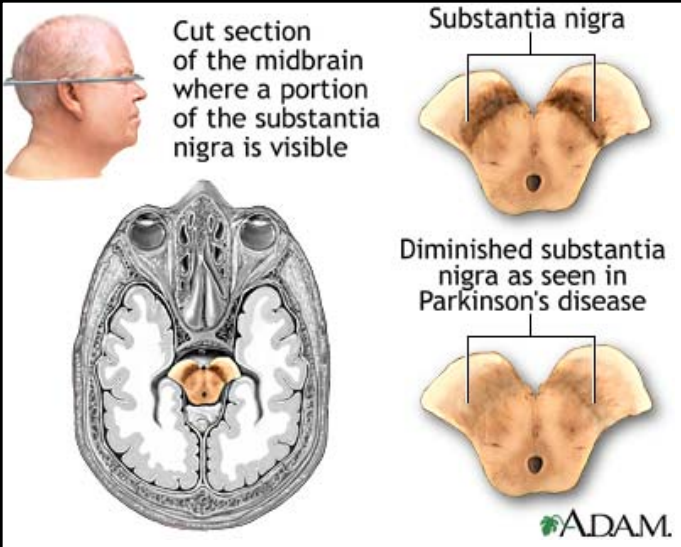
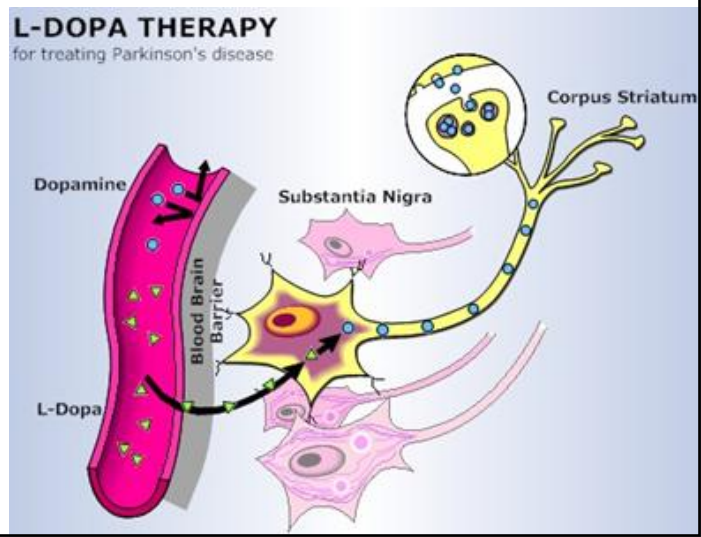


Anti Parkinson Drugs

NEPHAR 305

Pharmaceutical Chemistry I

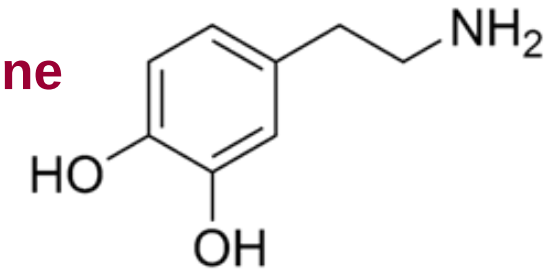


Assist.Prof.Dr. Banu Keşanlı

Parkinson's Disease (PD)

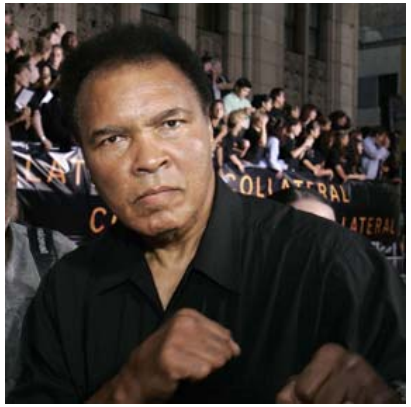
✓ Parkinson's disease (PD) is a neurodegenerative disorder that affects movement.
✓ In PD, cells in a part of the brain called the substantia nigra die off.
✓ The normal function of these cells is to regulate the action of other cells in other brain regions by releasing a neurotransmitter, **dopamine.**
✓ When substantia nigra cells release dopamine, the dopamine attaches to dopamine receptors on the other cells, which influences them in various ways depending on the specific type of cell.
✓ The actions of these cells work in concert with other systems that **influence movement.** When all cells are working properly together, the end result is controlled, fluid movement, speech and self-expression
✓ When substantia nigra cells die off, however, as they do in PD, **less dopamine** is available for release.
✓ Consequently, the cells that depend on receiving dopamine are not properly regulated. The result is an **imbalance in movement control** that causes slowed movements, stiffness, tremor, speech disorder —the classic signs of PD.

