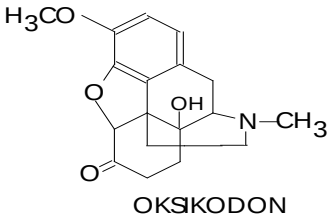
Morphine (%5-15)

acetylation



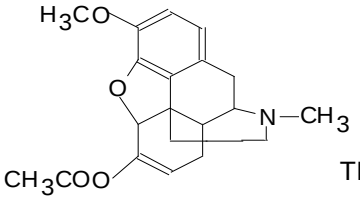
Hydroxycodeinone

+ H_2



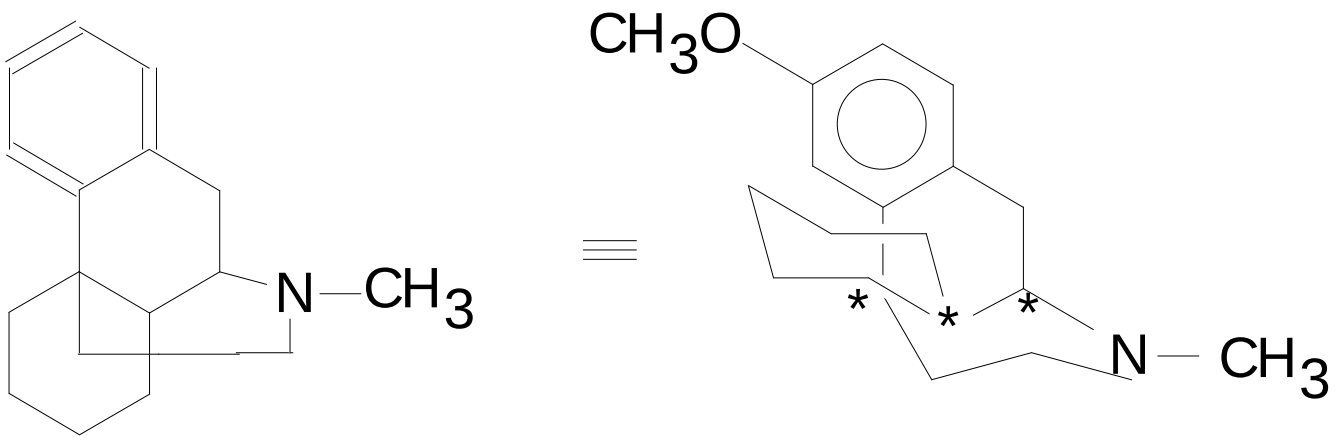
OKSİKODON

Oxycodone



TEBACON
(ACEDICON)

Dekstrometorphan



3-methoxy-N-methylmorphinan

It is a synthetic morphinan derivative.

The methane derivative of the d-enantiomer of levorphanol, a narcotic analgesic drug, has low affinity for conventional opioid receptors.

Does not have any analgesic effect..

Although it effects by inhibiting the cough center in the brain there are no constipation, central depression, and addictive effects. It does not dry mucosa.

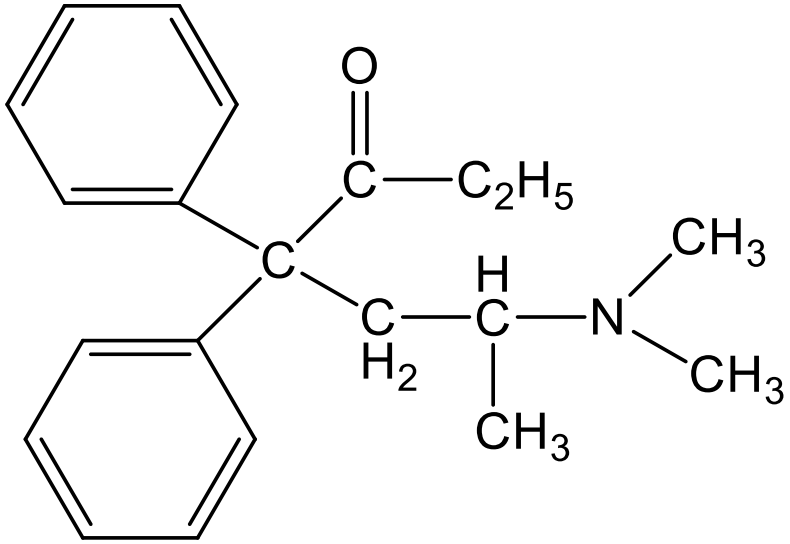
It should not be used using bronchial asthma.

Caution should be exercised in liver patients since demethylation is inactivated in the liver.

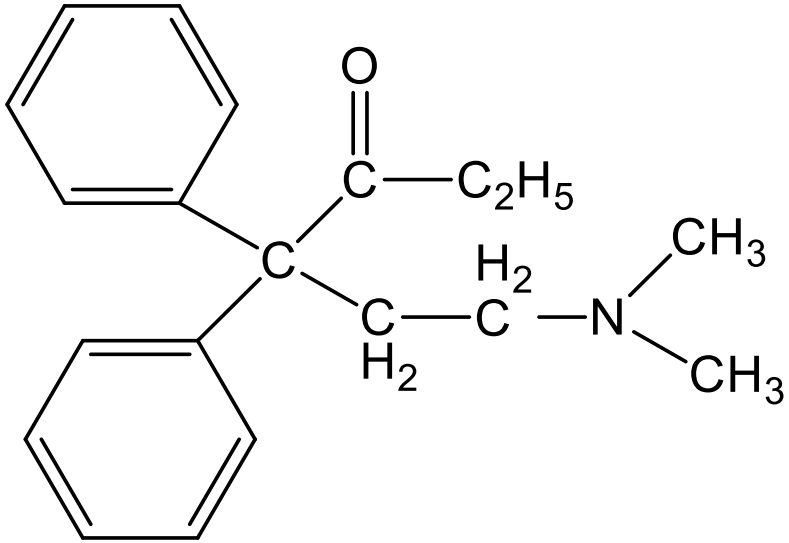
SYNTHETIC ANTITUSSIVES

- **They don’t have side effects of opioids, such as addiction, constipation, drowsiness and sedation .**
- **They inhibit the cough reflex with a peripheral effect.**

I. METHADONE LIKE ANTITUSSIVES

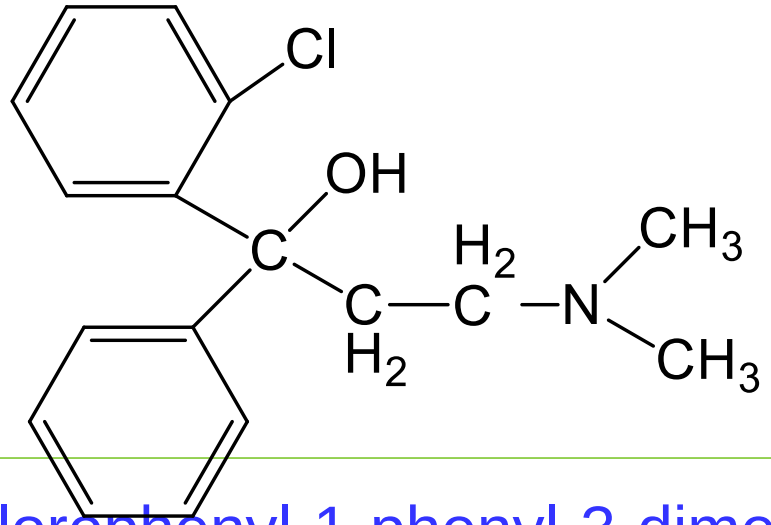


Methadone (analgesic)



Normethadone (antitussive)

Spasmolytic, bronchodilator,
selective effect on the respiratory system



Chlophedianol
DETIGON

1-*o*-chlorophenyl-1-phenyl-3-dimethylamino propanol

Selective effects to the respiratory system. It blocks the cough center with partially central and peripheral, spasmolytic and local anesthetic effects.

