Pharmaceutical Chemistry I – Laboratory Experiments and Commentary

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Preface

Pharmaceutical Chemistry summarizes the knowledge of synthesis, pharmacopoeial qualification and mechanism of action of the most important active pharmaceutical ingredients. The educational program of this integrated subject covers introduction of physiso-chemical basis of action and structure-activity relationship of the most important classes of medicines as well as Pharmacopoeial analysis of selected inorganic and organic substances including active pharmaceutical ingredients and excipients.

The present educational material has been compiled to introduce the most frequently used chemical methods (such as Identifications, Limit tests, and Assay) described in the 8th edition of the Hungarian Pharmacopoeia (Ph. Hg. VIII.), which is an official translation of the current, 8th edition of the European Pharmacopoeia (Ph. Eur. VIII.). The experiments described in the text are collected for pharmacy students who are in the introductory phase of their Pharmaceutical Chemistry studies. The description of the experiments are those of the 8th edition of the Hungarian Pharmacopoeia (Ph. Hg. VIII.), which are completed by comments and chemical equations to help students understanding the molecular basis of the methods. In addition, a brief chemical characterization of the most important groups of organic compounds is also provideol.

The editors express their special thank to Professor László Lázár (Albert Szent-Györgyi University, Szeged, Hungary) for his valuable comments and suggestions to improve the quality of the present educational material.

The module structure of the educational material provides the possibility to introduce new topics, new experiments, demonstrations and calculation problems in the future. Suggestions in relation to such extensions are welcome by the editors. Similarly, the editors are pleased to accept any proposal that improve the text.

March 31, 2014

The editors

I Laboratory safety and accident protection

I.1 Laboratory safety guidelines

I.1.1 Laboratory safety

When working in a chemical laboratory we handle several chemicals with more or less adverse effects to human health, and we perform experiments that have a number of potential hazards associated with them. Thus, a chemical laboratory can be a dangerous place to work in. With proper care and circumspection, strictly following all precautionary measures, however, practically all accidents can be prevented!

It is the prevention of accidents and damages posed by the speciality of the chemical laboratory experiments that requires you to follow the instructor's advice as well as keep the laboratory order during work in the laboratory. You should never forget that your carelessness or negligence can threaten not only your own safety but that of your classmates working around you!

This section has guidelines that are essential to perform your experiments safely, without accidents.

I.1.1.1 Preparation in advance

a) *Read through the descriptions of the experiments carefully!* If necessary, do study the theoretical background of the experiments from your textbook(s). After understanding, write down the outline of the experiments to be performed in your laboratory notebook. If any item is still unclear, do ask your instructor before starting work.
b) *Prepare your notebook before the laboratory practice!* Besides description of the outline of the experiments, preliminary preparation should also include a list of the work you did prior to the start of practical work.

I.1.1.2 Laboratory rules

a) The laboratory instructor is the first to enter and the last to leave the laboratory. Before the instructor's arrival students must not enter the laboratory.
b) Always wear laboratory coat and shoes in the laboratory. Sandals and open-toed shoes offer inadequate protection against spilled chemicals or broken glass.
c) Always maintain a disciplined attitude in the laboratory. Careless acts are strictly prohibited. Most of the serious accidents are due to carelessness and negligence.
d) Never undertake any unauthorised experiment or variations of those described in the laboratory manual.
e) Maintain an orderly, clean laboratory desk and cabinet. Immediately clean up all chemical spills from the bench and wipe them off the outer surface of the reagent bottles with a dry cloth.
f) Smoking, drinking, or eating is not permitted during the laboratory practice. Do not bring other belongings than your notebook, stationery, and laboratory manual into the laboratory. Other properties should be placed into the locker at the corridor.
g) Be aware of your bench neighbours' activities. If necessary, warn them of improper techniques or unsafe manipulation.

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h) At the end of the laboratory session, completely clean all glassware and equipment, and clean them with a dry cloth. After putting back all your personal labware into your cabinet, lock it carefully.
i) Always wash your hands with soap before leaving the laboratory.

I.1.1.3 Handling chemicals and glassware

a) At the beginning of the laboratory practices the instructor holds a short introduction when all questions related to the experimental procedures can be discussed.
b) Perform each experiment alone. During your work always keep your laboratory notebook at hand in order to record the results of the experiments you actually perform.
c) Handle all chemicals used in the experiments with great care. Never taste, smell, or touch a chemical or solution unless specifically directed to do so.
d) Avoid direct contact with all chemicals. Hands contaminated with potentially harmful chemicals may cause severe eye or skin irritations.
e) Reactions involving strong acids, strong bases, or chemicals with unpleasant odour should be performed under the ventilating hood. If necessary, safety glasses or goggles should be worn.
f) When checking the odour of a substance, be careful not to inhale very much of the material. Never hold your nose directly over the container and inhale deeply.
g) When performing an experiment, check the label on the bottle twice to make sure that you use the correct reagent. *The wrong reagent can lead to accidents or "inexplicable" results in your experiments*.
h) Do not use a larger amount of reagents than the experiment calls for. *Do not return any reagent to a reagent bottle!* There is always the chance that you accidentally pour back some foreign substance which may react with the chemical in the bottle in an explosive manner.
i) Do not insert your own pipette, glass rod, or spatula into the reagent bottles; you may introduce impurities which could spoil the experiment for the person using the stock reagent after you.
j) Always mix reagents slowly. Pour concentrated solutions slowly and stirring it continuously into water or into a less concentrated solution. *This is especially important when diluting concentrated sulphuric acid*.
k) Discard waste or excess chemicals as directed by your laboratory instructor!
l) Using clean glassware is the basic requirement of any laboratory work. Clean all glassware with a test-tube brush and a detergent, using tap water. Rinse first with tap water and then with distilled water. If dry glassware is needed, dry the wet one in drying oven, or rinse with acetone and air dry it.

I.1.2 Accident prevention, fire safety and first aid

I.1.2.1 Accident prevention and fire safety

a) Before starting the experiments make sure all the glassware are intact. Do not use cracked or broken glassware. If glassware breaks during the experiment, the chemical spill and the glass splinters should be cleaned up immediately. Damaged glassware should be replaced from the stock laboratory.
b) Fill the test-tube with not more than 4-5 cm^3 of reactants. *As you are performing the experiments, do not look into the opening of the test-tube and do not point it at anyone*. If you want to check the odour of a substance formed in a test-tube reaction, waft the vapours from the mouth of the test-tube toward you with your hand.
c) Before heating glassware make sure that its outer wall is dry. Wet glassware can easily break on heating. When heating liquids in a test-tube, hold it with a piece of tightly folded strip of paper or a test-tube holder.
d) When heating liquids in an Erlenmeyer flask or in a beaker, support the glassware on wire gauze placed on an iron tripod, and put a piece of boiling stone into the liquid to prevent bumping. Start heating with a law flame and intensify it gradually.
e) When lighting the Bunsen burner, close the air-intake holes at the base of the burner, open the gas cock of the outlet, and bring a lighted match to the mouth of the burner tube until the escaping gas at the top ignites. (It is advantageous to strike the match first and then open the gas cock.) After it ignites, adjust the air control until the flame is pale blue and the burner produces a slight buzzing sound.
f) If the Bunsen burner "burns in", which can be noticed from its green flame and whistling (whizzing) sound, the gas cock of the outlet should be turned off immediately. Allow the burner to cool, and light it again as described above.
g) When using an electric heater or other electric device, do not touch them with wet hands and prevent liquids from spilling over them. If it accidentally happens (e.g. a flask cracks on heating), unplug the device immediately and wipe off the liquid with a dry cloth.
h) As a general rule, a flame should be used to heat only aqueous solution. *When working with flammable organic solvents* (e.g. hexane, diethyl ether, petroleum ether) *use of any open flame in the laboratory is prohibited!* A hot water bath can be effectively used to heat these solvents. The vapours of the flammable substances may waft for some distance down their source; thus presenting fire danger practically in the whole laboratory.
i) Never blow the fire. This way you might turn the fire up and the flame can shoot into your face. *Do not use water to smother fires caused by water-immiscible chemicals (e.g. benzene) and alkali metals. Pouring water on a plugged electric device is also prohibited.*
j) If your clothing catches fire, you can smother the flames by wrapping yourself in a wet towel or a laboratory coat.
k) In case of a smaller fire (e.g. a few cm^3 of organic solvent burning in a beaker or an Erlenmeyer flask), it can be extinguished by placing a watch glass over the mouth of the flask. In case of a bigger fire and more serious danger, use the fire extinguisher fixed on the wall of the laboratory. At the same time alarm the University Fire Fighter Office by calling the N 2785 from the corridor or from the stock lab.

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l) In case of fire in the laboratory the main gas cock and the electric switch of the laboratory should be turned off immediately. (They are located in the corridor on the outer wall of the laboratory.) Besides fighting the fire, start giving first aid to the injured immediately.

I.1.2.2 Firs aid

a) In case of an accident or injury, even if it is minor, notify your laboratory instructor at once. The urgent first aid is an absolute must for the prevention of more serious adverse health effects.
b) Minor burns caused by flames or contact with hot objects should be cooled immediately by flooding the burned area with cold water, then treating it with an ointment. Severe burns must be examined by a physician.
c) In case of a cut, remove the contamination and the glass splinters from the wound. Disinfect its boundary with alcoholic iodine solution and bind it up with sterile gauze. In case of severe cases the wound should be examined and treated by a physician.
d) Whenever your skin gets into contact with chemicals, wash it quickly and thoroughly with water. In case of chemical burns, the chemical should be neutralized. For acid burns, the application of a *dilute solution of sodium hydrogen carbonate*, for burns by alkali, the application of a *dilute solution of boric acid* is used. After neutralization, wash the affected area with water for 5-10 minutes and apply an appropriate ointment if necessary.
e) *Concentrated sulphuric acid dripped onto your skin must be wiped away with a dry cloth*. Then the affected area should be treated as described for acid burns above.
f) Acids splashed onto your clothes could be neutralized with diluted solution of ammonia or sodium hydrogen carbonate.
g) If any chemical gets into your mouth, spit it out immediately, and wash your mouth well with water.
h) If any chemical enters your eyes, immediately irrigate the eyes with large quantities of water. *In case of any kind of eye damage consult a physician immediately.*
i) In case of inhalation of toxic chemicals the injured should be taken out to fresh air as soon as possible.
j) In case of an electric shock, the immediate cut-off of the electric current supply of the laboratory (main switch) is the most important step to avoid irreversible health damage. The injured should get medical attention as soon as possible. If necessary, artificial respiration should be given until the physician arrives.