Dopamine



2-(3,4-dihydroxyphenyl)ethylamine

Muhammad Ali



Drugs Treatment of Parkinson's Disease

➢ Drugs used in to increase levels of dopamine or to inhibit the actions of acetylcholine in the brain

I. Increases in dopamine synthesis capacity (L-DOPA)

replace dopamine, or mimic its action in the brain.

- Drugs that replace dopamine (e.g. **levodopa**)
- Drugs that mimic the action of dopamine (e.g. **bromocriptine**, **pergolide** and others in development)
- Drugs that release dopamine (e.g. **amantadine**)

II. Inhibition of dopamine metabolism (MAOIs)

delays the breakdown of dopamine, thus increasing the level in the brain

- MAO-B inhibitors (e.g. **selegiline**)

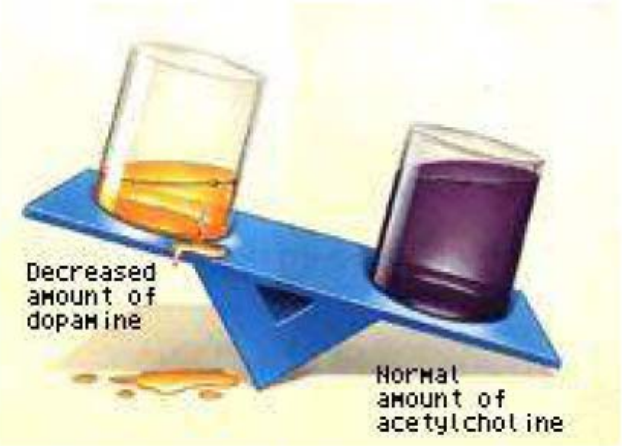
III. Alteration of the interaction/balance with other neurotransmitters (Ach)

prevent other systems that influence movement from being too active

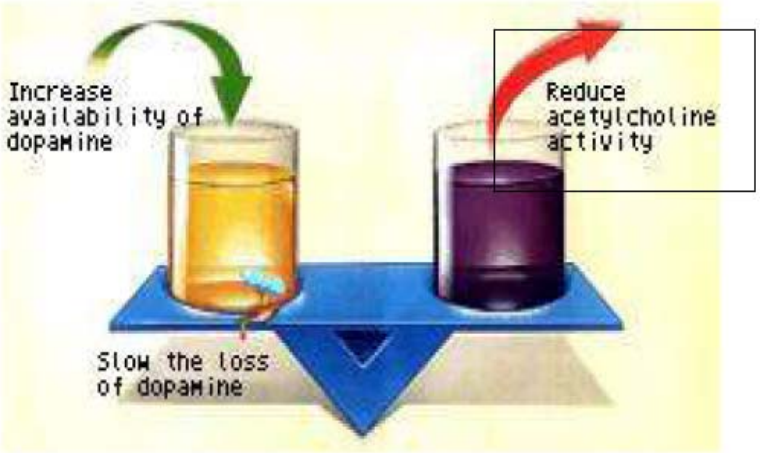
- Acetylcholine antagonists (e.g. **artane**)

How to alter the interaction/balance with other neurotransmitters (DA-ACh) ?