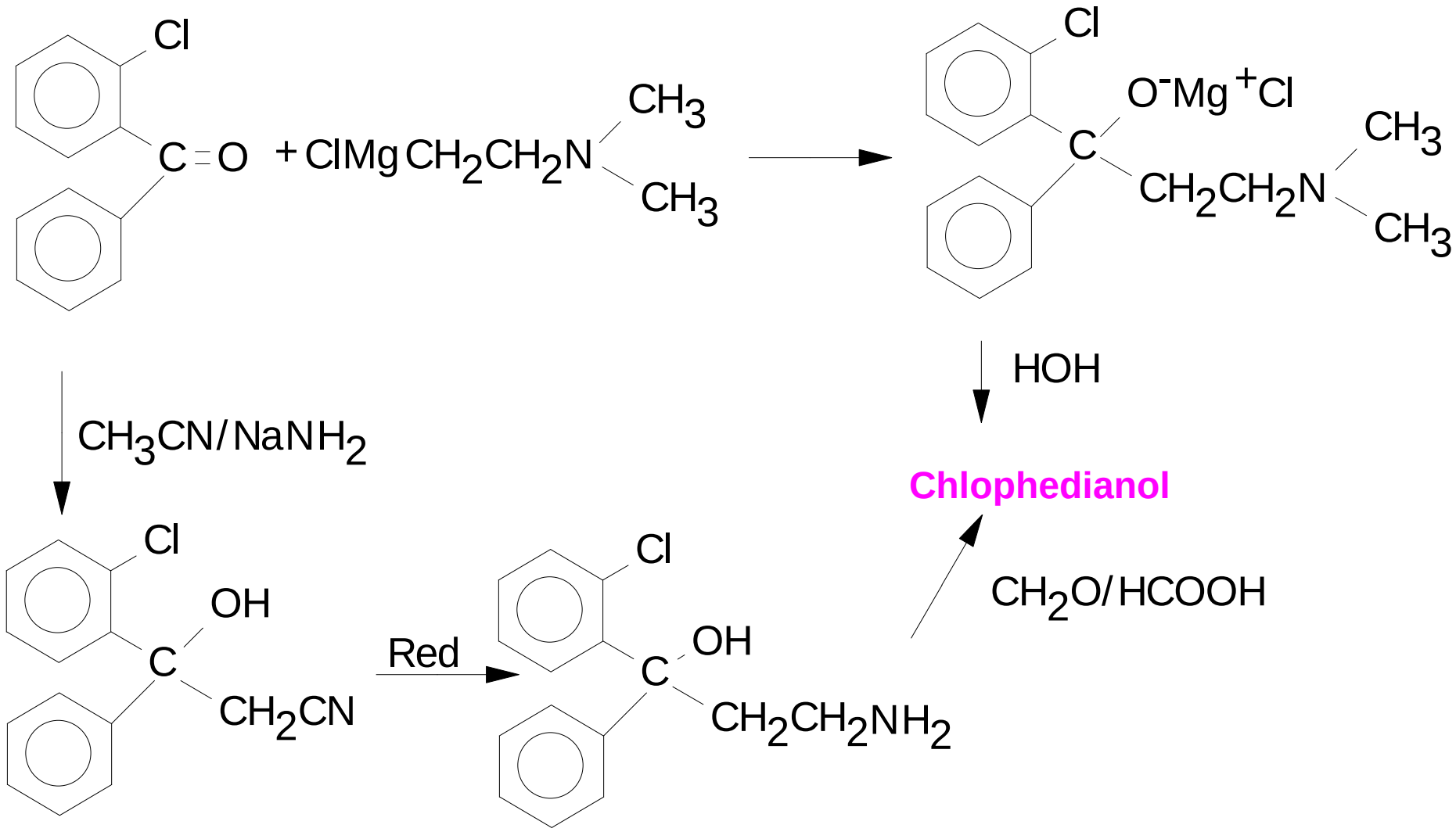
It has local anesthetic, spasmolytic and antihistaminic properties.

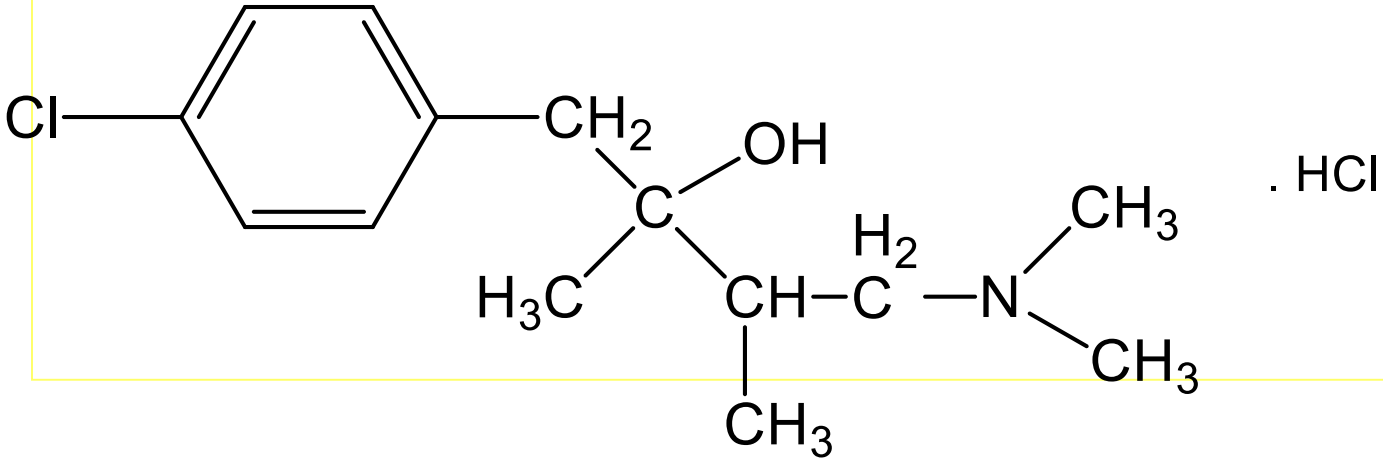
May perform anticholinergic effects and hallucinations in high doses.

Does not cause respiratory depression and drowsiness.

Side Effect: Nausea, vomiting

Synthesis of Chlophedianol





SILOMAT

1-(*p*-chlorophenyl)-2,3-dimethyl-4-dimethylamino-2-butanol

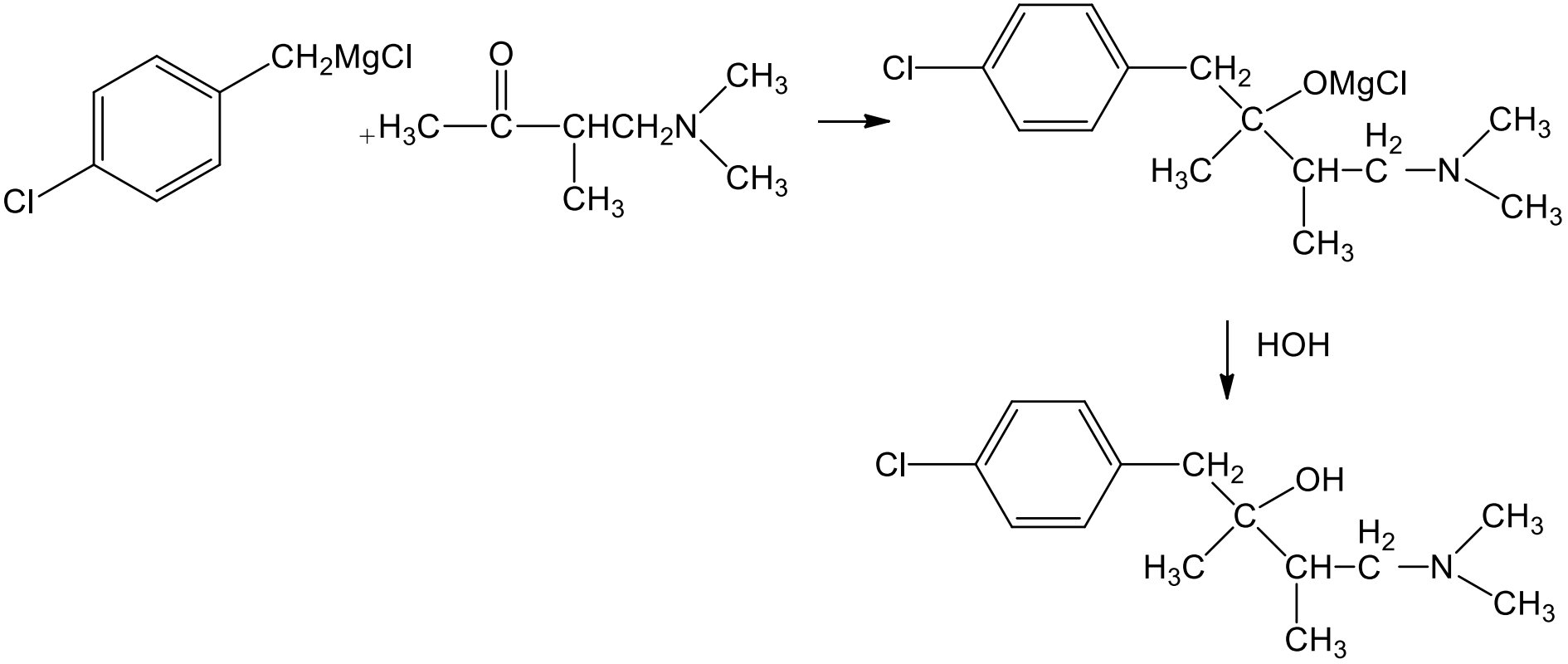
Spasmolytics

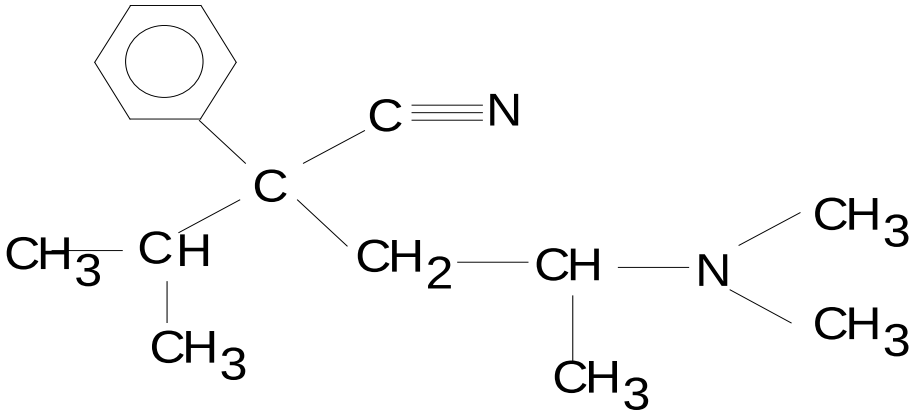
Local anesthetic

Inhibits the cough center

Does not cause respiratory depression and drowsiness.