II Units of measurements

A *physical quantity* is the product of a numerical value and a unit of measurement. The same physical quantity can be measured by different units of measurements. The International System of Units (Système International d'Unités) is a standard metric system of units adopted for official scientific use. The system has been adopted by most countries in the developed (OECD) world, though within English-speaking countries (e.g., The United Kingdom, The United States), the adoption has not been universal.

There are three classes of SI units:

(a) seven *base units* that are regarded as dimensionally independent;

(b) two *supplementary, dimensionless units* for plane and solid angles; and

(c) *derived units* that are formed by combining base and supplementary units in algebraic expressions; such derived units often have special names and symbols and can be used in forming other derived units.

1. **Base units of the SI system**

   There are seven base units, each representing, by convention, different kinds of physical quantities.

Quantity name	Quantity symbol	Unit name	Unit symbol
length	l (small letter L)	metre	m
mass	m	kilogram	kg
time	t	second	s
electric current	I (capital i)	ampere	A
thermodynamic temperature	T	kelvin	K
amount of substance	n	mole	mol
luminous intensity	I_v	candela	cd

Definition of base units of the SI system

1. The metre is the length of the path travelled by light in vacuum during a time interval of 1/299 792 458 of a second.
2. The kilogram is the unit of mass; it is equal to the mass of the international prototype of the kilogram.
3. The second is the duration of 9 192 631 770 periods of the radiation corresponding to the transition between the two hyperfine levels of the ground state of the caesium 133 atom.
4. The ampere is that constant current which, if maintained in two straight parallel conductors of infinite length, of negligible circular cross-section, and placed 1 metre apart in vacuum, would produce between these conductors a force equal to $2 \cdot 10^{-7}$ newton per metre of length.
5. The kelvin, unit of thermodynamic temperature, is the fraction 1/273.16 of the thermodynamic temperature of the triple point of water.

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6. The mole is the amount of substance of a system which contains as many elementary entities as there are atoms in 0.012 kilogram of carbon 12; its symbol is “mol.” When the mole is used, the elementary entities must be specified and may be atoms, molecules, ions, electrons, other particles, or specified groups of such particles.
7. The candela is the luminous intensity, in a given direction, of a source that emits monochromatic radiation of frequency $540 \cdot 10^{12}$ hertz and that has a radiant intensity in that direction of 1/683 watt per steradian.

2. **Supplementary units of the SI system**

Quantity name	Quantity symbol	Expression in terms of SI base units	Unit name	Unit symbol
plane angle	α, β, γ….	$m \cdot m^{-1}$	radian	rad
solid angle	Ω, ω	$m^2 \cdot m^{-2}$	steradian	sr

3. **Derived units of the SI system**

Derived units are expressed algebraically in terms of base units or other derived units. The symbols for the derived units are obtained by means of the mathematical operations of multiplication and division. For example, the derived unit for the derived quantity molar mass (mass divided by amount of substance) is the kilogram per mole, symbol kg/mol. Some derived units have special names and symbols. For example, the SI unit of frequency is specified as the hertz (Hz) rather than the reciprocal second (s^{-1}), and the SI unit of moment of force is specified as the newton meter ($N \cdot m$) rather than the joule (J).

The most important derived units used in the Pharmacopoeia as it follows:

Quantity name	Quantity symbol	Expression in terms of SI base units	Unit name	Unit symbol
Wavenumber	ν	m^{-1}	reciprocal metre	1/m
Wavelength	l	10^{-6} m	micrometre	mm
		10^{-9} m	nanometre	nm
Area	A, S	m^2	square metre	m^2
Volume	V	m^3	cubic metre	m^3
Frequency	ν	s^{-1}	hertz	Hz
Density, mass density	ρ	$kg \cdot m^{-3}$	kilogram/cubic-metre	$kg \cdot m^{-3}$
Force, weight	F	$m \cdot kg \cdot s^{-2}$	newton	N
Pressure, stress	p	$m^{-1} \cdot kg \cdot s^2$	Pascal	Pa
Dynamic viscosity	η	$m^{-1} \cdot k \cdot s^{-1}$	Pascal second	$Pa \cdot s$
Kinematic viscosity, diffusion coefficient	ν	$m^2 \cdot s^{-1}$	square metre/ second	m^2/s

Quantity name	Quantity symbol	Expression in terms of SI base units	Unit name	Unit symbol
Voltage, electrical potential difference	U	$m^2 \cdot kg \cdot s^{-3} \cdot A^{-1}$	volt	V
Electrical resistance	R	$m^2 \cdot kg \cdot s^{-3} \cdot A^{-2}$	ohm	Ω
Electric charge	Q	$A \cdot s$	coulomb	C
Molar concentration	c	$mol \cdot m^{-3}$	mole/cubic metre	mol/m^3
Mass concentration	ρ	$kg \cdot m^{-3}$	kilogram/cubic metre	kg/m^3

4. **Decimal multiples and submultiples of SI units: SI prefixes**

Te SI prefixes are used to form decimal multiples and submultiples of units. The prefix name attached directly to the name of the unit, and a prefix symbol attaches directly to the symbol of a unit.

Prefix	Factor	Symbol	Prefix	Factor	Symbol
deci-	10^{-1}	d	deca-	10^{1}	da
centi-	10^{-2}	c	hecto-	10^{2}	h
milli-	10^{-3}	m	kilo-	10^{3}	k
micro-	10^{-6}	μ	mega-	10^{6}	M
nano-	10^{-9}	n	giga-	10^{9}	G
piko-	10^{-12}	p	tera-	10^{12}	T
femto-	10^{-15}	f	peta-	10^{15}	P

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III Chemical nomenclature

The primary aim of the chemical nomenclature is to provide methodology for assigning descriptors (names and formulae) to chemical species so that they can be identified without ambiguity.

The first level of nomenclature, beyond the assignment of totally trivial names, gives some systemic information about the substance but does not allow the inference of its composition (e.g., sulphuric acid, perchloric acid).

When a name itself allows the inference of the stoichiometric formula of a compound according to general rules, it becomes truly systemic. Only a name of this kind of nomenclature becomes suitable for retrieval purposes.

The first systematic nomenclature of inorganic compounds was Guyton's system, extended by the contributions of Lavoisier, Berthollet and de Fourcoy.

When the atomic theory was developed to the point where it was possible to write specific formulae for the various oxides and their binary compounds, then names reflecting composition more or less accurately became common. As a number of inorganic compounds rapidly grew, the essential pattern of nomenclature was little altered until near the end of the 19th century.

In 1892 a conference in Geneva laid the basis for an internationally accepted system of organic nomenclature, but at that time there was nothing comparable for inorganic nomenclature. Thus, many ad hoc systems had developed for particular rather than general purposes („*Geneva nomenclature*").

The need for uniform practice was recognized at about the end of the 19th century. In 1921, the International Union of Pure and Applied Chemistry (IUPAC) appointed commissions on the nomenclature of inorganic, organic and biological chemistry. The first comprehensive report („*the Red Book*") of the inorganic commission was issued in 1940 followed by revisions in 1958 and 1971. In 1990 the IUPAC recommendations were again fully revised in order to bring together the various changes which occurred in the previous years. The committees continue their work to this day.

Since the Geneva nomenclature is still in use for some inorganic compounds, this chapter introduces both nomenclature systems.

III.1 Classification of matter

All materials, such as air, water, rocks, as well as plant and animal substances consist of matter. *Matter* is the general term for the material things around us and may be defined as whatever occupies space and has mass. All things we can see, touch or use are made of matter.

According to its chemical constitution, a material is either a *substance* or a *mixture*. A substance is a homogeneous material consisting of one particular kind of matter. A mixture is a material that can be separated by physical means into two or more substances.

A *substance* is a kind of matter that cannot be separated into other kinds of matter by any physical process. Substances can be classified into two classes. These are *elements* (e.g., hydrogen and oxygen) and c*ompounds* (e.g., water). We can transform elements into compounds with chemical change (reactions). A chemical change, or chemical reaction, is a change in which different substances with new properties are formed.

Mixtures can also be classified into two types. They are homogeneous and heterogeneous mixtures. *Heterogenous mixtures* are mixtures that consist of physically distinct parts with different properties. Salt and sand (or sand and water) that have been stirred together comprise a heterogeneous mixture.

Homogenous mixtures (also known as *solutions*) are mixtures that are uniform in their properties throughout. When sodium chloride or sugar is dissolved in water, we obtain a homogeneous mixture, or solution. Air is a gaseous solution, principally of two elementary substances, nitrogen and oxygen, which are physically mixed but not chemically combined.

A *chemical change*, or *chemical reaction*, is a change in which one or more kinds of matter are transformed into a new kind of matter or several new kinds of matter. Chemical reactions may involve the formation of compounds from elemental substances. Complex substances may be broken down into simpler compounds or into the constituent elements. Compounds may react with other compounds or elements to form new and different substances. For example, elementary zinc reacts with hydrochloric acid to yield zinc chloride and hydrogen gas.

III.2 Elements

Elements are substances that cannot be further decomposed by ordinary chemical means. An element is composed of the same kind of atoms.

Each element has its own set of properties. General similarities among the properties of large groups of elements provide one way of classifying them. In this sense, elements can be classified as metals, metalloids and non-metals.

An *atom* is the smallest individual structure of an element that retains the properties of the element. It is the smallest unit of an element which can exist either alone or in combination with atoms of the same or different elements.

An atom consists of two basic kinds of particles, a *nucleus* and one or more *electrons*. The nucleus is the central core of an atom; it has most of the mass of the atom and one or more units of positive charge. Nuclei are very small and very dense. They have diameters of about 10^{-15} m (10^{-5} Å), whereas atomic diameters are about 10^{-10} m (1Å) - a hundred thousand times larger. (1 angstrom (Å) = 10^{-10} m.)