"Balance" Hypothesis of DA-ACh Striatal Interactions



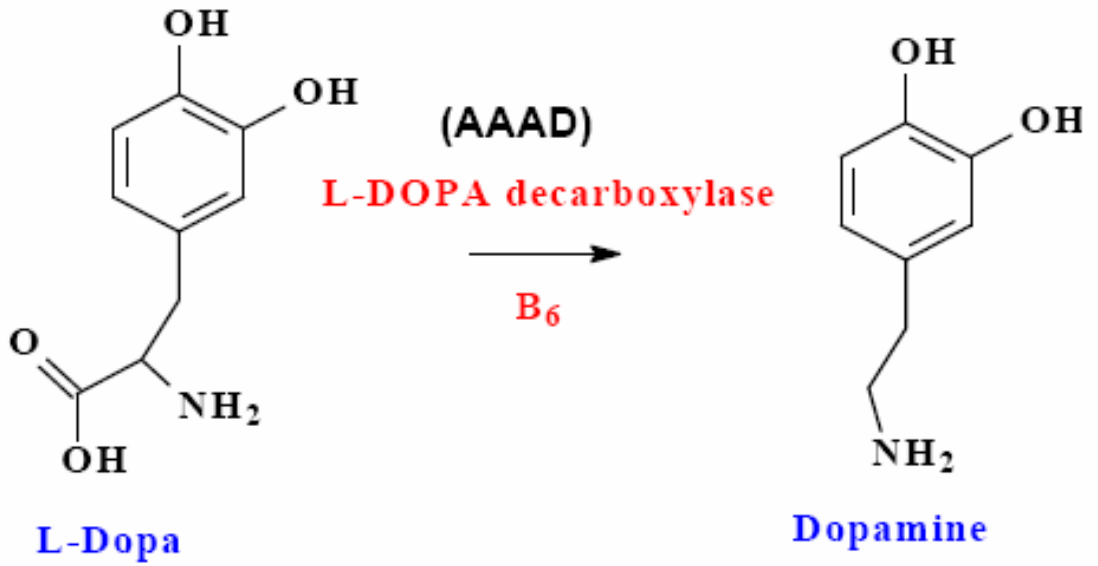
Imbalance of dopamine and acetylcholine in Parkinson's disease.



Effects of Parkinson's disease therapy.

Rationale for L-DOPA Precursor Loading

✓ **Dopamine** levels are low in Parkinson disease.
✓ Dopamine does not pass BBB and, hence, has no therapeutic effect in PD.
✓ **L-DOPA (levodopa)**, an amino acid, which is the metabolic precursor to dopamine, is transported across BBB so it is given instead.
✓ L-Dopa itself has minimal pharmacologic activity, in contrast to its **decarboxylated product, dopamine.**
✓ L-Dopa is rapidly decarboxylated in the gastrointestinal tract. High concentration of peripheral dopamine => side effects!
✓ L-Dopa combined with **Carbidopa** => increases the amount of L-Dopa that reaches the brain

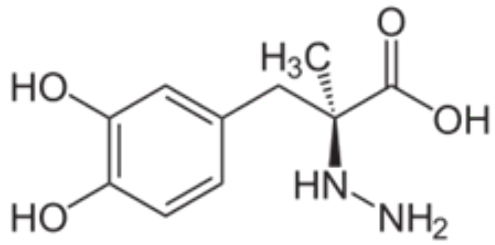


Carbidopa

✓ Carbidopa is an inhibitor of dopa decarboxylase. Because it is unable to penetrate the blood-brain barrier, it acts to reduce the peripheral conversion of levodopa to dopamine.

✓ Carbidopa is added to the levodopa to prevent the breakdown of levodopa before it crosses into the brain. As a result carbidopa and levodopa are given together (**Sinemet)**

✓ Inhibits peripheral metabolism of levodopa and allows a greater proportion of peripheral levodopa to cross the blood brain barrier for central nervous system effect.



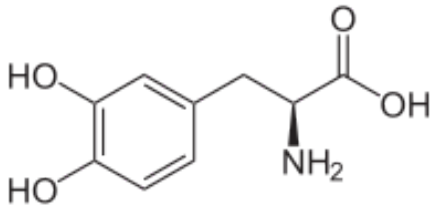
Carbidopa

(2*S*)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid

Levodopa (L-DOPA)