Silomat Synthesis





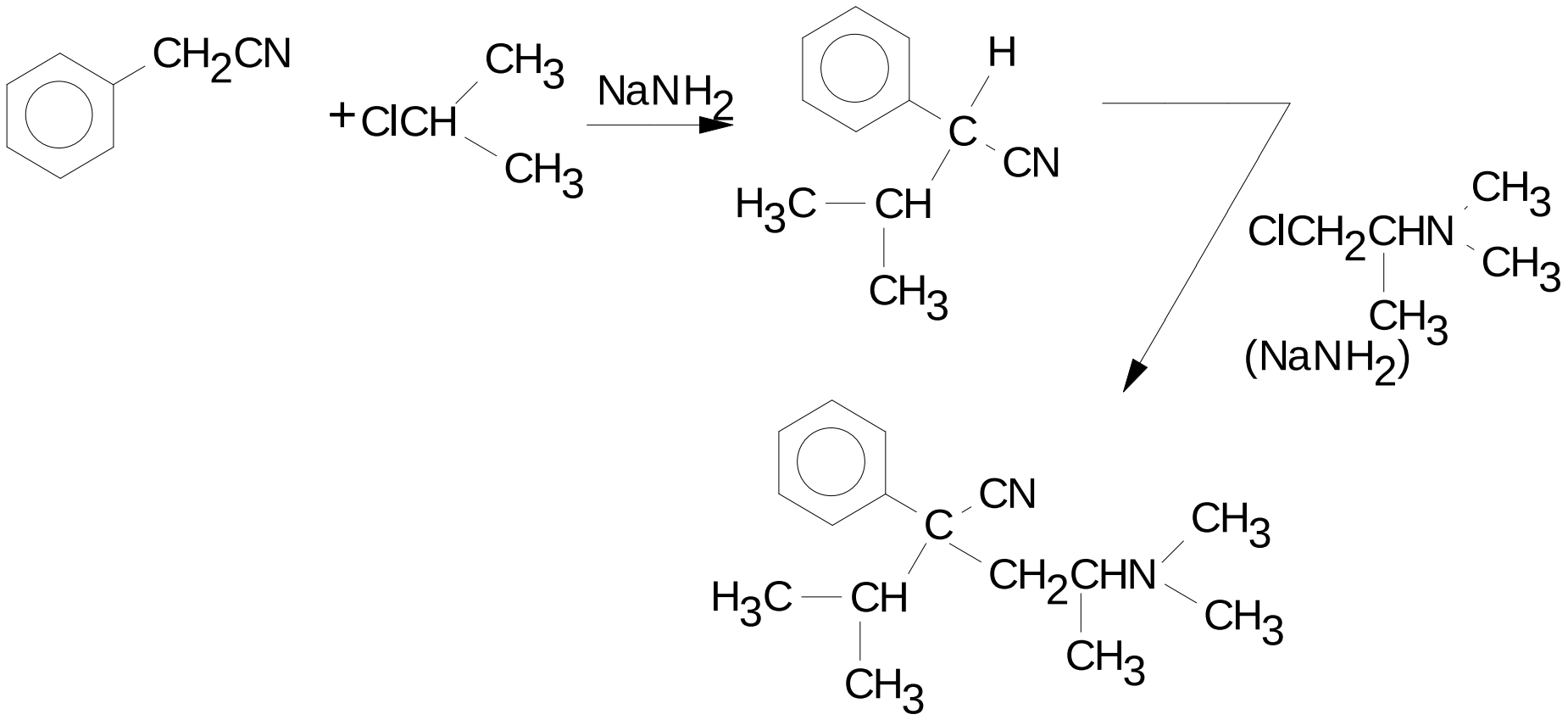
,Sitrik Ac. ISOAMINIL=PEROCAI

α-isopropyl-α-(2-dimethylaminopropyl) phenylacetonitril

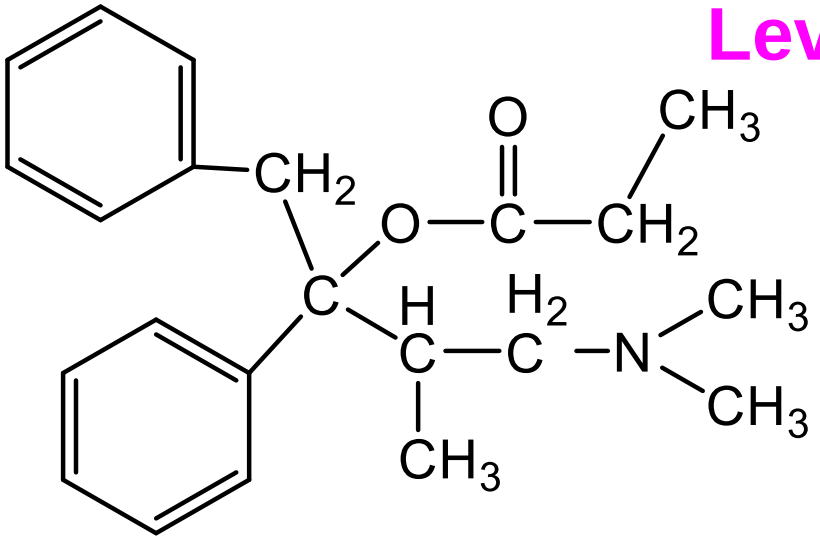
Supress the center of cough with its bronchodilator effect.

There is no suppressive effect on analgesic, sedative or respiratory center.

Synthesis of Isoaminyl



Levopropoxyphene- NOVRAD



. Naftalen-2-sülfonik asit

Napsilat Tuzu

(-)4-dimethylamino-1,2-diphenyl-3-methyl-2-butilpropiyonat

The (-) isomer of the compound exhibits much more antitussive activity than both the (+) isomer and the racemic mixture. The analgesic effect is dominant in the (+) isomer of the dextropropoxyphen compound.

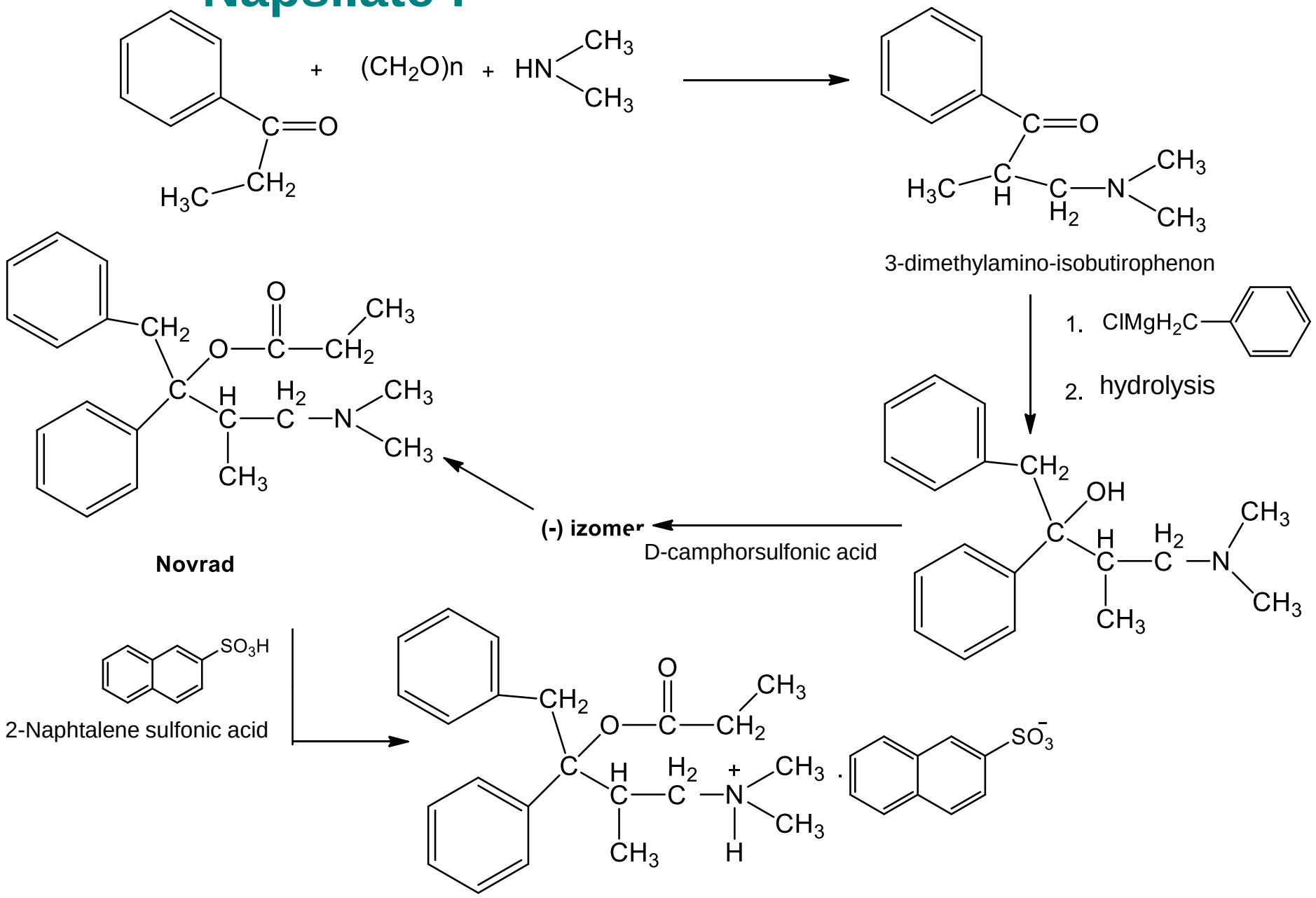
It acts by inhibiting the cough center.

It is used in the upper respiratory tract infections (cold, flu).