Atomic nuclei are composed of two kinds of particles, *protons* and *neutrons*. A *proton* is one of the nuclear particles having a unit positive charge and a mass over 1800 times that of the electron. A *neutron* is another particle found in the nucleus; it has a mass almost identical to that of the proton but has no electrical charge.

The other part of an atom lies outside the central nucleus. It is called *electron cloud*. The electron cloud gives an atom its volume and keeps out other atoms. The electron cloud is made up of electrons. An electron is a very light, pointlike particle having a unit negative electric charge.

All the atoms of one element have the same number of protons. Atoms of different elements have different number of protons, for example carbon atoms have 6 protons while oxygen atoms have 8 protons. The number of protons in an atom tells us which element the atom belongs to. It is called the *atomic number* and has the symbol Z. The atomic number of an element is the number of protons in each atom of the element. The atomic number is written as a subscript number in front of the symbol of the atoms.

Because most of the mass of an atom is in the nucleus, and because protons and neutrons have about the same mass, the total mass of an atom is approximately

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proportional to the total number of protons and neutrons in the nucleus. The total number of protons and neutrons of an atom is called the *mass number* of the atom. The mass number of an atom is frequently written as a superscript number in front of the symbol of the atom.

The *atomic number* of an atom characterizes an element, which always consists of atoms with the same atomic number. A pure element can, however, have atoms with the same numbers of protons (that is, with the same atomic number) but different numbers of neutrons. In such a case all atoms of an element have the same atomic number but they have different mass numbers because the number of neutrons varies.

Thus one form of carbon atoms has a mass number of 12 (6 protons and 6 neutrons) and another has a mass number of 13 (6 protons and 7 neutrons). They are called carbon-12 and carbon-13, respectively. Atoms of the same element having the same number of protons but different numbers of neutrons, such as carbon-12 and carbon-13, are known as *isotopes*. In other words, isotopes are atoms with the same atomic number but different mass numbers.

The names (and the symbols) of isotopes of an element are the same but those of hydrogen, where

Mass number	Name	Symbol
1	protium	^{1}H or H
2	deuterium	^{2}H or D
3	tritium	^{3}H or T

Isotopes have the same number of electrons and hence the same chemical properties, because chemical properties depend upon the transfer and redistribution of electrons. But isotopes have different numbers of neutrons, so they have different masses and hence different physical properties.

A naturally occurring element consists of either a single isotope (as in the case of sodium, which contains only sodium-23) or a definite mixture of two or more isotopes. Table III-1 shows a list of natural isotopes of some of the elements.

Table III-1: Isotopic distribution of some naturally occurring elements

Element	Mass number of isotope	Abundance (%)
Hydrogen	^{1}H	99.985
	^{2}H	0.015
	^{3}H	trace
Oxygen	^{16}O	99.757
	^{17}O	0.038
	^{18}O	0.205
Carbon	^{12}C	98.892
	^{13}C	1.108
	^{14}C	trace

III.3 Compounds

Most substances are *compounds*. A compound is a substance composed of more than one element, which are chemically combined.

Each compound has an *empirical formula* containing the symbols of the elements in it. The empirical formula of a compound is a notation that uses atomic symbols with numerical subscripts to express the relative proportions of atoms of the different elements in the compound. For example, carbon dioxide has the formula CO_2, which means that the compound is composed of carbon atoms and oxygen atoms in the ratio 1 to 2.

Additional information may be conveyed by different kinds of chemical formulas. To understand this, we need to look briefly at the two main types of substances: molecular and ionic.

A *molecular substance* is a substance that is composed of molecules, all of which are alike (e.g., water, H_2O; ammonia, NH_3; carbon dioxide, CO_2).

A *molecule* is a definite group of atoms that are chemically bound together. A molecular formula is a chemical formula that gives the exact number of different atoms of an element in a molecule. The water molecule contains two hydrogen atoms and one oxygen atom chemically bonded. Therefore its molecular formula is H_2O. Other examples of molecular substances are: ammonia, NH_3; carbon dioxide, CO_2; and methanol, CH_3OH.

Some elementary substances are molecular in nature and are represented by molecular formulas. Chlorine, for example, is a molecular substance and has the formula Cl_2. Other examples are hydrogen (H_2), nitrogen (N_2), oxygen (O_2), fluorine (F_2), phosphorous (P_4), sulphur (S_8), bromine (Br_2) and iodine (I_2).

The atoms in a molecule are bound together in a definite way. A *structural formula* is a chemical formula that shows how the atoms are bound to one another in a molecule. For example, the structural formula of water is H-O-H. A line joining two atomic symbols in such a formula represents the chemical bond connecting the atoms.

Although many substances are molecular, others are composed of ions. An *ion* is an electrically charged particle obtained from an atom or chemically bound group of atoms by adding or removing electrons.

An *ionic compound* is a compound composed of cations and anions. Sodium chloride, for example, consists of equal number of sodium ions, Na^+, and chloride ions, Cl^-. The strong electrostatic attraction between positive and negative charges holds the ions together in a regular arrangement in space. Such a regular arrangement gives rise to a crystal, a kind of solid having a definite geometrical shape as a result of the regular arrangement of the ions making up the substance.

The formula of an ionic compound expresses the lowest possible whole-number ratio of different ions in the substance, except that the charges on the ions are omitted. For example, sodium chloride contains equal numbers of Na^+ and Cl^- ions. The formula, that is called empirical formula, is written NaCl (not Na^+Cl^-).

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III.4 Naming compounds

The empirical formula of a compound expresses the stoichiometric composition, *the lowest possible whole-number ratio of different atoms in the substance.* For compounds composed of individual molecules the empirical formula corresponding to the relative molecular mass should be used. (e.g., S_2Cl_2 and $H_4P_2O_6$ not SCl or H_2PO_3.) If the relative molecular mass changes (e.g. due to thermal dissociation), the simplest formula is used (e.g., S, P, NO_2 not S_8, P_4, N_2O_4), except if we want to emphasize the presence of the polymeric modification. The formula of atomic lattice (e.g., SiO_2) or ionic (such as NaCl, $CaCl_2$) compounds only expresses the ratio of the number of atoms (ions) in the substance.

If the compound contains more than one electropositive (cation) or electronegative (anion) component, the atoms within each group are listed in alphabetical order of their chemical symbols. Ammonium (NH_4^+) ion should be considered as a two-letter symbol, so it is listed after Na. Hydrogen is an exception to this rule, because the acidic hydrogen is listed among the cations last.
For example:

$KMgF_3$	potassium magnesium fluoride
$KHCO_3$	potassium hydrogen carbonate
$MgNH_4PO_4.6\ H_2O$	magnesium ammonium phosphate-water (1/6)
$NaNH_4HPO_4$	sodium ammonium hydrogen phosphate
$KLiNaPO_4$	potassium lithium sodium phosphate

Simple covalent compounds are generally named by using prefixes to indicate how many atoms of each element are shown in the formula. The prefixes are Greek numbers as follows: 1=*mono*, 2=*di*, 3=*tri*, 4=*tetra*, 5=*penta*, 6=*hexa*, 7=*hepta*, 8=*octa*, 9=*ennea* (or *nona*), 10=*deca*. When number of atoms is too high or unknown, the *poly*- prefix is used. Half is noted by *semi*-, one and a half with the *sesqui*- prefixes.

In case of compounds containing more than one anions the order of the anions in the formula is as follows:

a. H^-, O^{2-}, OH^-
b. The other monatomic inorganic anions (other than H^- and O^{2-}) are listed in the following order: Rn, Xe, Kr, B, Si, C, Sb, As, P, N, Te, Se, S, A, I, Br, Cl, O, F.
c. Polyatomic inorganic anions (excluding OH^-) are listed according to their increasing number of atoms, while those with the same number of atoms according to the descending order of atomic number of the central ions (e.g. CO_3^{2-}, CrO_4^{2-} or CrO_4^{2-}, SO_4^{2-}).
d. Organic anions are listed in alphabetical order.

The name of a compound consisting of two non-metallic elements should be written in the order mentioned under b.) with the addition that hydrogen is in the line between N and Te. For example, NH_3, H_2S, CCl_4, ClO_2, OF_2.

When naming covalent molecules consisting of two different non-metal atoms, use the following steps:

a. The first (more electropositive) atom in the name gives the first name of the molecule. A Greek prefix is used to show the number of atoms. "*Mono*" is not used to name the first element.
b. The second (more electronegative) atom in the name has a Greek prefix showing the number of atoms followed by the name which ends in *-ide*.

For example:

NO_2	nitrogen dioxide
N_2O	dinitrogen oxide
N_2O_5	dinitrogen pentoxide
SF_6	sulphur hexafluoride

Latin or Greek multiplier names (*bis-*, *tris-*, *tetrakis-*, etc..) are used in the following cases:

a. when the name of group of atoms contains a number. For example, bisdisulphide, bistriphosphate,
b. before complex names (the name of which the multiplier name refers, is in brackets). For example, bis(hydrogen sulphide).

When a compound contains three or more electropositive or electronegative elements, the order generally follows the sequence related to the connection of the atoms in the molecule. For example, HOCN: cyanic acid, HNCO: isocyanic acid. Some common formulae (e.g., H_2SO_4, $HClO_4$, HNO_3) do not match this rule, but - because of their ubiquity - this order can be maintained. The number of the same atoms or groups in the formula is indicated by Arabic numerals. The number is placed in the lower right of the symbol or that of the parenthesis of the complex ion, as an index. The number of water molecules of crystallization and that of the loosely bound molecules are placed in front of their formula indicated by Arabic numerals. For example, $CaCl_2 \cdot 8\ H_2O$, $Na_2SO_4 \cdot 10\ H_2O$.

III.4.1 **Naming ions**

III.4.1.1 Naming cations

1. **Monoatomic cations**

The simplest ions are monoatomic ions. A monoatomic ion *is an ion formed from a single atom*. Metallic elements generally form monoatomic cations. Nonmetal elements generally form monoatomic anions.

