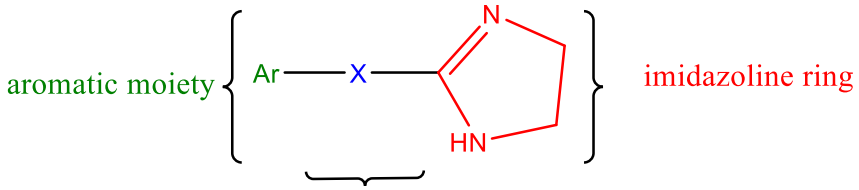
CAs without OH Groups

- Phenylethylamines that lack OH groups on the ring and the β-OH group on the side chain act almost exclusively by causing the release of NE from sympathetic nerve terminals and thus results in a **loss of direct sympathomimetic activity**
- substitution of OH groups on the phenylethylamine structure makes the resultant compounds less lipophilic, unsubstituted or alkylsubstituted compounds cross the BBB more readily and have more central activity. Thus, amphetamine and methamphetamine exhibit considerable CNS activity.
- CAs per oral have only a brief DOA and are almost inactive, because they are rapidly inactivated in the intestinal mucosa and in the liver before reaching the systemic circulation. In contrast, compounds without one or both phenolic OH substituents are, however, not metabolized by COMT, and they are orally active and have longer DOA

Imidazolines and α-Adrenergic Agonists.

★ Imidazolines, which give rise to α-agonists and are thus vasoconstrictors. These imidazolines can be nonselective, or they can be selective for either α_1- or α_2-receptors.

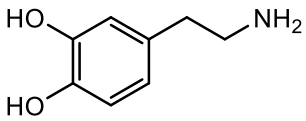


X= usually CH_2 (α_1 agonist), NH (α_2 agoinst)

★ The optimum bridging unit (X) is usually a single methylene group or amino group.
★ Although modification of the imidazoline ring generally results in compounds with significantly reduced agonist activity, there are examples of so-called open-ring imidazolines that are **highly active**.
★ agonist activity is enhanced when the aromatic ring is substituted with halogen substituents like chlorine (Cl) or small alkyl groups like methyl group, particularly when they are placed in the two ortho positions.
★ Because the SARs of the imidazolines are quite different from those of the β-phenylethylamines, it has been postulated that the imidazolines interact with α-receptors differently from the way the β-phenylethylamines do, particularly with regard to the aromatic moiety.

Endogenous catecholamine

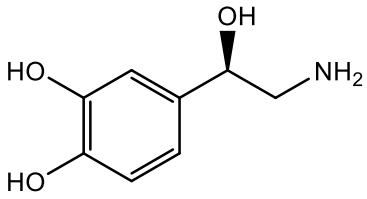
1. Dopamine (DA, 3,4-dihydroxyphenylethylamine)



Dopamine , Log P=0.12

- Differs from NE in lacking of 1-OH group.
- DA is rapidly metabolized by COMT and MAO and has a short DOA with no oral activity.
- It is used intravenously in treatment of shock. In contrast with the NE and E, DA increases blood flow to the kidney in doses that have no chronotropic effect on the heart or that cause no increase in blood pressure.
- The increased blood flow to the kidneys enhances glomerular filtration rate, Na^+ excretion, and, in turn, urinary output. The dilation of renal blood vessels produced by DA is the result of its agonist action on the $_{D1}$-DA receptor.
- In doses slightly higher than those required to increase renal blood flow, DA stimulates the β_1-receptors of the heart to increase cardiac output.
- Infusion at a rate greater than 10 μg/kg per minute results in stimulation of α_1- receptors, leading to vasoconstriction and an increase in arterial blood pressure

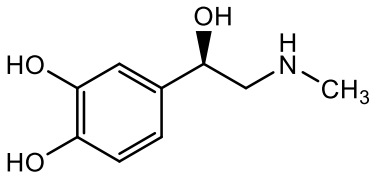
2. Norepinephrine (NE, Levophed)