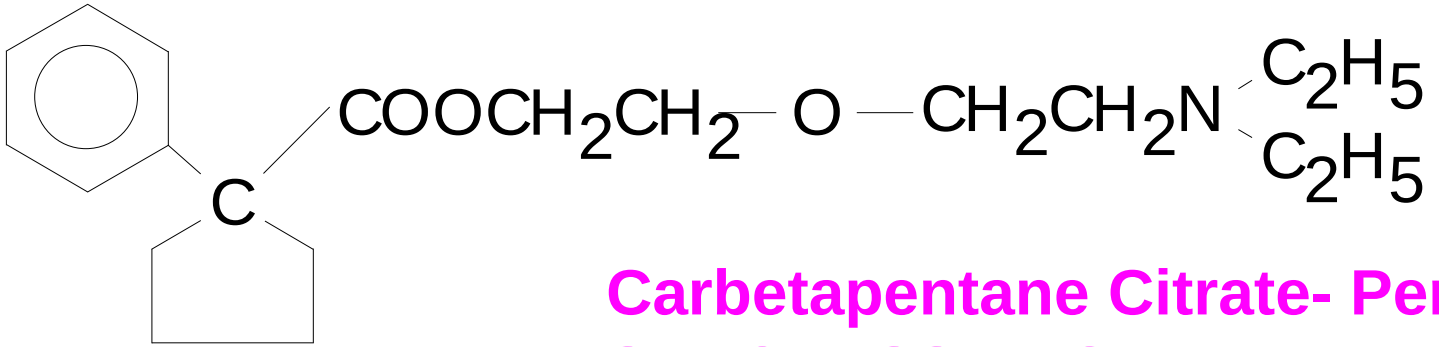
Used in cases of laryngitis due to smoking.

There is also a spasmolytic effect.

Synthesis of Levopropoxifene Napsilate :



II. BASIC ANTITUSSIVES Carrying ESTER GROUP



Carbetapentane Citrate- Pentoxiverine
SEDOTUSSIN--GAYABEN

1-phenyl-cyclopentanecarboxylic acid 2-(2-diethylaminoethoxy)ethyl ester

A little more effective than codeine.

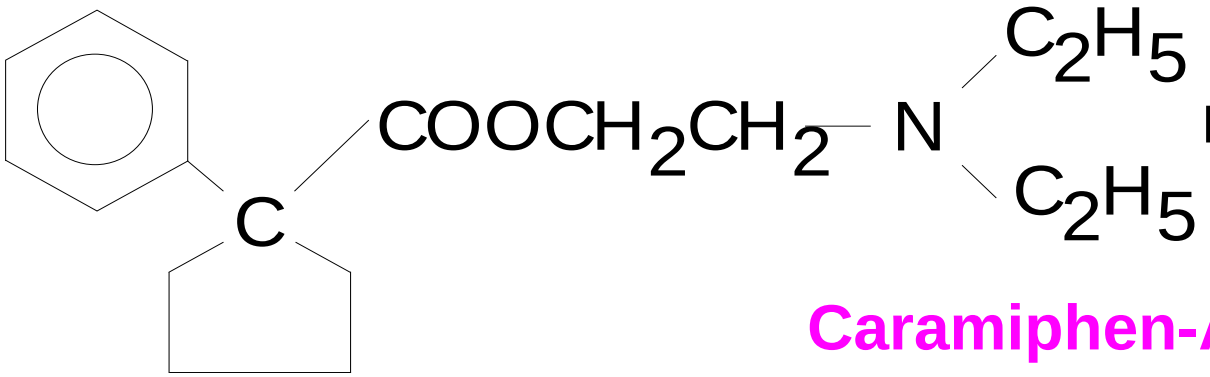
Suppresses cough caused by upper respiratory tract infection.

Spasmolitic.

Local anesthetic.

Parasympatholytic side effects are seen.

It can depress the heart if used in high doses.



Ethane sulphonic acid

Caramiphen-ALCOPON

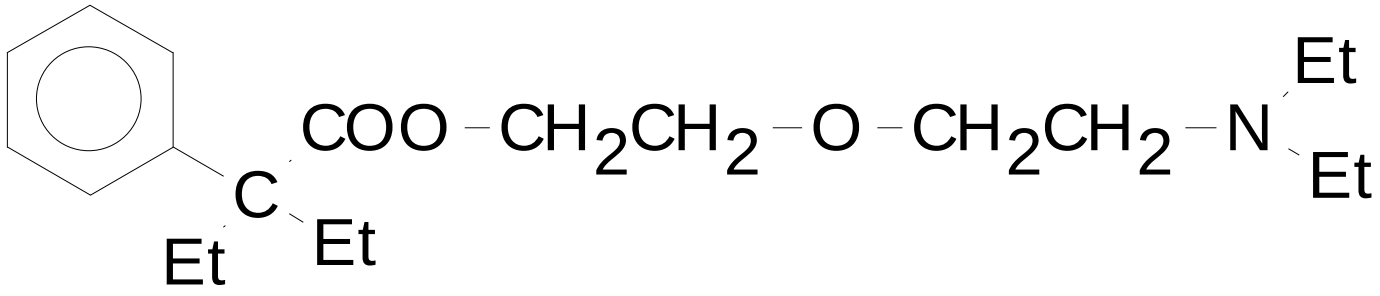
1-phenyl cyclopentanecarboxylic acid (2-diethylamino)ethyl ester

Bronchodilator.

It affects the cough center.

Less powerful than codeine.

Okseladin-PECTAMOL

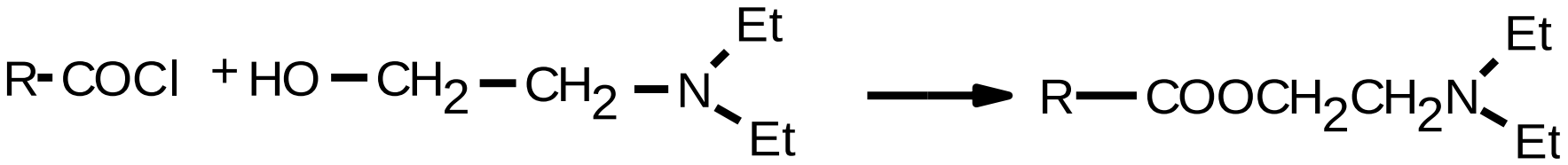


Citric Acid

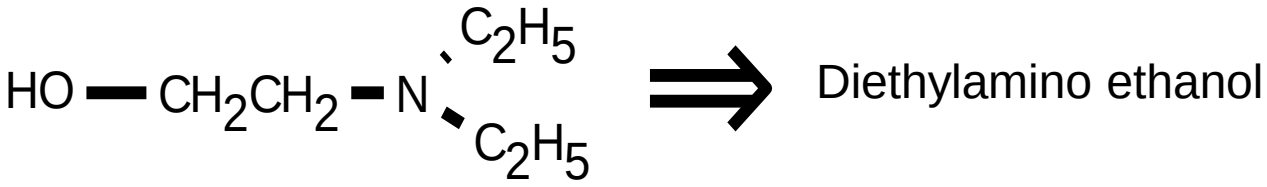
α,α- Diethylphenylacetic acid-2-[(2-diethylaminoethoxy)ethyl] ester

Less powerful than codeine, less side effect.