A monoatomic cation *is given the name of the element*. If there is more than one kind of cation of the element with different oxidation states (e.g., iron, which has the Fe^{2+} and Fe^{3+}) the charge is denoted by a Roman numeral in parentheses immediately following the element's name. The ion Fe^{2+} is called iron(II) ion.

For example:

Fe^{2+}	iron(II) ion	or	iron(2+) ion
Sn^{4+}	tin(IV) ion	or	tin(4+) ion
Ni^{3+}	nickel(III) ion	or	nickel(3+) ion

2. **Polyatomic cations**

The name of cations that are formed by combination of a hydrogen ion and a hydride of an element of the halogen-, oxygen- or the nitrogen-group is formed by adding the suffix *„-onium*" to the root of the name of the element: the name of H_4N^+ is *ammonium*, that of H_3O^+ is *oxonium*, and that of H_2F^+ is *fluoronium*. Ammonium is used instead nitronium, because the latter is widely used for naming the NO_2^+ cation.

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The name of polyatomic cations (*acyl groups*) obtained by (imaginary) removal of a *hydroxyl group* from an acid is obtained from the full or a stem name of the nonmetallic element followed by the suffix *–yl*.

For example:

IO_2^+	iodyl
SO^{2+}	thionyl
SO_2^{2+}	sulphuryl
CO^{2+}	carbonyl
PO^{3+}	phosphoryl
NO^+	nitrosyl (nitrosonium)
NO_2^+	nitryl (nitronium)

III.4.1.2 Naming anions

1. The names of **monoatomic anions** are obtained from a stem name of the element followed by the suffix *-ide*.

   For example:

H^-	hydr*ide* ion
Cl^-	chlor*ide* ion
F^-	fluor*ide* ion
S^{2-}	sulph*ide* ion
N^{3-}	nitr*ide* ion
C^{4-}	carb*ide* ion
O^{2-}	ox*ide* ion

2. *A* **polyatomic ion** *is an ion consisting of two or more atoms chemically bound together and carrying a net electric charge*. The names of polyatomic anions are obtained from a full name, or stem name, or the Latin name of the central element followed by the suffix *–ate*. In the first part of the name of the anion, the name(s) of the other element(s) – which are listed in the formula following the central element – is (are) named according to the following rules: Greek prefixes are used to designate the number of each type of atom followed by the full name, or stem name or Latin name of the atom(s) followed by the suffix *–o* (e.g., *oxo-* for oxygen, *thio-* for sulphur, etc.). In case of multivalent central atoms the oxidation state of the atom is given as a Roman numeral in parentheses, following the name of the atom.
   For example:

Formula	**IUPAC nomenclature**	**Geneva nomenclature**
SO_4^{2-}	tetraoxosulphate(VI)	sulphate
NO_2^-	dioxonitrate(III)	nitrite
PO_4^{3-}	tetraoxophosphate(V)	phosphate
$S_2O_3^{2-}$	trioxothiosulphate(VI)	thiosulfate
ClO_2^-	dioxochlorate(III)	chlorite
ClO_3^-	trioxochlorate(V)	chlorate

Many of the polyatomic ions are *oxoanions*, which consist of oxygen with another element (called the central element). If the central atom of the oxoanion can form ions with different number of oxygen atoms they can be distinguished by suffixes added to the stem name of the element.

The suffix *-ite* denotes the anion with the fewer number of oxygen atoms; the suffix *-ate* denotes the anion with the greater number of oxygen atoms. For example, SO_3^{2-} - is the sulph*ite* ion, and SO_4^{2-} is the sulph*ate* ion.

The formula and the name (Geneva nomenclature) of the most frequently occurring oxoanions are listed in Table III-2.

Table III-2: The formula and the name (Geneva nomenclature) of the most frequently occurring polyatomic ions.

Name	**Formula**	**Name**	**Formula**
Ammonium	NH_4^+	Nitrite	NO_2^-
Carbonate	CO_3^{2-}	Nitrate	NO_3^-
Hydrogen carbonate	HCO_3^-	Sulphite	SO_3^{2-}
Hydroxide	OH^-	Hydrogen sulphite	HSO_3^-
Hypochlorite	ClO^-	Sulphate	SO_4^{2-}
Chlorite	ClO_2^-	Hydrogen sulphate	HSO_4^-
Chlorate	ClO_3^-	Phosphate	PO_4^{3-}
Perchlorate	ClO_4^-	Hydrogen phosphate	HPO_4^{2-}
Cyanide	CN^-	Dihydrogen phosphate	$H_2PO_4^-$

When there are several oxoanions of a given central element, they can be distinguished by adding prefixes. The oxoanion with the greatest number of oxygen atoms is given the prefix *per-* and the suffix *-ate*. The oxoanion with the least number of oxygen atoms is given the prefix *hypo-* and the suffix *-ite*.

For example:

ClO^-	*hypo*chlor*ite* ion
ClO_2^-	chlor*ite* ion
ClO_3^-	chlor*ate* ion
ClO_4^-	*per*chlor*ate* ion

Acid anions are anions that have H atoms they can lose as hydrogen ion, H^+. For example, HSO_4^- (derived from H_2SO_4) has an H atom that can be removed to yield H^+ and SO_4^{2-}. The acid anion, HSO_4^-, is called *hydrogen sulphate ion*.

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III.4.2 **Naming acids**

Acids are substances that yield hydrogen ions (protons), H^+, in aqueous solution. An *oxoacid* is an acid that donate protons in aqueous solution, which protons were previously bound to oxygen atoms. Today the Geneva nomenclature is still widely used for naming acids and their salts.

The name of the oxygen-containing acids (oxoacids) is formed from the name of the oxoanion by replacing the suffix *-ite* by *-ous,* and the suffix *-ate* by *-ic*, then adding the word *acid*.
For example

Oxoanion		**Oxoacid**	
SO_3^{2-}	sulph*ite* ion	H_2SO_3	sulphur*ous* acid
SO_4^{2-}	sulph*ate* ion	H_2SO_4	sulphur*ic* acid
ClO_2^-	chlor*ite* ion	$HClO_2$	chlor*ous* acid
ClO_3^-	chlor*ate* ion	$HClO_3$	chlor*ic* acid
NO_2^-	nitr*ite* ion	HNO_2	nitr*ous* acid
NO_3^-	nitr*ate* ion	HNO_3	nitr*ic* acid
CO_3^{2-}	carbon*ate* ion	H_2CO_3	carbon*ic* acid

The aqueous (acidic) solutions of binary compounds of hydrogen and non-metals (e.g., HCl and HBr) are named like compounds by using the prefix *hydro-* and the suffix *-ic* with the stem name of the non-metal, followed by the name of the word *acid*.

For example:

HCl(*aq*)	*hydro*chlor*ic acid*
HBr(*aq*)	*hydro*brom*ic acid*
HI(*aq*)	*hydro*iodic *acid*

In the names of widely used salts the stoichiometric ratios are not necessarily indicated.

For example:

Na_2SO_4	sodium sulphate
$NaHSO_3$	sodium hydrogen sulphite
NaOCl	sodium hypochlorite
KIO_4	potassium periodate

In trivial names it is the *peroxo-* prefix which indicates replacement of (-O-) with (-O-O-).

For example:

H_2SO_5	peroxosulphuric acid
$H_2S_2O_8$	peroxodisulphuric acid

While naming thioacids, the *thio-* prefix should be added before the name of the oxoacid, from which the thioacid was formed by replacing oxygen with sulphur. The number of sulphur atoms should be indicated by Greek numbers.

For example:

$H_2S_2O_3$	thiosulphuric acid
H_3PO_3S	monothiophosphoric acid
$H_3PO_2S_2$	dithiophosphoric acid
H_2CS_3	trithiocarbonic acid

III.4.3 Naming functional derivatives of acids

Functional derivatives of acids are compounds derived from oxoacids by replacing a hydroxyl group (sometimes an O-atom) with another atom or group of atoms.

Acid halides (also known as *acyl halides*) are compounds derived from oxoacids by replacing a hydroxyl group with a halide group. The names of acid halides are formed by adding the name of the halide to the name of the acyl group.

For example:

NOCl	nitrosyl chloride
NO_2Br	nitryl bromide
POI_3	phosphoryl iodide
$COCl_2$	carbonyl chloride (phosgene)
CrO_2Cl_2	chromyl chloride

Acid amides are compounds derived from oxoacids by replacing a hydroxyl group with an amino (or substituted amino) group. The names of acid amides are formed by adding the word *amide* to the name of the acyl group.

For example:

$SO_2(NH_2)_2$	sulphonyl diamide
$PO(NH_2)_3$	phosphoryl triamide
$CO(NH_2)_2$	carbonyl diamide (carbamide)

When any of the hydroxyl groups of a polyprotic acid is not replaced with amino group, the name is formed by adding the *amido-* prefix to the name of the acid.

For example:

NH_2SO_3H	amidosulphuric acid
NH_2CO_2H	amidocarbonic acid (carbamic acid)

Regarding naming, esters of the inorganic acids should be considered as salts.

For example:

$(CH_3O)_2SO_2$	dimethyl sulphate
$(H_5C_2O)_3B$	triethyl borate

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III.4.4 Naming bases

Bases *are substances that yield hydroxide ions, OH^- in aqueous solution*. Inorganic bases are usually ionic and are named as ionic compounds.

For example:

NaOH	sodium hydroxide
NH_4OH	ammonium hydroxide
$Ca(OH)_2$	calcium hydroxide
$Fe(OH)_2$	iron(II) hydroxide

III.4.5 Coordination compounds

A *complex* is a substance in which a metal atom or ion is associated with a group of neutral molecules or anions called ligands. *Coordination compounds* are neutral substances (i.e. uncharged) in which at least one ion is present as a complex.

The formula of the complex group is enclosed in square brackets. The order of the constituents of the complex group as it follows: *central atom* (or ion), *ionic ligands*, *neutral ligands* (water, ammonia). The ion as well as the neutral molecules should be listed in alphabetical order.

III.4.5.1 Naming ligands

a. The name of the neutral ligand remains unchanged with the following exceptions: water (H_2O) – aqua, ammonia (NH_3) – ammin, nitrogen monoxide (NO) – nitroso, and carbon monoxide (CO) – carbonyl.

