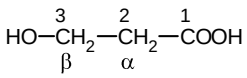
№ 30. CHARACTERISTICS OF THE HETEROFUNCTIONAL DERIVATIVES OF HYDROCARBONS. AMINOALCOHOLS, AMINOPHENOLS AND THEIR DERIVATIVES WITH MEDICO- BIOLOGICAL IMPORTANCE.

I. General considerations. **Functional groups.** A functional group (FG) is a part of larger molecule; it is composed of an atom or group of atoms that have a characteristic chemical behavior. The classification of organic compounds is based on the presence of such structural features as functional groups. Generally, a given functional group behaves in nearly the same way in every molecule it's part of. *The chemistry of every organic molecule, regardless of size and complexity, is determined by the functional groups it contains.*

Monofunctional derivatives of hydrocarbons are those that contain one functional group. Di- and polyfunctional derivatives of hydrocarbons contain two or more functional groups. They can be identical; then the nomenclature involves use of prefixes di-, tri-, tetra-, etc. If the functional groups *are different*, then the compound is *heterofunctional derivative* of a hydrocarbon, e.g. amino alcohols (not hydroxyamines according to the priority ranking of FG). Often the functional groups in a complex compound do not interfere with each other. In many cases, however, the functional groups influence each other resulting in rather altered reactivity. The chemical properties of a difunctional compound are often not the sum as of the properties of the monofunctional components, although there is similarity in qualitative aspect.

The IUPAC nomenclature for polyfunctional derivatives of hydrocarbons is based on the priority of substituents (substitutive nomenclature). The fundamental rule for naming such compounds is: "determine the kind of characteristic group to be cited as suffix (if any) or as a functional class name. Only one kind of characteristic group (known as the *principal group*) can be cited as suffix or functional class name. All substituents not so cited must be specified as prefixes." Some examples of often encountered, naturally occurring and biologically important difunctional compounds and their (FG) are: **amino alcohols** (NH_2, OH), **amino phenols** (NH_2, ArOH), **hydroxy acids** (OH, COOH), **formyl acids** (CHO, COOH), **keto acids** (=CO, COOH), **amino acids** (NH_2, COOH), and **carbohydrates** (OH, CHO, =CO). In order to name correctly a compound containing two different functional groups, one of the groups (the principal function) should be used suffix (ending) and the other - as a prefix, for example: 3-hydroxypropanoic acid is the correct class name - "carboxylic acid", because this FG has higher priority than hydroxyl FG (naturally, the name 2-carboxyethanol is incorrect).



3-hydroxypropanoic acid
β-hydroxypropionic acid

The general classes of compounds arranged in decreasing order of priority for choosing and naming a principal characteristic group are:

1	Zwitterionic compounds, ammonium
2	Acids (in the order COOH, C(O)O2H; then their sulfur derivatives followed by sulfonic and phosphonic acids)
3	Anhydrides
4	Esters
5	Acid halides
6	Amides
7	Nitriles
8	Aldehydes followed by thioaldehydes
9	Ketones followed by thioketones
10	Alcohols and Phenols followed by thiols
11	Amines
12	Ethers followed by sulfides
13	Peroxides followed by disulfides

Since alkenes and alkynes cannot be designated by prefixes, they are always indicated by a second suffix, which is placed before the final suffix of any FG that is higher in the order, e.g. 5-aminopent-3-enoic acid.