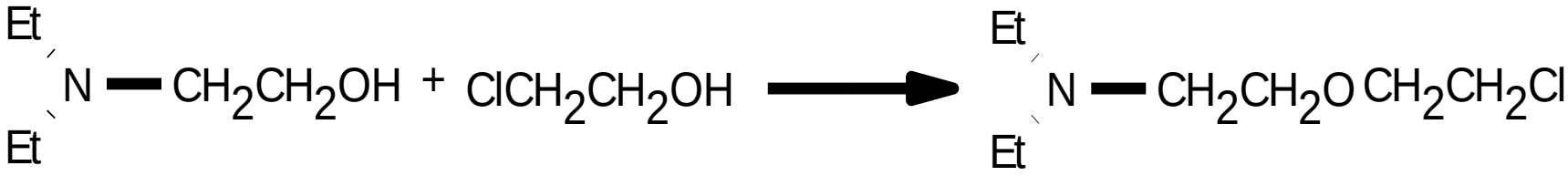
General Reaction Scheme



Amino Alcohol Division

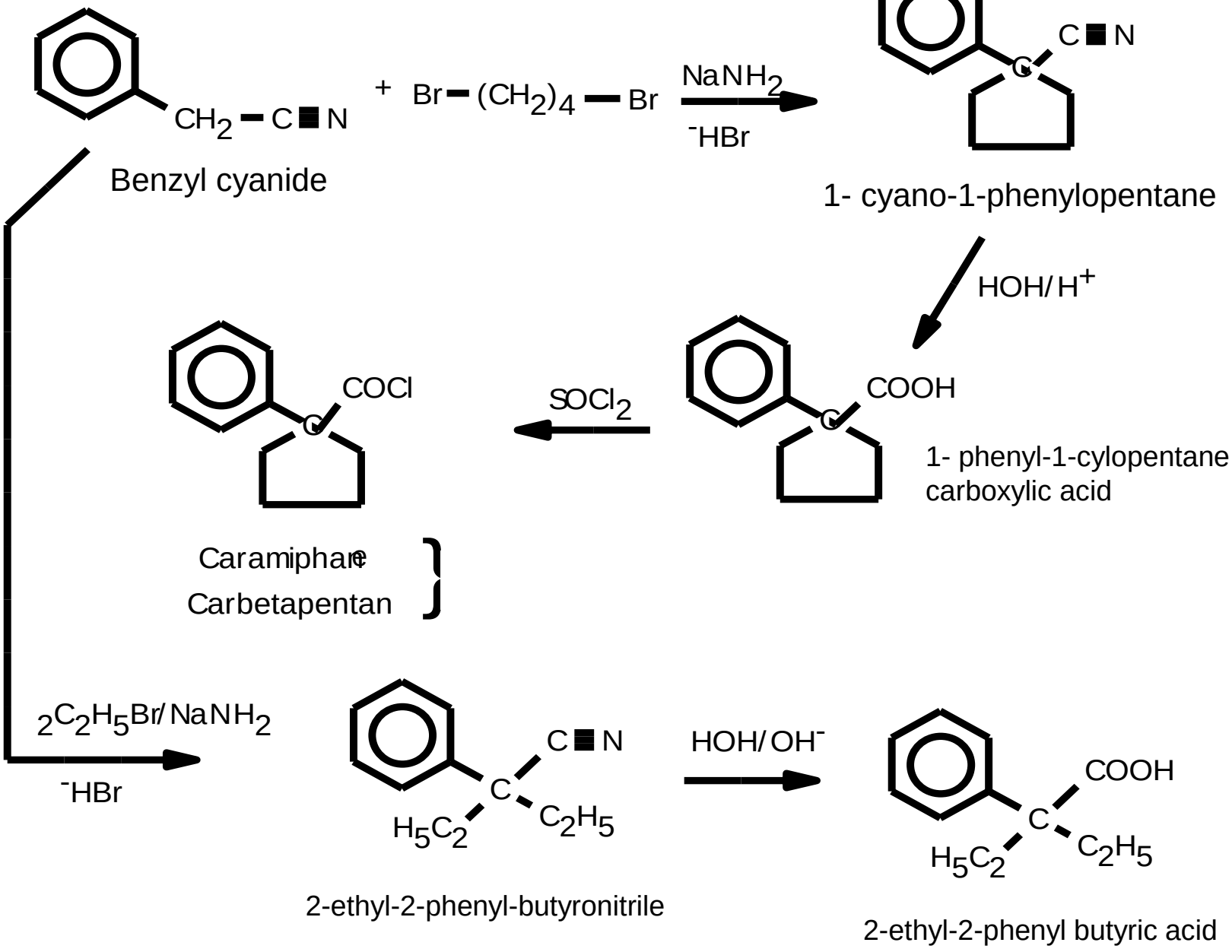


⇒ Diethylamino ethanol



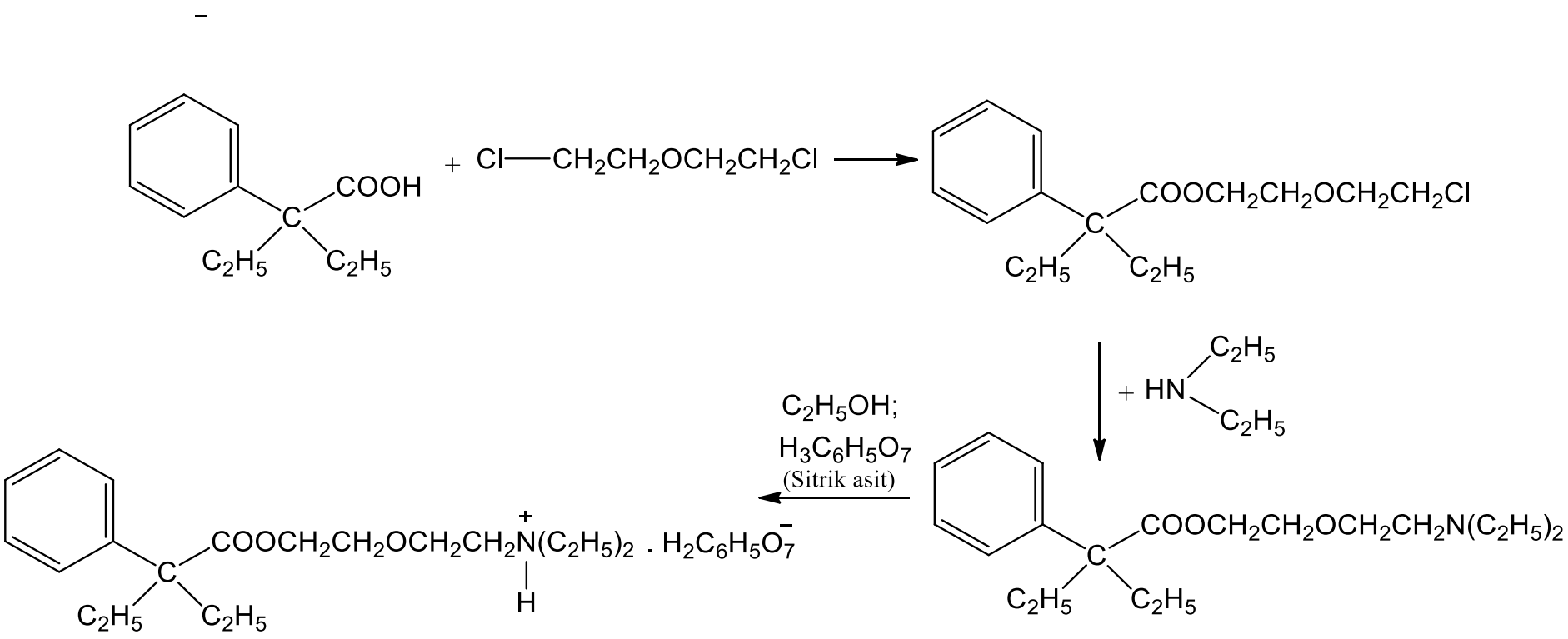
2-Diethylamino ethoxy ethyl chloride

Synthesis

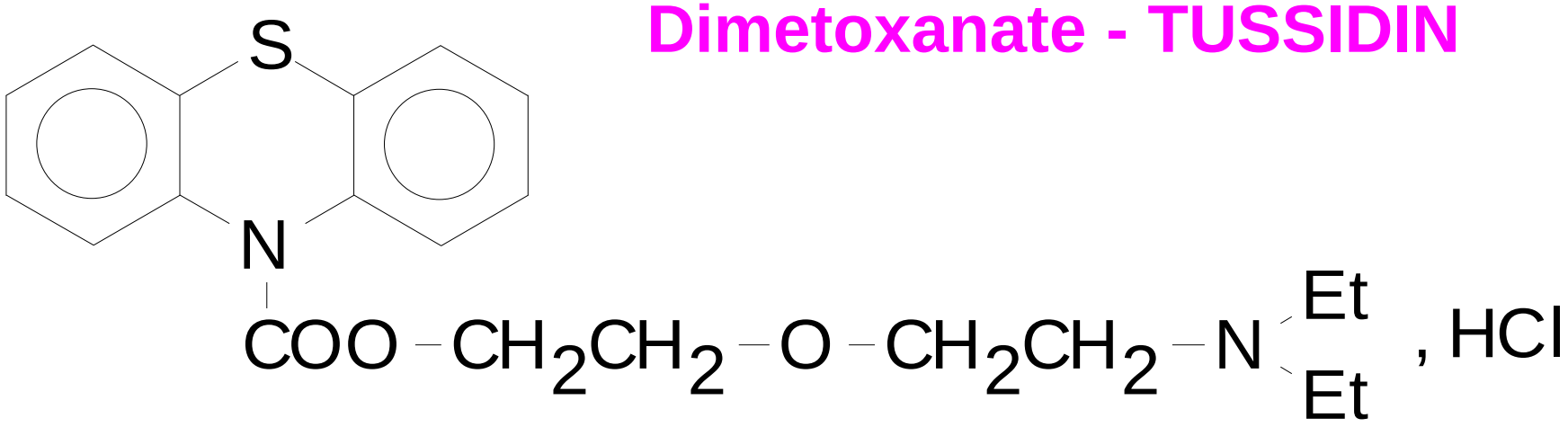


sit)