Formula	**Name of molecule**	**Name of ligand**
H_2O	water	aqua
NH_3	ammonia	ammin
NO	nitrogen monoxide	nitroso
CO	carbon monoxide	carbonyl

b. The names of anionic ligands are obtained from the full or the stem name of the anion followed by the suffix *–o.*

Formula	**Name of molecule**	**Name of ligand**
H^-	hydride	hydrido
S^{2-}	sulphide	thio
F^-	fluoride	fluoro
Cl^-	chloride	chloro
O^{2-}	oxide	oxo
OH^-	hydroxide	hydroxo
CN^-	cyanide	cyano
SCN-	thiocyanate	thiocyano
NO_2^-	nitrite	nitrito or nitro (depending on the nature of the bonding atom)

III.4.5.2 Naming complex compounds

To name a coordination compound, no matter whether the complex ion is the cation or the anion, *always name the cation before the anion*. (This is just like naming an ionic compound.).

In naming complex ions the ligand(s) is (are) named first and the central ion (atom) second. The complete ligand name consists of a Greek prefix denoting the number of ligands, followed by the specific name of the ligand. Regardless the number and the charge of each, the ligands are named in alphabetical order (disregarding Greek prefixes).

1. In names of complex cations and neutral complexes the central metal ion (atom) is named as the element. In case of multivalent metal ions the oxidation state of the metal in the complex is given as a Roman numeral in parentheses, following the name of the metal.
   Greek prefixes are used to designate the number of each type of ligand in the complex ion, e.g. *di-*, *tri-* and *tetra-*. If the ligand already contains a Greek prefix (e.g. ethylene*di*amine) or if it is a polydentate ligand (i.e. can attach at more than one binding site) the prefixes *bis-*, *tris-*, *tetrakis-*, *pentakis-*, are used instead.

For example:

$[Cu(NH_3)_4]SO_4$	tetraammincopper(II) sulphate
$[Al(OH)(H_2O)_5]Cl_2$	pentaaquahydoxoaluminium(III) chloride
$[Fe(SCN)(H_2O)_5]Cl_2$	pentaaquathiocyanoiron(III) chloride
$[Fe(SCN)_2[H_2O)_4]Cl$	tetraaquabis(thiocyano)iron(III) chloride
$[Fe(CO)_4]$	tetracarbonyliron(0)
$[Pt(NH_3)_2Cl_2]$	diammindichloroplatinum(II)

2. In name of complex anions the name of the central metal ion (atom) consists of the name of the metal followed by the suffix *–ate*. Following the name of the metal, the oxidation state of the metal in the complex is given as a Roman numeral in parentheses. For some metals, the Latin names are used in the complex anions e.g. Fe is called ferrate (not ironate).

For example:

$K_4[Fe(CN)_6]$	potassium hexacyanoferrate(II)
$[Cr(NH_3)_3(H_2O)_3]Cl_3$	triamminetriaquachromium(III) chloride
$[Pt(NH_3)_5Cl]Br_3$	pentaamminchloroplatinum(IV) bromide
$Na_2[NiCl_4]$	sodium tetrachloronickelate(II)
$Pt(NH_3)_2Cl_4$	diamminetetrachloroplatinum(IV)
$K_4[Fe(CN)_6]$	potassium hexacyanoferrate(II)
$Na_3[Ag(S_2O_3)_2]$	sodium bis(thioszulphato)argentate(I)]
$K_2[Cd(CN)_4]$	potassium tetracyanocadmiate(II)
$Na[BiI_4]$	sodium tetraiodobismuthate(III)
$K[Sb(OH)_6]$	potassium hexahidroxoantimonate(V)
$Na_2[Ni(CN)_2Br_2]$	sodium dibromodicyanonickelate(II)

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III.4.6 **Addition compounds**

III.4.6.1 Formula of addition compounds

An addition compound contains two or more simpler compounds that can be packed in a definite ratio into a crystal. A dot is used to separate the compounds in the formula. For example, $CuSO_4 \cdot 5\ H_2O$ is an addition compound of copper(II) sulphate and water.

III.4.6.2 Naming addition compounds

In name of addition compounds the names of components are linked by a hyphen. The number of the molecules is indicated by Arabic numbers, separated by a slash.

For example:

$Na_2CO_3 \cdot 10\ H_2O$	sodium carbonate-water(l/10)
$3\ CdSO_4 \cdot 8\ H_2O$	cadmium sulphate-water (3/8)
$8\ Kr \cdot 46\ H_2O$	krypton-water (8/46)
$CaCl_2 \cdot 8\ NH_3$	calcium chloride-ammonia (1/8)
$Al_2Ca_4O_7 \cdot n\ H_2O$	dialuminium tetracalcium heptoxide-water (l/n)

III.5 Pharmacopoeial nomenclature

The principles of nomenclature in the Hungarian Pharmacopoeia (Ph. Hg. VIII.) are based on regulation by IUPAC (introduced in 1957, and supplemented several times) and on the so-called Geneva nomenclature. In the Pharmacopoeia the naming of elements and inorganic compounds is based on the guidelines mentioned below. In case of organic compounds usually international (nonpropietary) names (INN) are given.

Elements

In the Pharmacopoeia traditional Latin names of elements are mostly used. The termination of the names is usually the suffix „um”.

English name	Latin name	Chemical symbol
helium	Helium	He
carbon	Carbo	C
nitrogen	Nitrogenium	N
oxygen	Oxygenum	O
iodine	Iodum	I
sulphur	Sulphur	S
iron	Ferrum	Fe

Compounds

Pharmacopoeial nomenclature is based on two different systems. The older one, which is used in the VII. Edition of the Hungarian Pharmacopoeia (Ph. Hg. VII.) gives names of inorganic and organic compounds in adjectival constructions. In these formulas the cation is a noun and the anion is an adjective. For example, Natrium chloratum = chlorous sodium.

The nomenclature which is also used in the VIII. Edition of the Hungarian Pharmacopoeia (Ph. Hg. VIII.) is based on genitive constructions. Cation and anion names are both nouns; name of the cation is in genitive form and that of the anion is in nominative form. For example, Natrii chloridum = chloride of sodium.

III.5.1 Inorganic compounds - Nomenclature of adjectival constructions

In case of salts the name(s) of cation(s) is given in nominative form, which is followed by a prefix (e.g. „*hypo*"), occasionally, and by the adjective form of the anion (with the appropriate suffix).

III.5.1.1 Oxides

The suffix „*ide*" of the anion is changed to „*atum*".

For example:

zinc oxide	zincum oxidatum
magnesium oxide	magnesium oxidatum

III.5.1.2 Acids

The Latin name of aqueous solution of hydrogen halides is formed using the word „*acidum*", and the suffix of the halide („*ide*") is changed to „*atum*".

For example:

hydrochloric acid	(hydrogen chloride)	acidum chloratum

Name of oxoacids is formed using the word „*acidum*" which is followed by Latin name of the anion. The suffix „*ite*" is changed to „*osum*", the suffix „*ate*" to „*icum*".

For example:

sulphurous acid	(dihydrogen sulphite)	acidum sulfurosum
sulphuric acid	(dihydrogen sulphate)	acidum sulfuricum
nitrous acid	(hydrogen nitrite)	acidum nitrosum
nitric acid	(hydrogen nitrate)	acidum nitricum
phosphoric acid	(trihydrogen phosphate)	acidum phosphoricum

III.5.1.3 Ions

In case of metal ions with different oxidation states, the name of the cation with lower oxidation number contains the syllable „*os*".

For example:

iron(III) chloride	ferrum chloratum
iron(II) sulphate	ferrosum sulfuricum

In simple anions with the suffix „*ide*" the ending is replaced to „*atum*".

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For example:

chloride (ion)	chloratum
bromide (ion)	bromatum
sulphide (ion)	sulfatum

In case of complex anions the suffix „*ite*” is changed to „*osum*”, the suffix „*ate*” to „*icum*”.

For example:

sulphite (ion)	sulfurosum
sulphate (ion)	sulfuricum
nitrite (ion)	nitrosum
nitrate (ion)	nitricum
phosphate (ion)	phosphoricum

If the non-metallic central atom in the anion of an oxoacid occurs in more than two oxidation states, then the prefixes „*hypo*” or „*hyper*” are used, respectively.

For example:

hypochlorous acid	(hydrogen hypochlorite)	acidum hypochlorosum
chlorous acid	(hydrogen chlorite)	acidum chlorosum
chloric acid	(hydrogen chlorate)	acidum chloricum
perchloric acid	(hydrogen perchlorate)	acidum perchloricum

III.5.1.4 Salts

Salts of hydrogen halides and regular salts of oxoacids are named regularly, as written before.

For example:

sodium chloride	natrium chloratum
potassium bromide	kalium bromatum
ammonium chloride	ammonium chloratum
sodium sulphate	natrium sulfuricum
sodium nitrite	natrium nitrosum

The name of an acid salt of a polyvalent acid contains the word „hydrogen”.

For example:

sodium hydrogen carbonate	natrium hydrogencarbonicum
disodium hydrogen phosphate	dinatrium hydrogenphosphoricum
sodium dihydrogen phosphate	natrium dihydrogenphosphoricum

The name of a basic salt of a polyvalent base contains the word „hydroxydatum” or the prefix „*sub*”.

For example:

magnesium hydroxide carbonate	magnesium carbonicum hydroxydatum
bismuth(III) subnitrate	bismuthum subnitricum

Occasionally the trivial name of the compound is used in the Pharmacopoeia.

For example:

potassium aluminium sulphate	alumen

III.5.2 **Inorganic compounds - Nomenclature of genitive construction**

According to the genitive construction cations are in genitive case and anions are in nominative case.

III.5.2.1 Oxides

Oxides are named according to the above rules.

For example:

zinc oxide	zinci oxidum
titanium dioxide	titanii dioxidum

III.5.2.2 Ions

In simple anions the suffix „*ide*" is replaced with „*idum*".