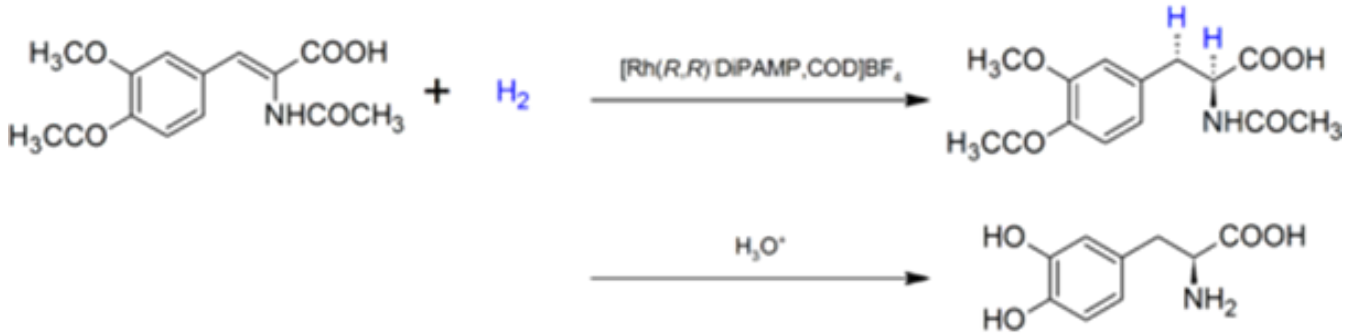
Levodopa, L-DOPA (**L-3,4-dihydroxyphenylalanine**) is the most widely prescribed antiparkinson medication and is the prototype

✓ Levodopa is chemically similar to amino acids, it converts to dopamine in the brain.