Example Synthesis: Oxeladine citrate



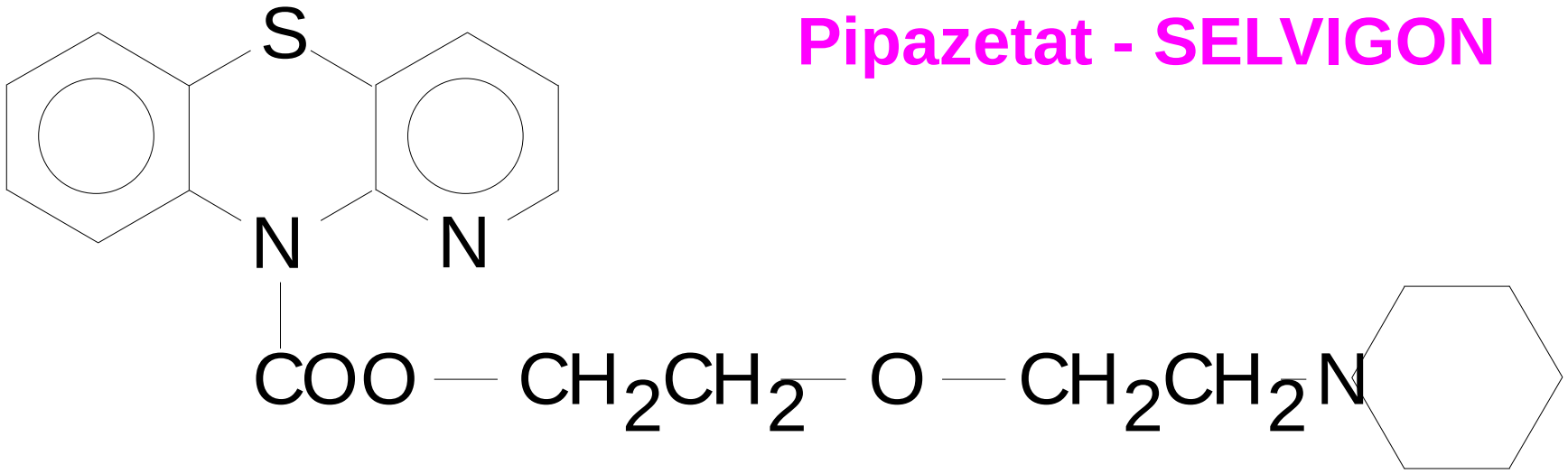
Oxeladine citrate **Oxeladine**



Dimetoxanate - TUSSIDIN

β-Diethylaminoethoxy ethylphenothiazine-10-carboxylate

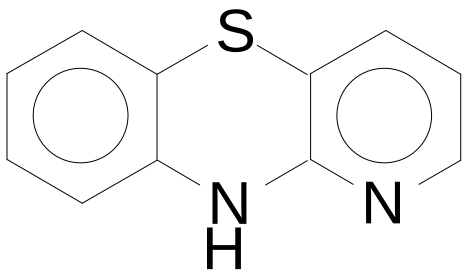
Pipazetat - SELVIGON



1-Azaphenothiazine-10-carboxylic acid[2-(2-piperidino ethoxy) ethyl ester

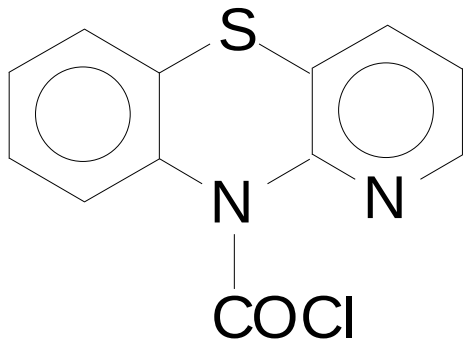
Less potent than codeine, less side effects.

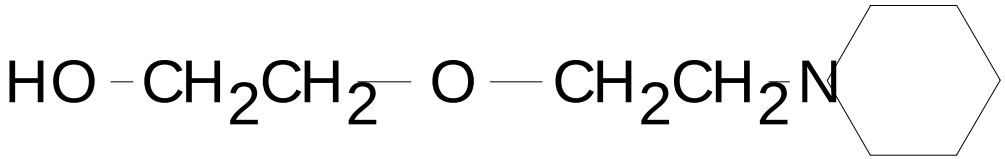
Synthesis of Pipazethate



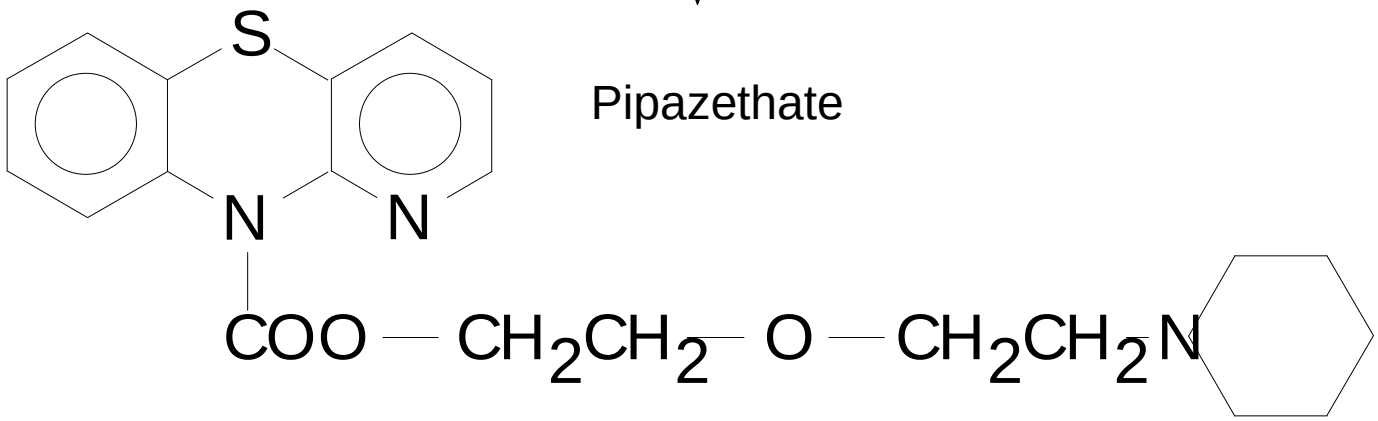
1-Azaphenotiazin

+ $COCl_2$



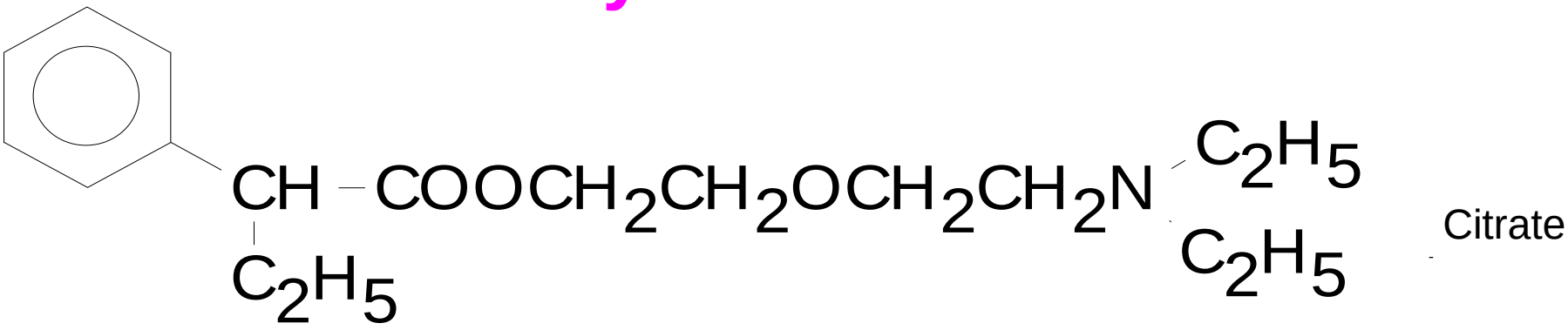


2-(2-piperidino ethoxy)ethanol



Pipazethate

Butamyrate Citrate = SINECOD

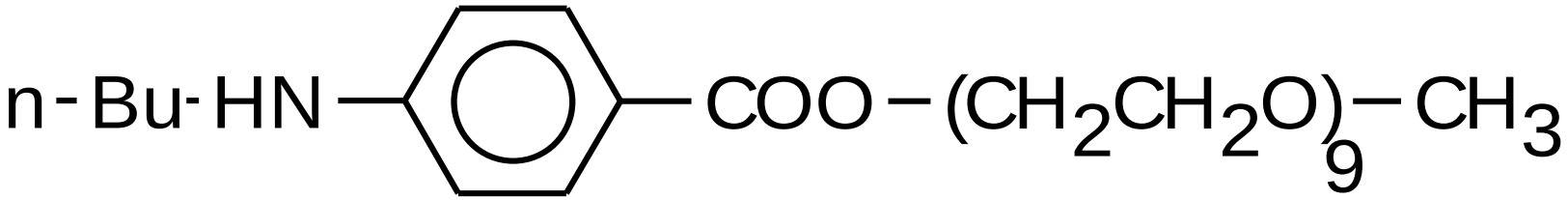


2-[2-(diethylamino) ethoxy]ethyl-2-phenyl butyrate

Used in cases of bronchitis.

3. LOCAL ANESTHETIC EFFECTIVE ANTITUSSIVES

Benzonatate - TESSALON



4-butylamino-benzoic acid-(o-methyl)- nona ethylene glycol ester

A viscous liquid.

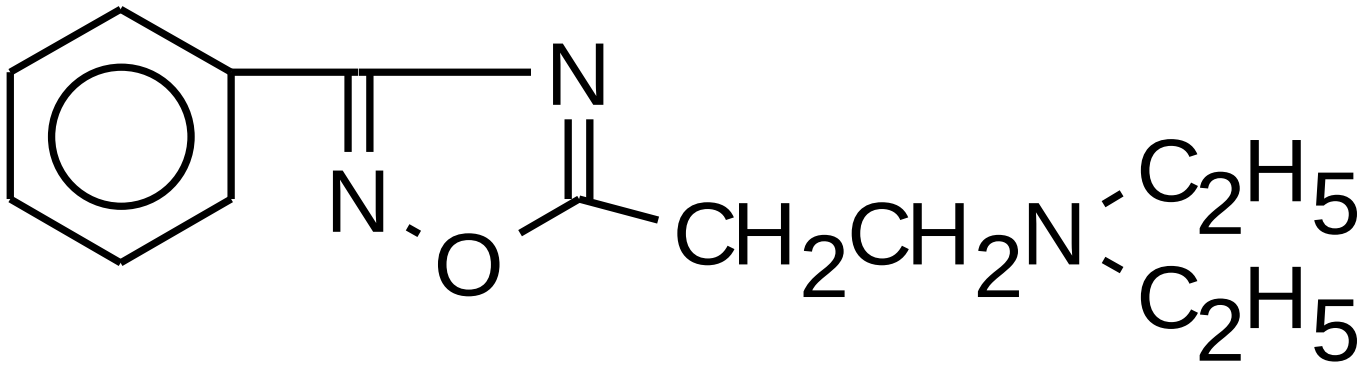
Both central and peripheral effective.