For example:

chloride (ion)	chloridum
bromide (ion)	bromidum
sulphide (ion)	sulfidum
hydroxide (ion)	hydroxidum

In case of complex anions, when the central atom occurs in higher oxidation state, the suffix „*ate*" is changed to „*as*". If the central atom occurs in lower oxidation state the suffix „*ite*" is replaced with „*is*".

For example:

sulphite (ion)	sulfis
sulphate (ion)	sulfas
nitrite (ion)	nitris
nitrate (ion)	nitras
phosphate (ion)	phosphas
silicate (ion)	silicas

The rule is the same in case of anions formed from organic acids, the suffix „*ate*" is changed to „*as*".

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For example:

acetate (ion)	acetas
benzoate (ion)	benzoas
salicylate (ion)	salicylas
tartrate (ion)	tartaras

III.5.2.3 Acids

The name of aqueous solution of hydrogen halides is formed using the word „*acidum*", which is followed by the modified name of the hydrogen halide.

For example:

hydrochloric acid	(hydrogen chloride)	acidum hydrochloridum

Name of an oxoacid is formed using the word „acidum", as well, and using the Latin name of the anion, similar to the adjectival nomenclature. The suffix „ite" is changed to „osum", the suffix „ate" to „icum".

For example:

sulphurous acid	(dihydrogen sulphite)	acidum sulfurosum
sulphuric acid	(hydrogen sulphate)	acidum sulfuricum
nitrous acid	(hydrogen nitrite)	acidum nitrosum
nitric acid	(hydrogen nitrate)	acidum nitricum

Name of organic acids is formed similarly.

acetic acid	acidum aceticum
benzoic acid	acidum benzoicum
salicylic acid	acidum salicylicum
tartaric acid	acidum tartaricum

III.5.2.4 Salts

Salts of hydrogen halides and regular salts of oxoacids are named regularly, the suffix „*ide*" is replaced with „*idum*", the suffix „*ate*" is changed to „*as*", and the suffix „*ite*" is replaced with „*is*".

For example:

sodium chloride	natrii chloridum
potassium bromide	kalii bromidum
ammonium chloride	ammonii chloridum
sodium sulphate	natrii sulfas
sodium nitrite	natrii nitris

The name of a sour salt of a polyvalent acid contains the prefix „*hydrogeno*".

For example:

sodium hydrogen carbonate	natrii hydrogenocarbonas
sodium dihydrogen phosphate	natrii dihydrogenophosphas
disodium hydrogen phosphate	dinatrii phosphas

The latest example does not contain the prefix „*hydrogeno*", but the name „*dinatrii*" refers to it.

The name of a basic salt of a polyvalent base contains the prefix „*sub*".

For example:

bismuth(III) subnitrate	bismuthi subnitras

In case of metal ions with different oxidation states, the name of the cation with lower oxidation number contains the syllable „*os*".

For example:

iron(II) sulphate	ferrosi sulfas
iron(III) chloride	ferri chloridum
copper(II) sulphate	cupri sulfas

The phrase „*anhydricus*" or „*hydricus*" refers to the water of crystallization.

For example:

anhydrous sodium sulphate	natrii sulfas anhydricus
sodium sulfate decahydrate	natrii sulfas decahydricus
sodium sulfate heptahydrate	natrii sulfas heptahydricus

III.5.3 **Nomenclature of organic compounds**

Naming of organic compounds according to the IUPAC regulation is inadequate for general application because of its complexity. Therefore the trivial names and INN names of the compounds are used in the Pharmacopoeia. The suffix „*um*" is attached to the word.

For example:

chloroform	chloroformium
chloramine	chloraminum
vanillin	vanillinum
glucose	glucosum
camphor	camphora (exception!)
carbachol	carbacholum
lidocaine	lidocainum

Naming of acids and salts is formed as prescribed above.
In case of esters - in adjective case - the suffix „*ium*" is attached to the alkyl group derived from the alcohol. (Formation of trivial names of esters follows the nomenclature of salts.)

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For example:

name	adjectival nomenclature	genitive nomenclature
ethyl acetate	aethylium aceticum	ethylis acetas
benzyl benzoate	benzylium benzoicum	benzylis benzoas
amyl nitrite	amylium nitrosum	amylis nitris

Salts, which contain quaternary ammonium ion or protonated nitrogen atom, are named as a substituted ammonium salt, and the suffix „ium" is attached to the name of the base.

For example:

name	adjectival nomenclature	genitive nomenclature
choline chloride	cholinium chloratum	cholini chloridum
strychnine nitrate	strychninium nitricum	strychnini nitras
morphine hydrochloride	morphinium chloratum	morphini hydrochloridum
homatropine hydrobromide	homatropinium bromatum	homatropini hydrobromidum
methyl homatropine bromide	methylhomatropinium bromatum	homatropini methylbromidum

IV Pharmacopoeia (Ph. Hg. VIII.) test methods

IV.1 Physical and physicochemical methods

IV.1.1 Clarity and degree of opalescence of liquids (Ph. Hg. VIII.)

Visual method

Using identical test-tubes made of colourless, transparent, neutral glass with a flat base and an internal diameter of 12-25 mm, compare the liquid to be examined with a reference suspension freshly prepared as described below, the depth of the layer being 40 mm. Compare the solutions in diffused daylight 5 min after preparation of the reference solutions, viewing vertically against a black background. The diffusion of light must be such that reference suspension I can readily be distinguished from water R, and that reference suspension II can readily be distinguished from reference suspension I.

A liquid is considered clear if its clarity is the same as that of water R or of the solvent used when examined under the conditions described above, or if its opalescence is not more pronounced than that of reference suspension I.

IV.1.2 Degree of coloration of liquids (Ph. Hg. VIII.)

The examination of the degree of coloration of liquids in the brown-yellow-red range is carried out by one of the 2 methods described below, as prescribed in the monograph.

A solution is colourless if it has the appearance of water R or the solvent or is not more intensely coloured than reference solution B_9.

Method I

Using identical tubes made of colourless, transparent, neutral glass with 12 mm external diameter, compare 2.0 ml of the liquid to be examined with 2.0 ml of water R or of the solvent or of the reference solution prescribed in the monograph. Compare the colours in diffused daylight, viewing horizontally against a white background.

Method II

Using identical tubes made of colourless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm, compare the liquid to be examined with water R or the solvent or the reference solution prescribed in the monograph, the depth of the layer being 40 mm. Compare the colours in diffused daylight, viewing vertically against a white background.

IV.1.3 Dissolution

At dissolving a compound, a homogenous system, a solution is formed from a heterogeneous system of components with different material qualities. The quantity of the dissolved compound depends on the quality of the solvent and the solute, and, in case of gases, the temperature and the pressure.

If a solid compound is to be dissolved, it has to be powdered in a mortar to increase the contact surface between solute and solvent. The dissolution can be accelerated by heating and mixing. Homogenization of liquids can be made by tools made of glass or metal. If the homogenization requires extended time, the homogenizer can be operated by an electric motor. Magnetic stirrer is a frequently used device. This is a small sized iron bar surrounded by glass or plastic, and it has to be placed into the

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vessel containing the solution. The vessel is to be placed onto the device, which affects a rotating magnetic field and the small magnetic stirrer is going to rotate in the solution. This procedure ensures the homogenization of the solution. The concentration provides information on the quantitative relations of the solute and the solvent. Depending on quantity of the solute and the solvent, the solutions can be *saturated*, *unsaturated* or *supersaturated*.

Solubility is the mass of a compound (in g) that can be dissolved in 100 g solvent at a given temperature. Solubility of a substance depends on both the solvent and temperature. A solution is unsaturated if it is possible to dissolve more solute in it at the given temperature. A saturated solution contains the quantity of solute that equals the solubility value at the actual temperature.

Solubility is an important physico-chemical characteristics of pharmaceutically active compounds. In the Hungarian Pharmacopoeia (Ph. Hg. VIII.) solubilty of substances (between 15 ^{o}C – 25 ^{o}C) is characterized by the terms summarized in Table IV-1.

Table IV-1: Descriptive terms used in the Pharmacopoeia (Ph. Hg. VIII.) to characterize solubility of substances.

Descripitive term	**Approximate volume of solvent in millilitres per gram of solute**
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10 000
Practically insoluble	>10 000

Objective: Collect a list of 5 compounds of each different solubility groups from the European Pharmacopoiea. Evaluate the structure-solubility relationship on the basis of structure of the compounds.

IV.1.4 **Melting point determination**

The *melting point* of a solid is defined as the temperature at which the solid and the liquid phases are in equilibrium at a total pressure of 760 Hgmm (101.325 kPa). The melting point is a physical property fundamentally dependent on the structure of a compound. The melting point can be determined with high accuracy because the temperature of pure crystalline solids remains constant until the solid phase is present. During the melting process the amount of the convected heat provides the *heat of fusion*. While melting, the temperature of the melting solid remains constant; the transferred amount of heat is required to provide the *heat of fusion* for the solid–liquid transformation. Pure crystalline substances have a sharp melting point that can be measured within the range of 1 °C.

Factors that affect melting point of a substance are: a.) the degree of purity; b.) the amount and nature of impurity; and c.) crystallization water and moisture content.

Factors affecting accuracy of melting point determinations are: a.) the amount of available substance; b.) the equipment used for determination; and c.) the rate of heating.

Soluble impurities in the molten substance reduce its melting point. Furthermore, a contaminated substance generally does not melt at a fixed temperature, but the melting process takes place over a certain temperature range. The so called *eutectic mixtures* behave different way; they have a sharp melting point like pure compounds: they have a definite melting point specific to the eutectic composition.

There are compounds that undergo decomposition around their melting point. In such cases, the melting process is prolonged; before melting, the compound gets discoloured, turns brown and gases might be evolved. Such substances have *decomposition range*.

There are several methods for melting point determination, and the method of choice depends mainly upon how much material is available. An approximate melting point can be determined in a relatively short time by the apparatus shown on the Figure IV-1. The main body of the apparatus is a loop-shaped glassware (*Thiele tube*) which is filled up with silicone oil. A thermometer is fitted to the top of the glassware and a capillary tube closed at one end, containing the sample, can be placed through side tubes. The bottom part of the thermometer and that of the capillary is immersed into the silicone oil.