Norepniphrine , Log P=-0.63

- Differs from DA only by addition of a 1-OH substituent (β-OH-DA) and from E only by lacking the N-methyl group
- Like DA, it is polar and rapidly metabolized by both COMT and MAO, resulting in poor oral bioavailability and short DOA (1 or 2 minutes even when given intravenously).
- It is a stimulant of α_1-, α_2-, and β_1-adrenoceptors (notice that lacking the N-methyl group results in lacking β_2- and β_3-activity).
- It is used to counteract various hypotensive crises, because its α-activity raises blood pressure and as an adjunct treatment in cardiac arrest because its β-activity stimulates the heart.

3. Epinephrine (E, Adrenalin)



Epinephrine , Log P= 0.28

- Differs from NE only by the addition of an N-methyl group.
- Like the other CAs, E is light sensitive and easily oxidized on exposure to air because of the catechol ring system.
- It lacks oral activity and has short DOA
- E is a potent stimulant of all α_1-, α_2-, β_1-, β_2-, and β_3- adrenoceptors, and thus it switches on all possible adrenergic receptors, leading to a whole range of desired and side effects.

✓ In general, greater β-activity caused by an additional N-methyl group. Therefore, E is used to stimulate the heart in cardiac arrest.

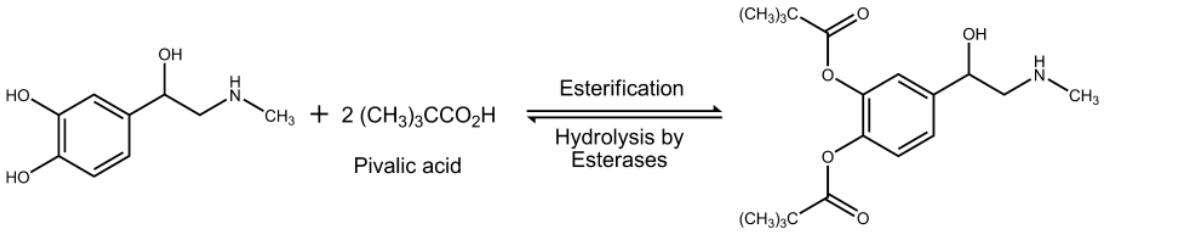
✓ The ability of epinephrine to stimulate β_2-receptors has led to its use by injection and by inhalation to relax bronchial smooth muscle in asthma and in anaphylactic reactions.

✓ It is also used in inhibiting uterine contraction.

✓ Because of its α-activity, E is used to treat hypotensive crises and nasal congestion, to enhance the activity of local anesthetics, and as a constrictor in hemorrhage.

✓ In addition, E is used in the treatment of open-angle glaucoma, where it apparently reduces intraocular pressure by increasing the rate of outflow of aqueous humor from the anterior chamber of the eye.

4. Dipivefrin (Propine, Dipivalyl Epinephrine)



Epinephrine (E)
catechol: easily oxidized
less lipophilic than dipivefrin
poor absorption and poor penetration of the eye
irritating to eyes when used in treatment of glaucoma

Dipivefrin: Ester and prodrug of E
Noncatechol: less easily oxidazied
more lipophilic than E
better absorption and penetration of the eye
less irritating to the eye than E

Dipivefrin is a prodrug of E that is formed by the esterification of the catechol OH groups of E with pivalic acid.

Advantages

1. Improved bioavailability, The greatly increased lipophilicity allows much greater penetrability into the eye through the corneal epithelial and endothelial layer.
2. Dipivefrin has 1-OH group and cationic nitrogen (the eye drops contain the hydrochloride [HCl] salt). This dual solubility permits much greater penetrability into the eye than the very hydrophilic E hydrochloride.
3. Increased DOA is also achieved because the drug is resistant to the metabolism by COMT.
4. Increased in vivo stability, it is also less easily oxidized by air due to the protection of the catechol OH groups.
5. Dipivefrin also offers the advantage of being less irritating to the eye than E.