It provides local anesthesia in the lungs, afferent nerve endings and receptors when systemically taken.

It blocks the receptors responsible for the cough reflex.

Side effects: Nasal obstruction, urticaria, constipation, drowsiness.

Oxolamine Phosphate - PEREBRON - FENKO



5-(2-diethylaminoethyl)-3-phenyl-1,2,4-oxadiazole

Bronchodilator.

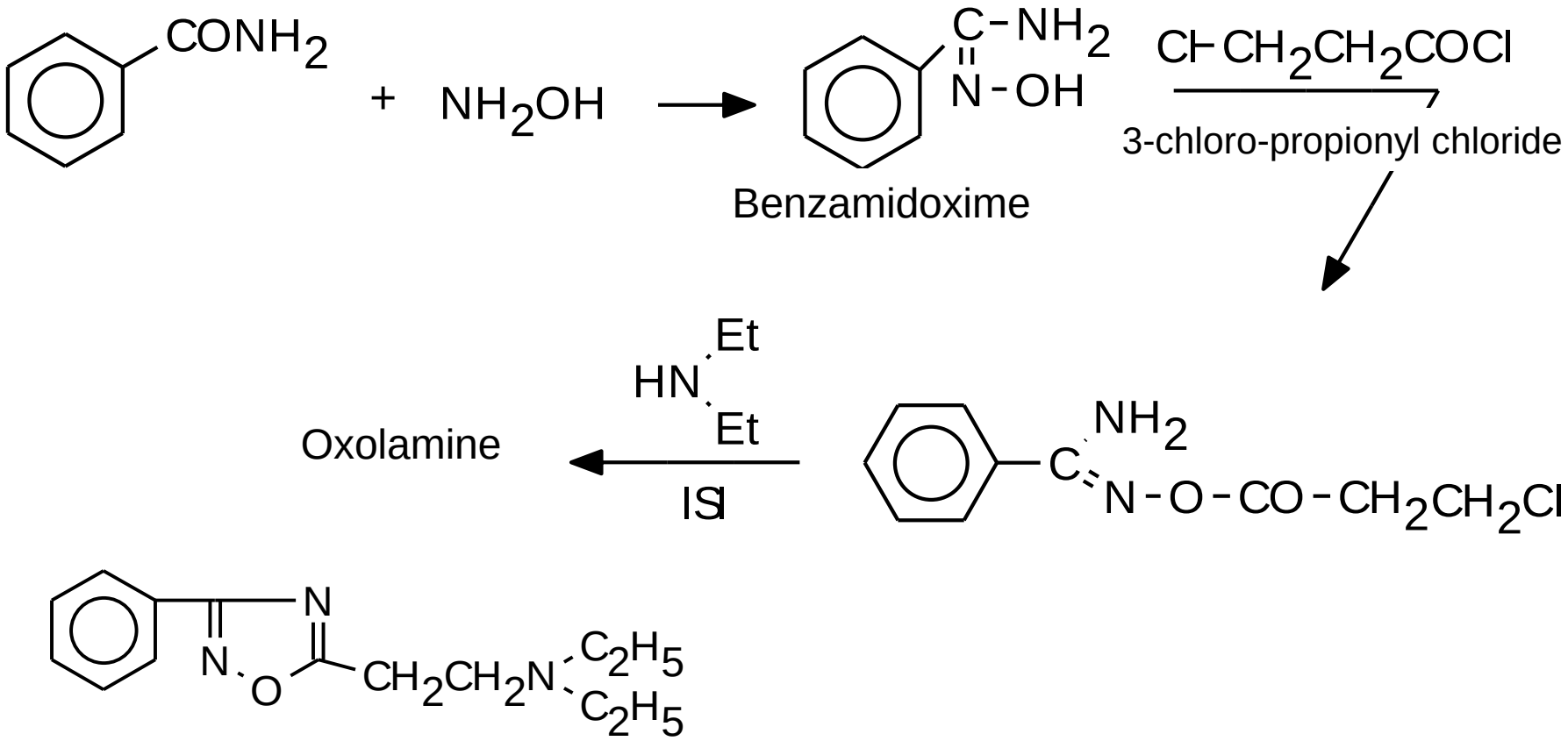
Local anesthetic.

Spasmolitic.

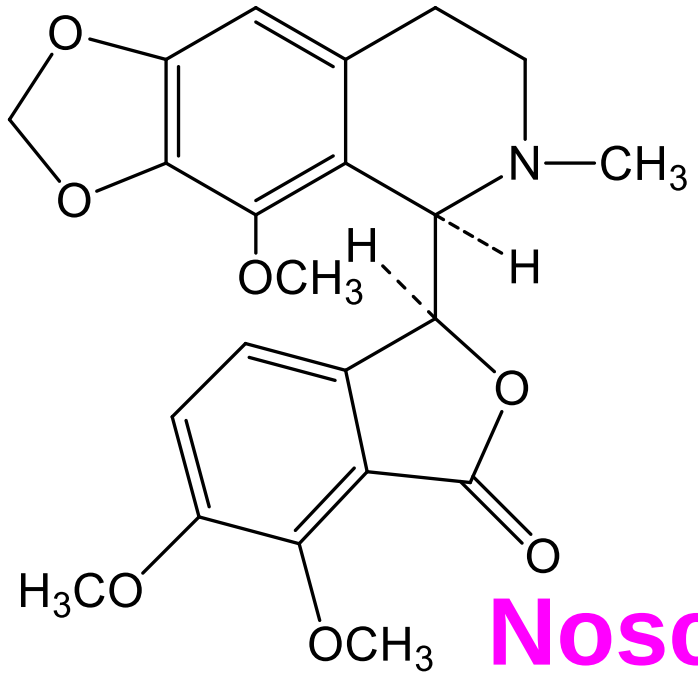
Antipyretic, anti-inflammatory.

It is used in inflammatory diseases of the respiratory tract.

Synthesis of Oxolamine



4- OTHER ANTITUSSIVES



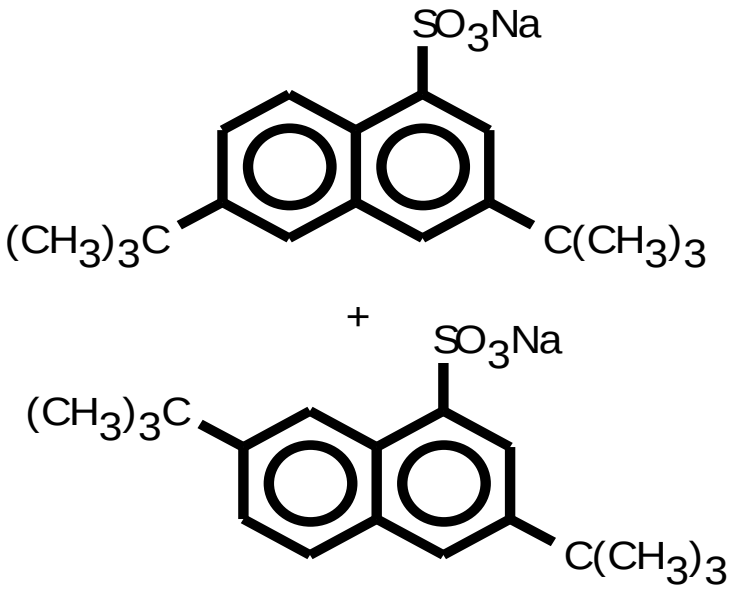
Noscapine (1-Narkotin)

Isoquinoline derivative alkaloid in opium.
Does not create dependency.

It is used in cough caused by bronchial asthma and pulmonary emphysema.
Slight bronchodilator effect
It has no analgesic effect.
It is the candidate to be an effective compound as anticancer.

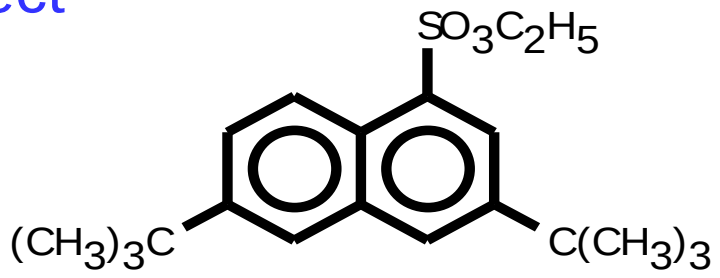
Dibunate BEBEKO - ,BEKANTIL

Sedative effect



Dibunate Na

3,7-Bis(1,1-dimethyl ethyl)-1-napthalen sulphonic acid sodium salt

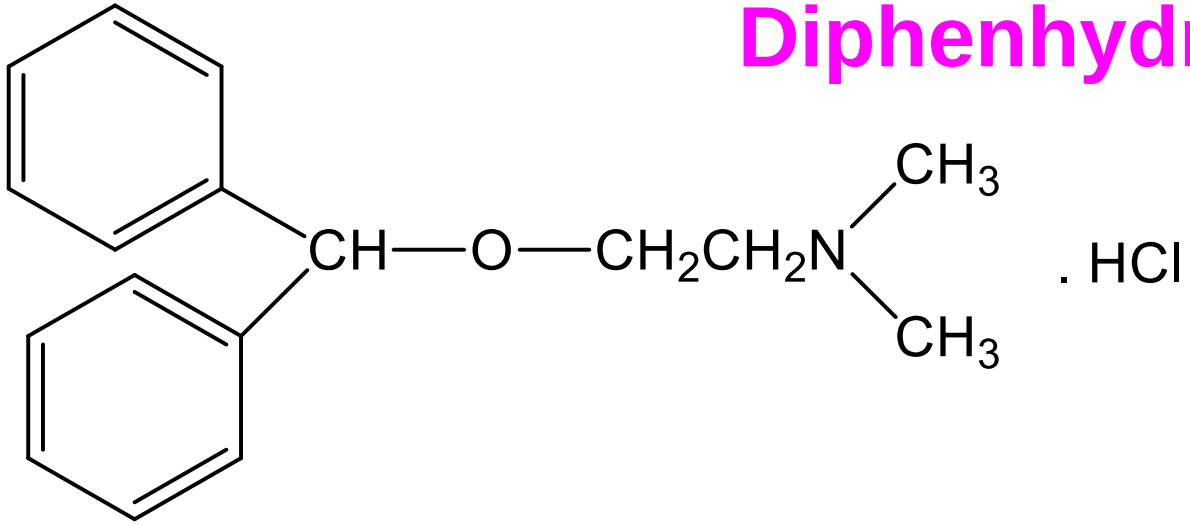


Ethyldibunate

3,6-Di-ter-buthyl-1-napthalen sulphonic acid ethyl ester

This mixture is found in Turkey.