Once the setup has been complete, the lower part of the side arm of the Thiele tube is carefully heated with a small flame from a *Bunsen burner* moving the flame back and forth along the arm. The shape of the *Thiele tube* allows for formation of convection currents in the oil when it is heated. The thermometer and sample must be at the same temperature while the sample melts, so the rate of heating must be slow as the melting point is approached (about 1 ^{o}C/min). Otherwise, the temperature of the thermometer bulb and the temperature of the crystals in the capillary may not be the same. The transfer of heat energy by conduction takes place rather slowly. The melting point determined by the capillary method is the temperature at which the last solid particle of a compact column of a substance in a tube goes into the liquid phase.

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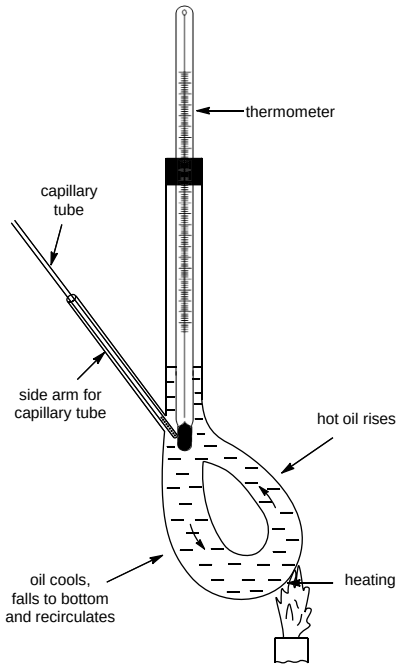
Figure IV-1: Equipment for melting point determination (*Thiele tube*)**.**



IV.1.4.1 Melting point determination (Ph. Hg. VIII.)

When prescribed in the monograph, the same apparatus and method are used for the determination of other factors, such as meniscus formation or melting range, that characterize the melting behaviour of a substance.

Apparatus.
The apparatus consists of:

- A suitable glass vessel containing a liquid bath (for example, water, liquid paraffin or silicone oil) and fitted with a suitable means of heating,
- A suitable means of stirring, ensuring uniformity of temperature within the bath,
- A suitable thermometer with graduation at not more than 0.5 °C intervals and provided with an immersion mark. The range of the thermometer is not more than 100 °C,
- Alkali-free hard-glass capillary tubes of internal diameter 0.9 mm to 1.1 mm with a wall 0.10 mm to 0.15 mm thick and sealed at one end.

Method

Unless otherwise prescribed, dry the finely powdered substance in vacuum and over *anhydrous silica gel R* for 24 h. Introduce a sufficient quantity into a capillary tube to give a compact column 4 mm to 6 mm in height.

Raise the temperature of the bath about 10 °C below the presumed melting point and then adjust the rate of heating to about 1 °C/min. When the temperature is 5 °C below the presumed melting point, correctly introduce the capillary tube into the instrument. For the apparatus described above, immerse the capillary tube so that the closed end is near the centre of the bulb of the thermometer, the immersion mark of which is at the level of the surface of the liquid. Record the temperature at which the last particle passes into the liquid phase.

Calibration of the apparatus.

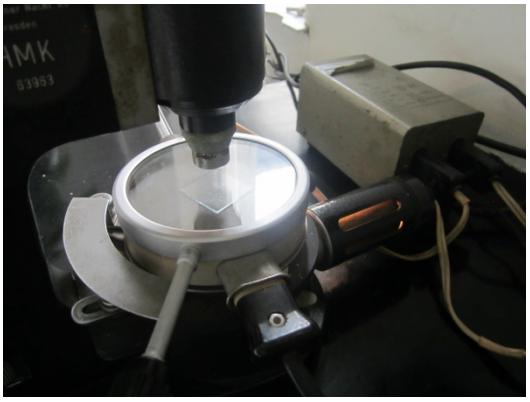
The apparatus may be calibrated using melting point reference substances such as those of the World Health Organization or other appropriate substances.

A quick and easy method to determine the melting point of a solid is to heat the capillary tubes containing the sample in an electrically heated metal block, while observing the crystals with the aid of a magnifying glass (see Figure IV-2). This method requires as little as a few crystals and it is very convenient.

Figure IV-2: Electrically heated melting point measurement devices.

Melting point of a very small amount of a substance (as little as a few crystals) can be determined by the *Kofler's microscope with a heatable stage* (Figure IV-3). The most important parts of the device are a heatable metal block and a microscope. The temperature of the metal block can be finely controlled and heated up to 350 °C. In the middle of the block table there is an opening of 1.5 mm in diameter for transmission of light. A few crystals of the sample between a pair of microscope cover glasses are placed on the electrically heated metal block while observing the crystals with the aid of the microscope. Graduation of a thermometer – showing the actual temperature of the heating block - can also be displayed on the field of vision of the microscope, so the temperature and melting of the compound can be simultaneously observed.

Figure IV-3: Kofler's microscope with a heatable stage.



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Objective: Melting point determination of a known (urea) and an unknown compound

1. **Training measurement with urea**

a. The urea sample is pulverized in a mortar if necessary and placed in a capillary tube carefully sealed on one end. Usually, the melting point capillary can be filled by pressing its open end into a small heap of the crystals of the substance, turning the capillary open end up, and vibrating it by drawing a file across the side to rattle the crystals down to the bottom. If filing does not work, drop the tube, open end up, down a length of glass tubing about 1 cm in diameter (or a long condenser) onto a hard surface such as a porcelain sink, stone desk top, or a watch glass. It is practical to fill the capillary in a 1–1.5 cm length; the sudden contraction of the compound clearly indicates the formation of the new phase.
b. Immerse the capillary into the *Thiele tube* that the test sample has to be exactly in front of the mercury bulb of the thermometer. Thus, the temperature close to the capillary and the mercury bulb of the thermometer is very much the same.
c. The thermometer and sample must be at the same temperature while the sample melts, so the rate of heating must be slow as the melting point is approached (about 3-5 ^{o}C/min). Otherwise, the temperature of the thermometer bulb and the temperature of the crystals in the capillary may not be the same.
d. Warm the lower part of the side arm of the Thiele tube carefully with a small flame from the Bunsen burner moving the flame back and forth along the arm. At the first preliminary measurement warm the apparatus allowing the temperature to rise at a rate of 10 °C/min.
e. Note the temperature when the edges of the crystals start to melt. The temperature range over which the sample is observed to melt is taken as the melting point.
f. Remove the capillary containing the molten compound and allow the apparatus to cool 30 °C below the measured melting point.
g. After the preliminary measurement, perform at least two more accurate determination, with a low rate of heating (about 3–4 °C/min) near the melting point. Provided that the average of the two latter measurements is close to 133 °C, the melting point of urea, melting point determination of the unknown compound can be started.

2. **Melting point determination of an unknown substance**

a. The unknown compound, can be pulverized in a mortar if necessary, then similar to the previous determination, the compound is filled into a capillary carefully sealed on one end. If it is possible, larger crystals should be used, because the melting edges of the crystals can be observed better on them.
b. The capillary is placed into the melting point measuring apparatus so that the sample is in front of the mercury bulb (see above).
c. Warm the apparatus with a Bunsen burner at a rate of 10 °C/min, and note the temperature when edges of the crystals start to melt. The temperature range over which the sample is observed to melt is taken as the melting point.
d. Remove the capillary containing the molten compound and allow the apparatus to cool 30 °C below of the measured melting point.
e. After the preliminary measurement, perform at least two more accurate determination, with a low rate of heating (about 3–4 °C/min) near the melting point.

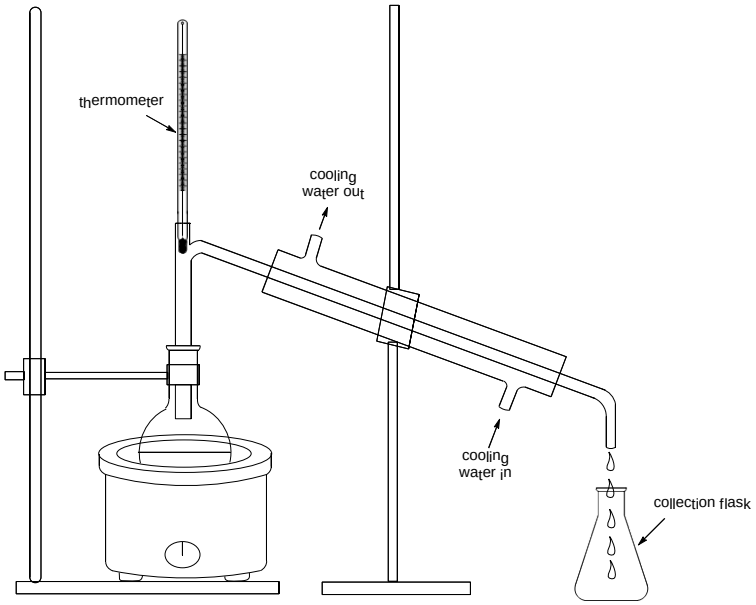
IV.1.5 **Distillation range**

Distillation is a process, during which the liquid is evaporated, and the vapour is condensed and captured in an another flask. The product of the process is called distillate.

Distillation is a method of separating mixtures based on differences in the composition of the liquid mixture and its vapour formed at a certain temperature – unless it is an azeotropic mixture. This method is suitable for separation of volatile and non-volatile compounds, or for separation of volatile compounds having different boiling points.

A simple distillation apparatus can be seen on Fig. IV-4. The vapour forms in the distilling flask, and it is liquefied again in the *Liebig condenser*, which leads into the collection flask. The *Kugelrohr* and the *coil condenser* have larger cooling surface area, but they must be vertically arranged, otherwise the distillate cannot pass through consistently.

Figure IV-4: A simple distillation apparatus.



Before heating, a few pieces of pumice stone, glass beads, unglazed porcelain, or glass capillary should be placed into the distilling flask to promote boiling. These materials prevent boiling delay, during which the sudden excessive bubble formation may result in rupture of the distilling flask.