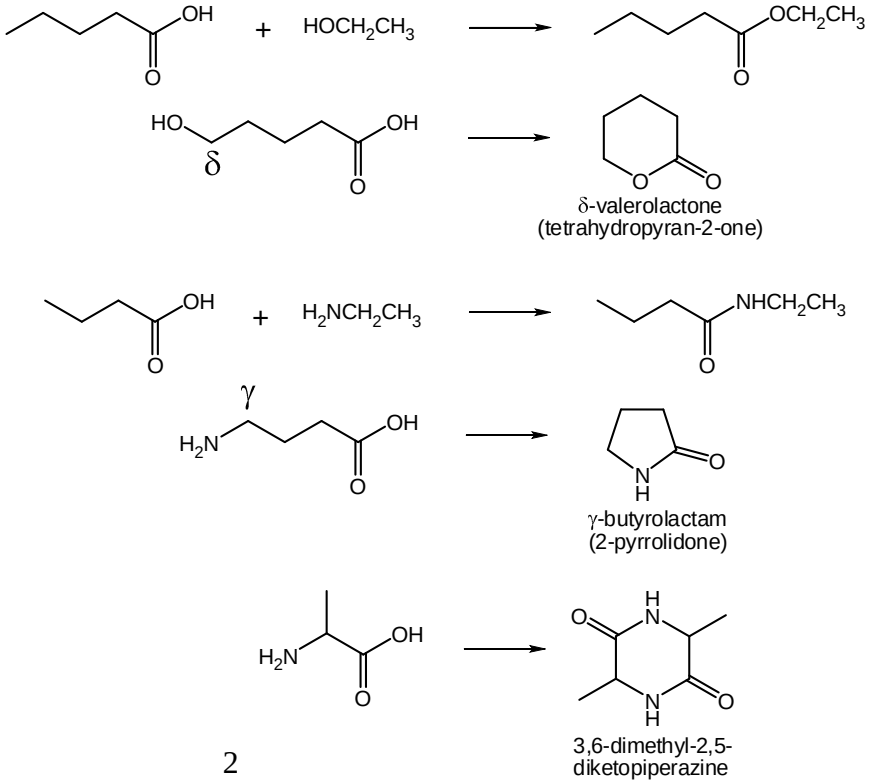
The following table contains a list of common functional groups with their appropriate prefix and suffix used to designate each one in a name of polyfunctional derivative.

Priority	Functional group	Formula	Prefix	Suffix
1	Cations		-onio-	-onium
	e.g. Ammonium	$–NH^{4+}$	ammonia-	-ammonium
2	Carboxylic acids	–COOH	carboxy-	-oic acid*
	Thiocarboxylic acids	–COSH	thiocarboxy-	-thioic acid*
	Sulfonic acids	$–SO_3H$	sulfo-	-sulfonic acid
3	*Carboxylic acid derivatives*			
	Esters	–COOR	R-oxycarbonyl-	-R-oate
	Acyl halides	–COX	halidealcanoyl-	-oyl halide*
	Amides	$–CONH_2$	carbamoyl-	-amide*
4	Nitriles	–CN	cyano-	-nitrile*
5	Aldehydes	–CHO	formyl-	-al*
	Thioaldehydes	–CHS	thioformyl-	-thial*
6	Ketones	>CO	oxo-	-one
	Thioketones	>CS	thiono-	-thione
7	Alcohols	–OH	hydroxy-	-ol
	Thiols	–SH	sulfanyl-	-thiol
8	Hydroperoxides	–OOH	hydroperoxy-	-hydroperoxide
9	Amines	$–NH_2$	amino-	-amine
	Imines	=NH	imino-	-imine
10	Ethers	–O–	-oxy-	
	Thioethers	–S–	-thio-	
11	Peroxides	–OO–	-peroxy-	
	Disulfides	–SS–	-disulfanyl-	

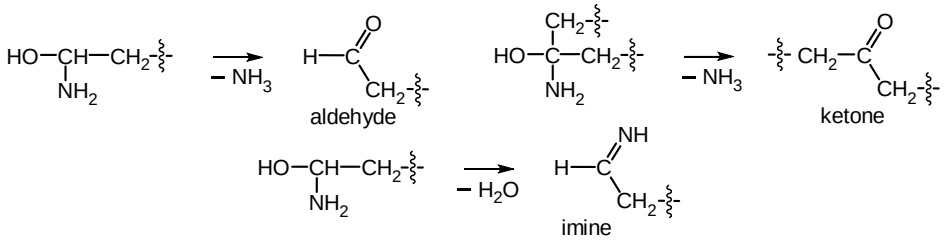
The highest precedence group takes the suffix, with all others taking the prefix form.