Diphenhydramine HCl

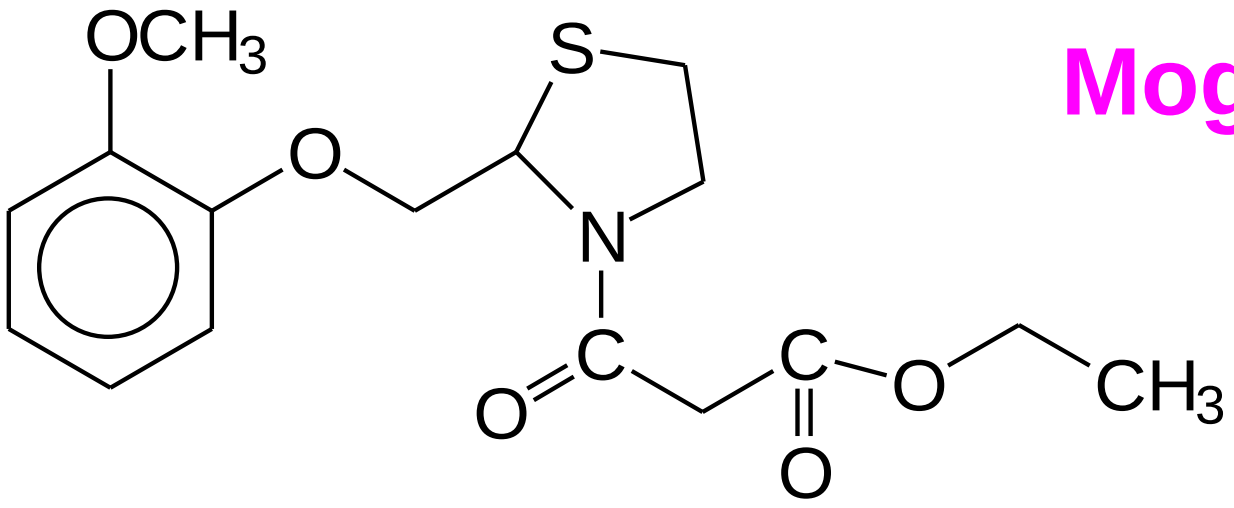


2-(diphenylmethoxy)-N,N-dimethylethylamine

The classical histamine is the H1-receptor blocker.

It has antitussive effect by inhibiting cough center.

As with classical antihistaminic drugs, side effects: sedation and anticholinergic.



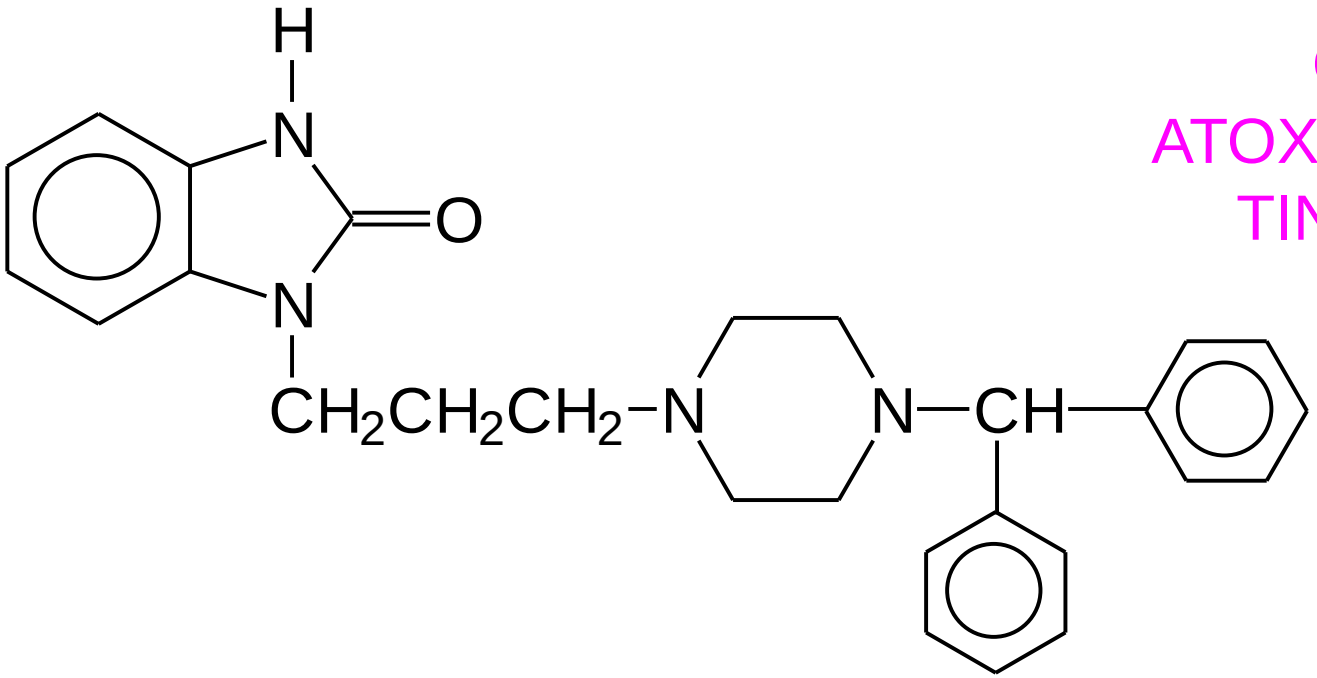
Moguisteine

(R,S)-2-(2-methoxyphenoxy)-methyl-3-ethoxy-carbonyl-acetyl-1,3-thiazolidine

It shows effect with peripheral pathway.

There is no bronchodilator feature.

The antitussive activity of both enantiomers is identical.



Oxatomide

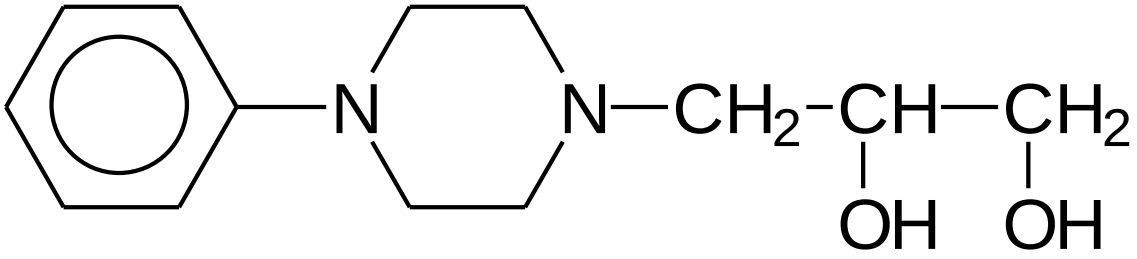
ATOXAN,FLAVORASE
TINSET,TANZOL

1-[3-(4-(diphenylmethyl)-1-piperazinyl) propyl]-1,3-dihydro-2H-benzimidazole-2-one

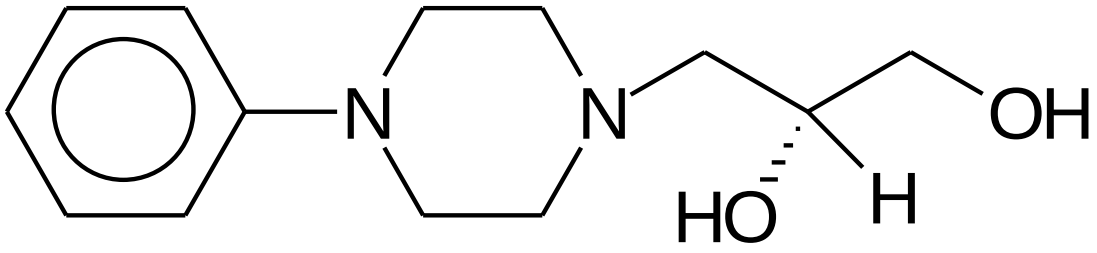
It's antiallergic.

It can be used in patients with asthma.

Dropropizine



3-(4-phenyl piperazinyl)-propane-1,2-diol



Levodropropizine

Dropropizin's S derivative

The –OCH3 coming into the 4nd position of the phenyl ring decreases the effect.

-Cl, F increases effect

The –OCH_3 at the 2nd position of the phenyl ring increases the side effect.

There is not effect difference between the R and S isomers of the substituted and nonsubstituted derivatives.