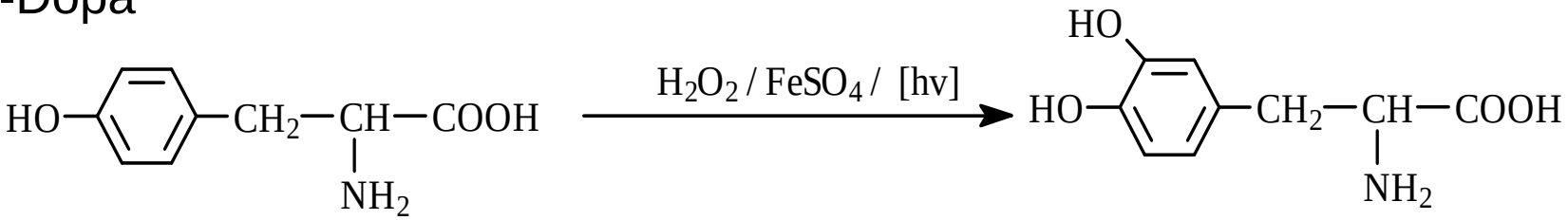


(*S*)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid

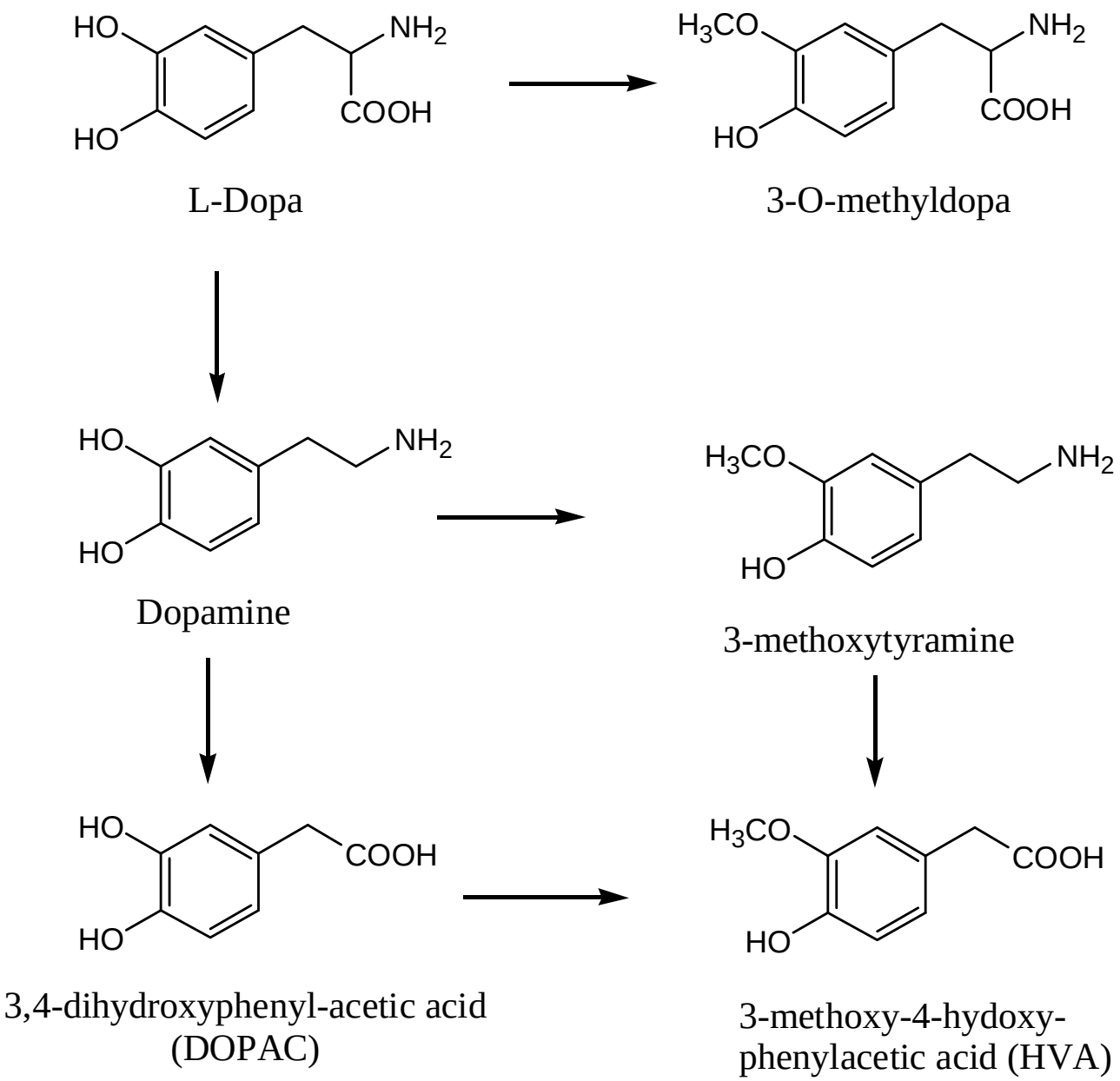
Synthesis: The 2001 Nobel Prize in Chemistry was awarded to William S. Knowles for his work on chirally catalysed hydrogenation reactions, the most noted example of which was used for the synthesis of L-DOPA.



Alternative Synthesis: Oxidation of **Tyrosine** with hydrogen peroxide / ferro sulfate gives L-Dopa



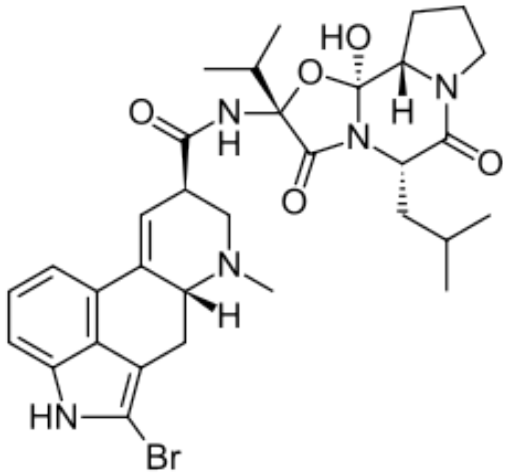
Metabolism of L-DOPA



Bromocriptine (Parlodel, Cycloset)

Bromocriptine an ergoline derivative, is a dopamine agonist that is used in the treatment of Parkinson's disease

✓ It is a **dopamine agonist** is a compound that activates dopamine receptors in the absence of dopamine
✓ Used with levodopa/carbidopa to prolong the effectiveness



How to inhibit dopamine metabolism

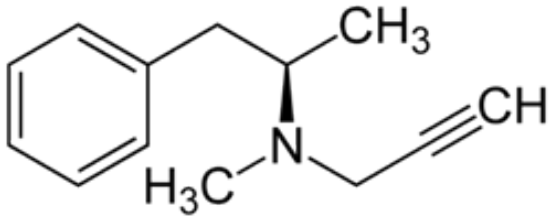
Selective MAO-B inhibition

✓ MAO-B is the predominant form in the brain and is responsible for the oxidative metabolism of dopamine

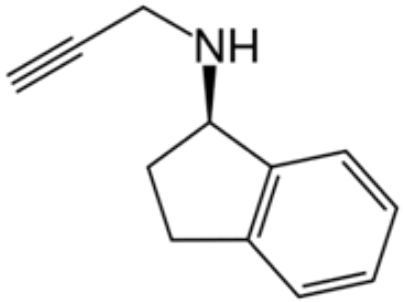
✓ At low concentrations these drugs irreversibly inhibit MAO-B selectively in CNS

✓ Monoamine oxidase inhibitors (MAOIs) prolong the effects of dopamine in the brain by preventing its breakdown. They also may prevent the removal of dopamine between nerve endings and enhance release of dopamine from nerve cells.