One fundamental difference in the reactivity of heterofunclional derivatives with regard to monofunctional is the possibility of **intramolecular reactions** in a heterofunctional compound. Some examples of formation of intramolecular ester, called lactone from hydroxy acid, and intramolecular amide, named lactam from amino acid are shown.

Formation of polymers is also possible with hetero-functional derivatives.

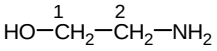


II. Amino alcohols Amino alcohols are organic compounds that contain both an amine functional group (NH_2) and an alcohol functional (OH) group. The mutual position of these groups is expressed by the terms geminal for 1,1-location, and vicinal for 1,2-location. Geminal (from Latin *gemini* = twins refers to the relationship between two functional groups that are attached to the same atom) amino alcohols are usually unstable, releasing ammonia to reverse the addition product to aldehyde or ketone. Dehydration of a 1,1-amino alcohol produces an imine (Schiff's base).

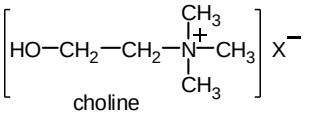


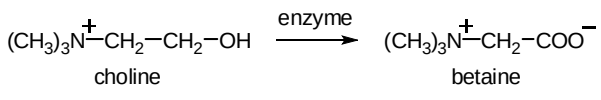
Vicinal (from Latin *vicinus* = neighbor stands for any two functional groups bonded to two adjacent carbon atoms) amino alcohols are stable and abundant.

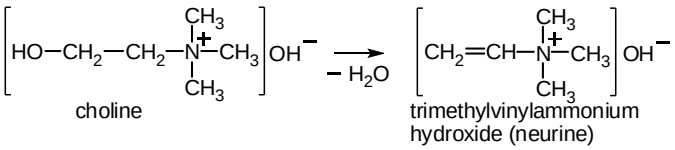
Representatives: **a) 2-aminoethanol** (more often called **Ethanolamine** (ETA) or monoethanolamine (MEA) is both a primary amine and a primary alcohol. The common trivial name usage is justified by the existence of diethanolamine (secondary amine) and triethanolamine (tertiary amine). Like other amines, monoethanolamine acts as a weak base. Ethanolamine is a toxic, flammable, corrosive with an odor similar to that of ammonia. It can form simple esters and ether as well as derivatives of the NH_2 group. Ethanolamine is the second-most-abundant head group for phospholipids, substances found in biological membranes. It is part of cephalins (complex lipids) via ester group with phosphoric acid.



b) Choline is a quaternary saturated ammonium salt where X^- is a counterion such as chloride, hydroxide or tartrate. It is classified as a water-soluble essential nutrient and usually grouped within the Vitamin B complex. Sources with high contents of choline are egg yolks, soy, wheat germ and cooked beef, chicken, veal and turkey livers. Choline and its metabolites are needed for three main physiological purposes: structural integrity and signaling roles for cell membranes (as component of complex lipids named lecithins), cholinergic neurotransmission (acetylcholine synthesis), and as a major source for methyl groups via its metabolite, trimethylglycine (**betaine** (TMG), obtained by humans from foods, either as betaine or choline-containing compounds). Betaine is product of enzymatic oxidation of choline *in vivo.*

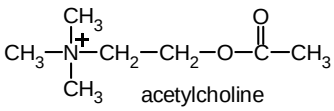


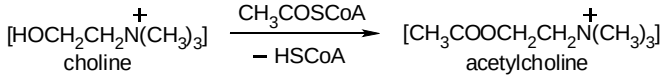




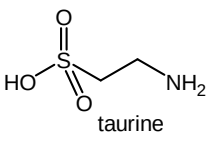
Intramolecular dehydration of choline during putrefaction (decomposition of animal proteins, especially by anaerobic microorganisms) leads to neurine (trimethylvinylammonium hydroxide) which is poisonous.

Acetylcholine (abbreviated ACh) is ester of choline with acetic acid. Acetylcholine is a neurotransmitter in both the peripheral nervous system (PNS) and central nervous system (CNS) in many organisms including humans.

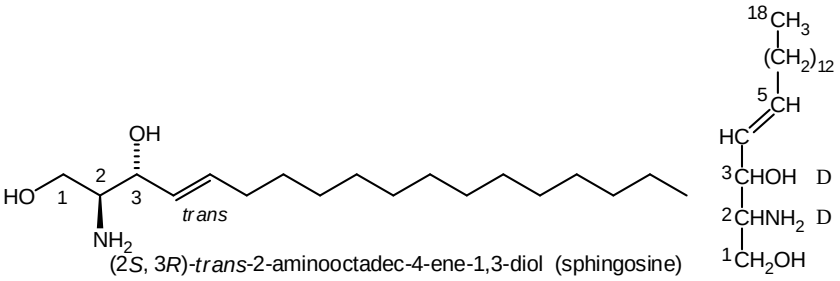




c) Taurine (2-aminoethanesulfonic acid, $H_2NCH_2CH_2SO_3H$) is a major constituent of bile and can be found in the lower intestine and in small amounts in the tissues of many animals and in humans as well. Taurine participates in the formation of conjugated bile acids. Taurine is one of the few known naturally occurring sulfonic acids.

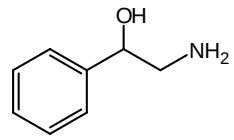


d) Sphingosine (2-amino-4-octadecene-1,3-diol) is an 18-carbon amino diol with an unsaturated hydrocarbon chain, which forms a primary part of sphingolipids, a class of cell membrane lipids that include sphingomyelin, an important phospholipid .



(2*S*, 3*R*)-*trans*-2-aminooctadec-4-ene-1,3-diol (sphingosine)

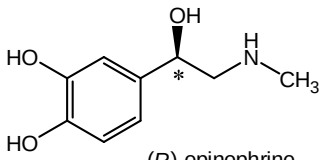
III. Representative physiologically active amino alcohols and amino phenols. 1. Natural.



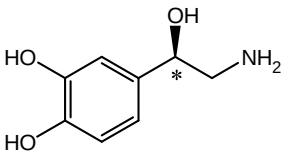
1-phenyl-2-aminoethanol
(β-phenylethanolamine)

1-Phenyl-2-aminoethanol (β-phenylethanolamine) is a simple amino alcohol found in the brain. Numerous derivatives of this basic structure are adrenal glands hormones or adrenergic drugs which either stimulate a response (agonists) or inhibit a response (antagonists). The Latin roots ***ad- + renes*** and the Greek roots ***epi- + nephros*** both literally mean "on/to the kidney" (referring to the adrenal gland, which sits atop the kidneys and secretes epinephrine).

a) Epinephrine (also called **adrenaline**) is a hormone and neurotransmitter. (Hormones are chemicals released by cells that affect cells in other parts of the body. Only a small amount of hormone is required to alter cell metabolism. It is essentially a chemical messenger that transports a signal from one cell to another. Hormones in animals are often transported in the blood.) Epinephrine increases the "fight or flight" response of the sympathetic division of the autonomic nervous system. It is a catecholamine, containing one chiral center – the natural (-) enantiomer is more active than (+). Playing a central role in the short-term stress reaction, epinephrine is released from the adrenal glands when danger threatens or in an emergency, hence an “Adrenaline rush” and the expression “get the adrenaline flowing”. Such triggers may be threatening, exciting, or environmental stressor conditions (high noise levels, or bright light and high ambient temperature). Epinephrine is used as a drug to treat cardiac arrest and other cardiac dysarhythmias.