✓ Increases dopamine in the brain by inhibiting metabolism by MAO-B



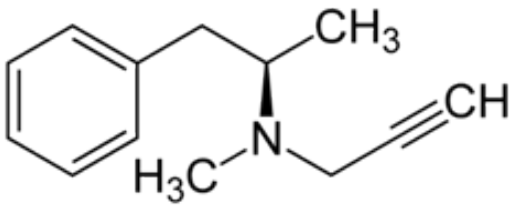
Selegiline



Rasagiline

Selegiline (Eldepryl)

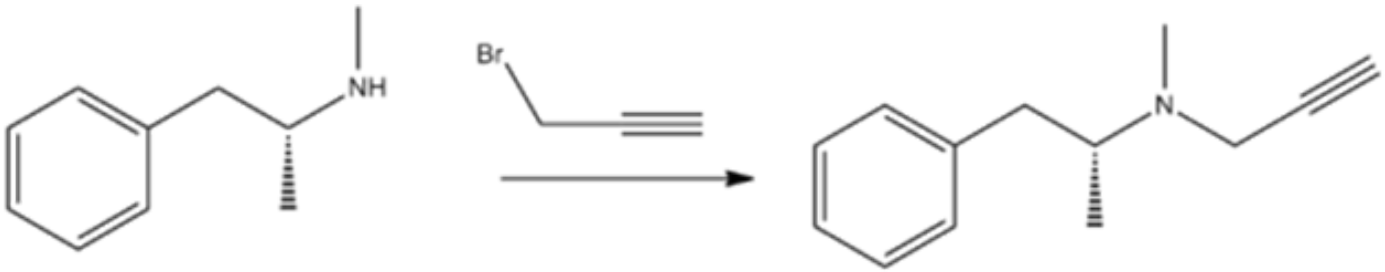
- ✓ A selective inhibitor of monoamine oxidase, MAO-B
- ✓ Prolong the effects of dopamine in the brain by preventing its breakdown



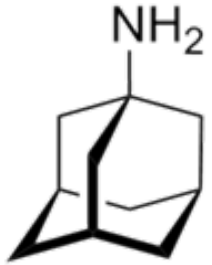
(*R*)-*N*-methyl-*N*-(1-phenylpropan-2-yl)prop-1-yn-3-amine

Synthesis of Selegiline

It is synthesized by the alkylation of (–)-methamphetamine using 3-bromo-1-propyne.



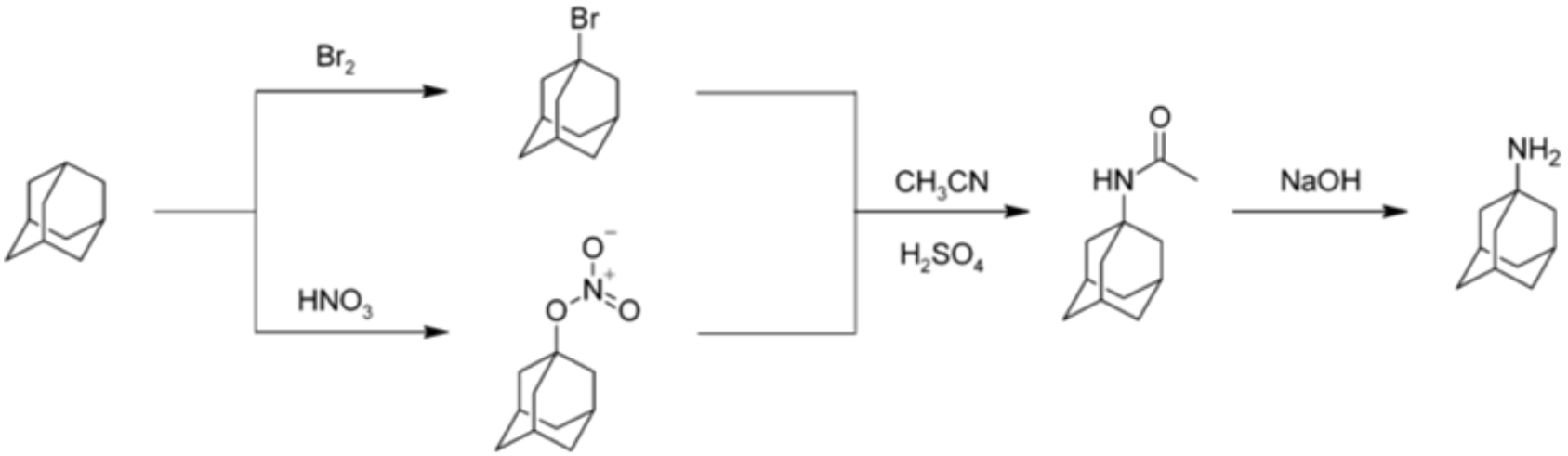
Amantadine (Symmetrel)