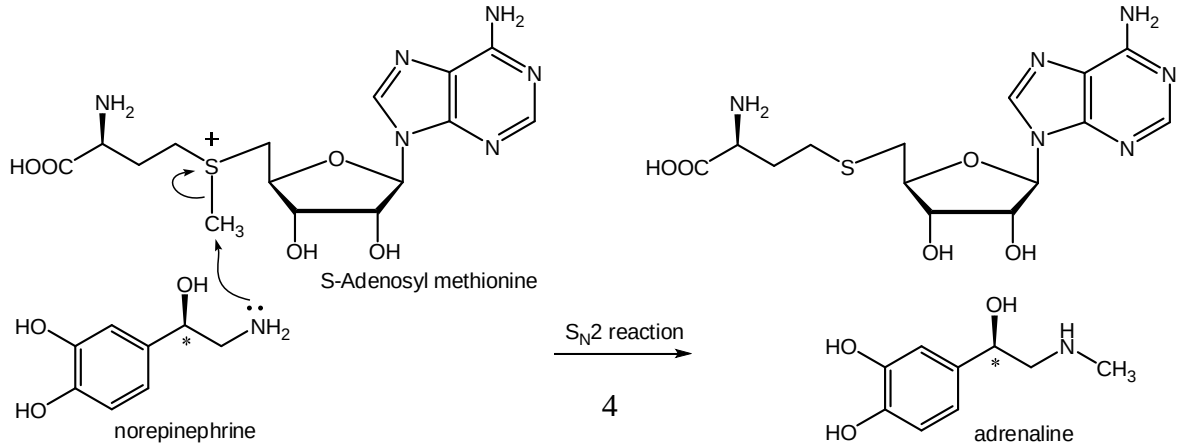
(*R*)-epinephrine
(adrenaline)



(*R*)-norepinephrine

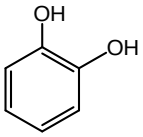
When in the bloodstream, epinephrine rapidly prepares the body for action in emergency situations. The hormone boosts the supply of oxygen and glucose to the brain and muscles, while suppressing other non-emergency bodily processes (digestion in particular). Similar action has norepinephrine. (In the chemical nomenclature, *nor*- refers to one methylene group shorter and *homo*- refers to one methylene group longer.)

b) Norepinephrine is a catecholamine with dual roles as a hormone and a neurotransmitter. As a stress hormone, norepinephrine affects parts of the brain where attention and responding actions are controlled. Along with epinephrine, norepinephrine also underlies the “fight-or-flight” response, directly increasing heart rate, triggering the release of glucose from energy stores, and increasing blood flow to skeletal muscle, thus preparing the body to respond to the threat. Cat and dog example: these animals show body arching, hair standing on end, pupil dilation when threatened. Both adrenaline and norepinephrine are secreted by the adrenal gland, and therefore, are called adrenergic agents.

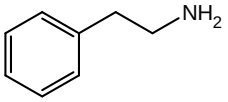


Adrenaline is obtained biochemically by a simple methylation reaction. Such reaction is the transfer of a methyl group from an electrophilic donor to a nucleophile which, in this case, is the nitrogen atom in norepinephrine. *S*-Adenosyl methionine is a coenzyme involved in methyl group transfers. Since the sulfur atom has a positive charge (a sulfonium ion), it is an excellent leaving group for S_N2 displacements on the methyl (activated group) carbon (see also above - betaine).

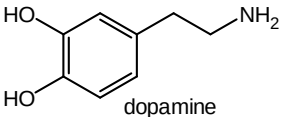
Catecholamines as a class of compounds are based on catechol (1,2-dihydroxybenzene). Physiologically active catecholamines combine also a residue from β-phenylethylamine. The most abundant catecholamines are epinephrine (adrenaline), norepinephrine (noradrenaline) and **dopamine**, all of which are produced *in vivo* from phenylalanine and tyrosine. Catecholamines are water-soluble and are mostly bound to plasma proteins, so they circulate in the bloodstream. Epinephrine and norepinephrine cause general physiological changes that prepare the body for physical activity (response to stress). Some typical effects are increases in heart rate, blood pressure, blood glucose levels, and a general reaction of the sympathetic nervous system.