✓ It is the organic compound 1-adamantylamine or (1-aminoadamantane) meaning it consists of an adamantane backbone that has an amino group substituted at one of the four methyne positions.

Amantadine was found to improve parkinsonian symptoms by **stimulating the release of dopamine** from dopaminergic nerve terminals in the nigro striatum and **delaying its reuptake**.

Synthesis: by reacting adamantane with bromine or nitric acid to give the bromide or nitroester at position one. Reaction of either compound with acetonitrile affords the acetamide, which is hydrolyzed to give 1-adamantylamine

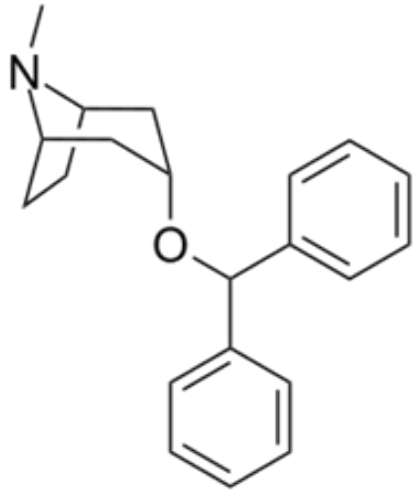


Anticholinergics

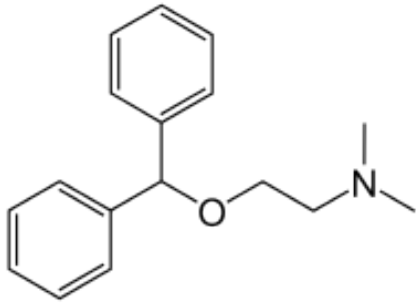
- Anticholinergics decrease the effects of acetylcholine which decreases the excess of acetylcholine to dopamine
- Examples: benztropine (Cogentin) and diphenhydramine (Benadryl)

✓ **Benzatropine** is an anticholinergic drug used in the treatment of Parkinson's disease. It is used to treat the symptoms of Parkinson's disease, such as muscle spasms, stiffness, tremors, sweating, drooling, and poor muscle control.

✓ **Diphenhydramine** is also used in the management of drug-induced parkinsonism



Benztropine

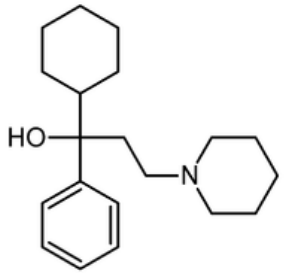


Diphenhydramine

Trihexyphenidyl

Trihexyphenidyl (Artane) is used to treat symptoms of Parkinson's disease or involuntary movements due to the side effects of certain psychiatric drug

- ✓ Trihexyphenidyl is an anticholinergic that work by blocking a certain natural substance (acetylcholine).
- ✓ This helps decrease muscle stiffness, sweating, and the production of saliva, and helps improve walking ability in people with Parkinson's disease.



(*RS*)-1-cyclohexyl-1-phenyl-3-(1-piperidyl)propan-1-ol

Synthesis: by the aminomethylation of acetophenone using paraformaldehyde and piperidine in a so-called Mannich reaction. In the second step the 2-(1-piperidino)propiophenone is reacted with cyclohexylmagnesiumbromide in a Grignard reaction to give **trihexyphenidyl**.