catechol

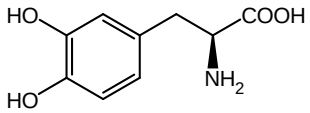


phenethylamine



dopamine
(a catecholamine)

c) Dopamine is a neurotransmitter occurring in the brain of wide variety of animals, including both vertebrates and invertebrates. Dopamine is produced in several areas of the brain and is also a neurohormone released by the hypothalamus. Dopamine is commonly associated with the pleasure system of the brain, providing feelings of enjoyment and reinforcement to motivate a person to perform certain activities. Dopamine administered by *IV* dilates blood vessels, increasing blood flow to renal and coronary arteries; therefore has a diuretic effect.

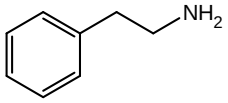


L-DOPA

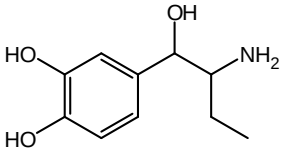
Levodopa (**L-DOPA**, 3,4-dihydroxy-L-phenylalanine) is a naturally occurring amino acid (but non-proteinogeneic) found in food and made from L-tyrosine in the human body. L-DOPA is converted into dopamine in the brain and body. L-DOPA is also used in the clinical treatment of Parkinson's disease.

Adrenaline, noradrenaline and dopamine can be considered also as biogenic amines.

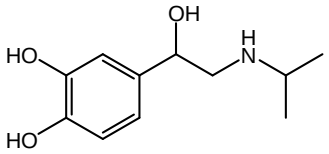
2. Synthetic physiologically active amino alcohols. Synthetic, substituted *phenethylamines* are a broad and diverse class of compounds that *include stimulants, hallucinogens, entactogens* (feeling of empathy, being sensitive), *anorectics* (reducing appetite), *bronchodilators*, and *antidepressants*.



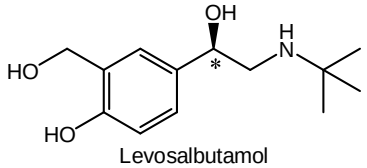
phenethylamine



ethylnorepinephrine



isoproterenol



Levosalbutamol
(racemic: salbutamol, albuterol)

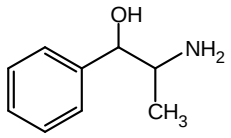
Ethylnorepinephrine is an old bronchodilator, used as HCl salt in treatment of bronchial asthma.

Isoproterenol (Isoprenaline) is a sympathomimetic beta adrenergic agonist medication. It is structurally similar to epinephrine (adrenaline) but acts selectively on beta receptors, activating β_1 and β_2 receptors equally. Its primary use is for bradycardia (heart's beat below 50 beat/min) or heart block.

(*An agonist produces an action. An antagonist blocks an action of an agonist.*)

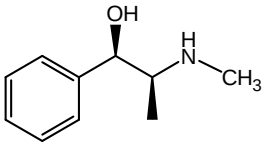
Salbutamol (or albuterol) is a short-acting β_2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease. Salbutamol was the first selective β_2-receptor agonist to be marketed. With this instant success drug and isoproterenol we enter the realm (domain) of trade names of medications. Often physicians should know several trade names and synonyms of the same compound in order to write prescriptions.

Phenylpropanolamine is a fragment in drugs (when such fragment in several physiologically active substances is associated with their action, it is called pharmacophore) of the phenethylamine family used as decongestant in prescription and nonprescription cough and cold, and sinus remedies, and some combination allergy medications.

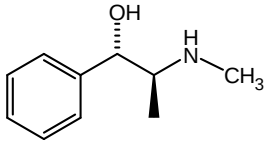


1-phenyl-2-aminopropanol
(phenylpropanolamine)

Ephedrine is an alkaloid and sympathomimetic amine commonly used as a stimulant, appetite suppressant, mental concentration aid, decongestant, and to treat hypotension associated with anesthesia.

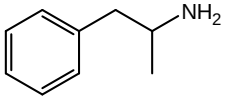


ephedrine

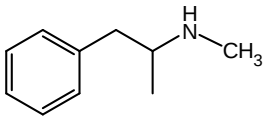


pseudoephedrine

Pseudoephedrine is a diastereomer of ephedrine and is also used as a decongestant (commonly in combination with antihistamines, paracetamol (acetaminophen) and/or ibuprofen). Unlike antihistamines, which modify the systemic histamine-mediated allergic response, pseudoephedrine only relieves nasal congestion commonly associated with colds or allergies. (*Notice*: diastereomer *vs*. enantiomer; the diastereomeric pseudoephedrine has identical constitution with ephedrine, and identical configuration of the α-center, but opposite configuration of β-carbon.)



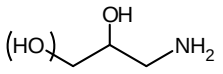
amphetamine



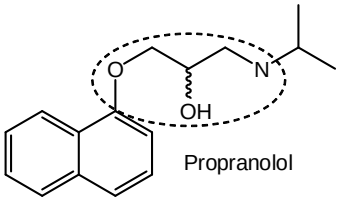
methamphetamine

Amphetamine is a psychostimulant drug which is known to produce increased wakefulness and focus in association with decreased fatigue and appetite. Dexedrine is the (+)-enantiomer. Common street names in illegal sales of amphetamine include "speed", "crank", and "whizz". **Methamphetamine** is a psychostimulant and sympathomimetic drug. The (-)-(*R*)-enantiomer is an over-the-counter drug and is used in inhalers for nasal decongestion, and does not possess the CNS activity of dextro or racemic methamphetamine. The (+)-(S)-enantiomer can be prescribed to treat attention-deficit hyperactivity disorder. Methamphetamine is a potent CNS stimulant affecting neurochemical mechanisms responsible for regulating heart rate, body temperature, blood pressure, appetite, attention, mood and responses associated with alertness or alarm conditions. The acute effects of the drug closely resemble the physiological and psychological effects of an epinephrine-provoked response (increased heart rate and blood pressure, bronchodilation, and increased blood sugar). Users experience an increase in mental focus, increased mental alertness, and the elimination of fatigue, as well as a decrease in appetite. For these properties methamphetamine is used illegally. Nicknames for illegal sales of methamphetamine include "crank", "meth", "ice", "crystal", "glass". Methamphetamine addiction typically occurs when a person begins to use it because of its powerful enhancing effects on mood and energy, weight loss and appetite suppression, among its other psychological and physical effects. Over time effectiveness decreases, and users find that they need to take higher doses to get the same results.

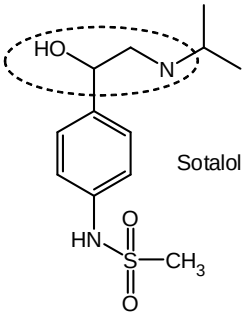
1-Amino-2-propanol or 3-amino-1,2-propanediol fragment is found in many drugs. Noticeably among them are the modern β-blockers. *Beta blockers* (β-blocker) are a class of drugs used for various indications, but particularly *for the management of cardiac arrhythmias, cardioprotection after myocardial infarction (heart attack), and hypertension.*



1-amino-2-propanol
(3-amino-1,2-pronanediol)



Propranolol

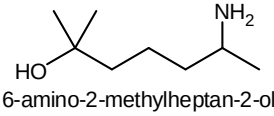


Sotalol

Non-selective β-blockers are Nadolol, Timolol, and Propranolol which was the first clinically useful beta adrenergic receptor antagonist.

Sotalol is an antiarrhythmic agent because it inhibits the potassium ion channels in the heart. It is also a beta blocker drug.

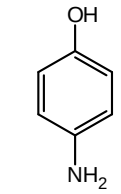
Heptaminol is an amino alcohol which is classified as a vasodilator (widening of blood vessels agent, like ethanol). It is



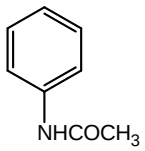
6-amino-2-methylheptan-2-ol

sometimes used in the treatment of low blood pressure.

IV. *p*-Aminophenol and its derivatives. Derivatives of *p*-aminophehol are among the first analgesic drugs (also known as painkiller), which form a diverse group of drugs used to relieve pain (achieve *analgesia*). The word *analgesic* derives from Greek *an-* ("without") and *algos* ("pain").



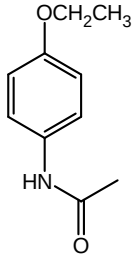
p-aminophenol



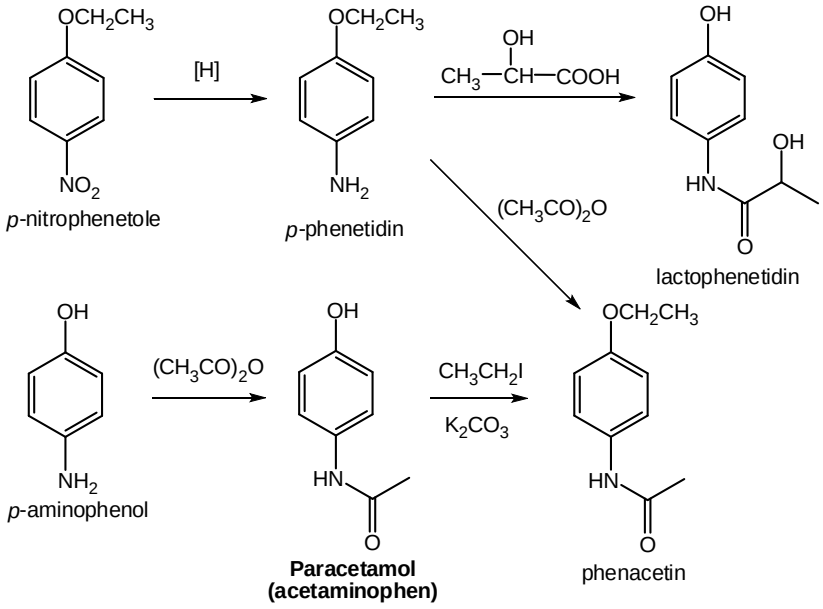
acetanilide

Acetanilide was the first aniline derivative serendipitously found to possess analgesic as well as antipyretic properties, and was quickly introduced into medical practice in 1886. But its unacceptable toxic effects prompted the search for less toxic aniline derivatives. *Antipyretic* (literally "against the fire") are drugs that reduce body temperature in situations such as fever) substances.

Phenacetin, introduced in 1887, was used principally as an analgesic, and was one of the first synthetic fever reducers to go on the market. It is also known historically to be the first analgesic without anti-inflammatory properties. Recently, its use as an analgesic has declined due to its association with several adverse side effects. A popular brand of phenacetin was Saridon® (Roche), which was reformulated (without phenacetin) in 1983 to contain propyphenazone, paracetamol and caffeine.



phenacetin



p-nitrophenetole

p-phenetidin

lactophenetidin

p-aminophenol

Paracetamol (acetaminophen)

phenacetin

Paracetamol or **acetaminophen** is a widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer). It is commonly used for the relief of fever, headaches, and other minor aches and pains, and is a major ingredient in numerous cold and flu remedies. In combination with **n**on-**s**teroidal **a**nti-**i**nflammatory **d**rugs (NSAID) or opioid analgesics, paracetamol is used also in the management of more severe pain (such as cancer pain). Both phenacetin and acetaminophen (it is the active metabolite of phenacetin) are *effective alternatives to aspirin*. In recommended doses, paracetamol does not irritate the lining of the stomach, affect blood coagulation as much as NSAIDs, or affect function of the kidneys. *Acetaminophen is well tolerated and lacks significant side effects*. Many formulations are available under various trade names (synonyms).