The method of heating depends on the boiling point and flammability of the solution. E.g. in the case of a flammable solution, whose boiling point is under 100 ºC, a water bath should be used. The method of cooling is as follows: in the case of solutions with boiling point under 120 ºC, a tap water is circulated in the cooler; when the boiling point of the solution is between 120 and 160 ºC still water is used for cooling; while above 160 ºC, the condenser is air-cooled.

Some compounds (e.g. camphor, arsenic) turns to gas when heated, without turning into a liquid first at atmospheric pressure. This phenomenon is called *sublimation.* It occurs at temperatures and pressures below a substance's triple point in its phase diagram. Sublimation can also be used for purification of substances.

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IV.1.5.1 Determination of distillation range (Ph. Hg. VIII.)

The *distillation range* is the temperature interval, corrected for a pressure of 101.3 kPa (760 Torr), within which a liquid, or a specified fraction of a liquid, distils in the following conditions.

Apparatus

The apparatus consist of a distillation flask, a straight tube condenser which fits on to the side arm of the flask and a plain-bend adaptor attached to the end of the condenser (Figure IV-4). The lower end of the condenser may, alternatively, be bent to replace the adaptor. A thermometer is inserted in the neck of the flask so that the upper end of the mercury reservoir is 5 mm lower than the junction of the lower wall of the lateral tube. The thermometer is graduated at 0.2 °C intervals and the scale covers a range of about 50 °C. During the determination, the flask, including its neck, is protected from draughts by a suitable screen.

Method

Place 50.0 ml of the liquid to be examined and a few pieces of porous material in the flask. Collect the distillate in a 50 ml cylinder graduated in 1 ml. Cooling by circulating water is essential for liquids distilling below 150 °C. Heat the flask so that boiling is rapidly achieved and note the temperature at which the first drop of distillate falls into the cylinder. Adjust the heating to give a regular rate of distillation of 2-3 ml/min and note the temperature when the whole or the prescribed fraction of the liquid, measured at 20 °C, has distilled.

Table IV-2: Temperature correction (Ph. Hg. VIII.).

Distillation temperature (^{o}C)	**Correction factor (*k*)**
< 100	0.30
100-140	0.34
140-190	0.38
190-240	0.41
> 240	045

Correct the observed temperatures for barometric pressure by means of the formula:

$$t_1 = t_2 + k\,(101.3\text{-}b)$$

where

t_1 = the corrected temperature,

t_2 = the observed temperature, at the barometric pressure b,

k = the correction factor (**Table IV-2**)

b = the barometric pressure, expressed in kilopascals, during the distillation.

IV.1.6 **Warming and boiling**

Laboratory instruments can be warmed with direct or indirect heating equipment. The *Bunsen burner*, the *electric hot plate*, or the *electric heating mantles* operate by direct heat transfer. Frequently, especially when working with flammable compounds, warming should be performed using heat-transfer mediators (e.g. heating baths). As a heat-transfer mediator, water, oil and sand is used in most of the cases.

Solid compounds are heated in crucibles. Generally, crucibles are made of porcelain; they are placed into a *clay triangle* put onto a *Bunsen-tripod* and heated with direct flame from a *Bunsen burner*.

When large number of samples has to be ignited or high temperature should be applied, automatically controlled *electric ovens* can be used.

Small volumes of aqueous solutions can be warmed in test tubes heated with direct flame from a *Bunsen burner*. Direct heating of test tubes should be done cautiously with mild shaking. Care has to be taken that the volume of liquid in the test tube (with a volume of 20 cm^3) should not be more than 4-5 cm^3, even after mixing of all the reactants. When boiling, the test tube can be held with the use of a *test tube clamp*. *The mouth of the tube is never to be pointed at ourselves or anyone else.*

A larger amount of non-flammable and not too volatile liquid can be boiled in an *Erlenmeyer flask* or a *beaker* placing the glassware onto an *asbestos wire gauze* (heated by a *Bunsen burner*) or an *electric hot plate*. In order to avoid overheating or foaming, a few pieces of boiling stone should be put into the liquid. Heating always has to be started with a small flame.

Small quantities of flammable liquids can be heated under the hood on an electric *hot plate* or in an *electric water bath*. A larger quantity of such liquids can be heated in a ground glass flask equipped with a reflux condenser in an *electric water bath* or in an *electric heating mantle.*

If a sample of a liquid is placed in an otherwise empty, closed container, some of it will vaporize, and the pressure in the space above the liquid will rise to some constant value. The pressure under these conditions is due entirely to the vapour of the liquid, and is called the *equilibrium vapour pressure.* The vapour pressure depends on the temperature: the higher the temperature the higher the equilibrium vapour pressure. The temperature at which the equilibrium vapour pressure equals the pressure of the pressure above the liquid (outer pressure) is the *boiling temperature*. The *boiling point* of liquids – if there are no other specific criteria – is the temperature, at which the vapour pressure equals the see-level atmospheric (101.3 kPa) pressure. To get the boiling point, the determined boiling temperature has to be converted to 760 Hgmm (101.3 kPa), by means of a simple tool, called *nomograph* (Fig. IV-5). Application of this chart is rather useful, since vapour pressure does not show an easily computable linear, but an exponential temperature dependence (*Clausius-Clapeyron equation*).

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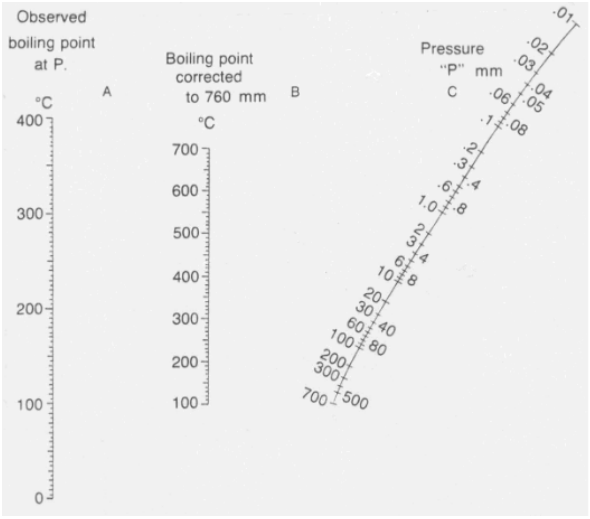
Figure IV-5: Pressure nomograph.



While boiling – if the outer pressure is constant - the temperature of the boiling liquid remains constant; the transferred amount of heat is used to provide the *heat of evaporation* needed for the liquid–vapour transformation. The boiling point of a substance available in a large quantity can be determined by distillation. Care must be taken during distillation that boiling should be consistent, and the thermometer should be surrounded by sufficient quantity of equilibrium vapour.

IV.1.6.1 Determination of boiling point (Ph. Hg. VIII.)

The *boiling point* is the corrected temperature at which the vapour pressure of a liquid is equal to 101.3 kPa.

Apparatus

The apparatus is that used for *distillation range* with the exception that the thermometer is inserted in the neck of the flask so that the lower end of the mercury reservoir is level with the lower end of the neck of the distillation flask and that the flask is placed on a plate of isolating material pierced by a hole 35 mm in diameter.

Method

Place 20 ml of the liquid to be examined and a few pieces of porous material in the flask. Heat the flask so that boiling is rapidly achieved and record the temperature at which liquid runs from the side-arm into the condenser.

Correct the observed temperature for barometric pressure by means of the formula:

$$t_1 = t_2 + k\,(101.3\text{-}b)$$

where

t_1 = the corrected temperature,
t_2 = the observed temperature, at the barometric pressure b,
k = the correction factor (**Table IV-2**)
b = the barometric pressure, expressed in kilopascals, during the distillation.

IV.1.7 **Measurement of density**

Density (ρ) is the mass (m) of the volume (V) unit of a substance:

$$\rho = \frac{m}{V}$$

$$\rho = \frac{m}{V} \rightarrow m = \rho \cdot V$$

The SI unit of density is the $kg \cdot m^{-3}$. In practice, both $g \cdot cm^{-3}$ and $g \cdot dm^{-3}$ units are also used.

The density of a material varies with temperature and pressure. This variation is typically small for solids and liquids but much greater for gases. Increasing the pressure on an object decreases the volume of it and thus increases its density. Increasing the temperature of a substance (with a few exceptions) decreases its density by increasing its volume.

The density of a compound determined at 0 °C is called *normal density*. Density of the same compound at a t temperature (ρ_t) can be calculated from the change in the volume. Densities and volumes measured at different temperatures are inversely proportional to each other.

$$\rho_t : \rho_0 = V_0 : V_t$$

So:

$$\rho_t = \frac{\rho_0 \cdot V_0}{V_t} = \frac{\rho_0 \cdot V_0}{V_0(1+\alpha t)}$$

where α is the *cubic heat expansion coefficient.*

The density determined above is called *absolute density*. To simplify comparisons of density across different systems of units, it is sometimes replaced by the dimensionless quantity *relative density*, i.e. the ratio of the density of the material to that of a reference material. The reference material for the gases is usually dry air, while for liquids and solids is water. The *relative density* is the ratio of two absolute densities that are in the same physical conditions (same pressure and temperature).

If the reference material is not explicitly stated then it is normally assumed to be water at 4 °C (or, more precisely, 3.98 °C, which is the temperature at which water reaches its maximum density). Thus, the *relative density* of solids or liquids is the ratio of mass of unit volume of the tested material measured at 20 °C to the mass of unit volume of water measured at 4 °C. The symbol for relative density is d_4^{20}. The (absolute) density of the water on 4 (3.98) °C is approximately 1000.00 (999.9720) kg/m^3 = 1.00000 (0.999972) g/cm^3, which makes relative density calculations particularly convenient: the density of the object only needs to be divided by 1000 or 1, depending on the units.

Relative density can be calculated directly by measuring the density of a sample and dividing it by the (known) density of the reference substance. In practice, density of liquids is determined most frequently. For determination of densities of liquids *hydrometer*, *pycnometer*, *hydrostatic balance* (Mohr-Westphal balance) and *digital densitometers* can be used.

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The density of liquids can be conveniently and quickly determined by hydrometers. This consists of a bulb attached to a stalk of constant cross-sectional area (Figure IV-6; a).

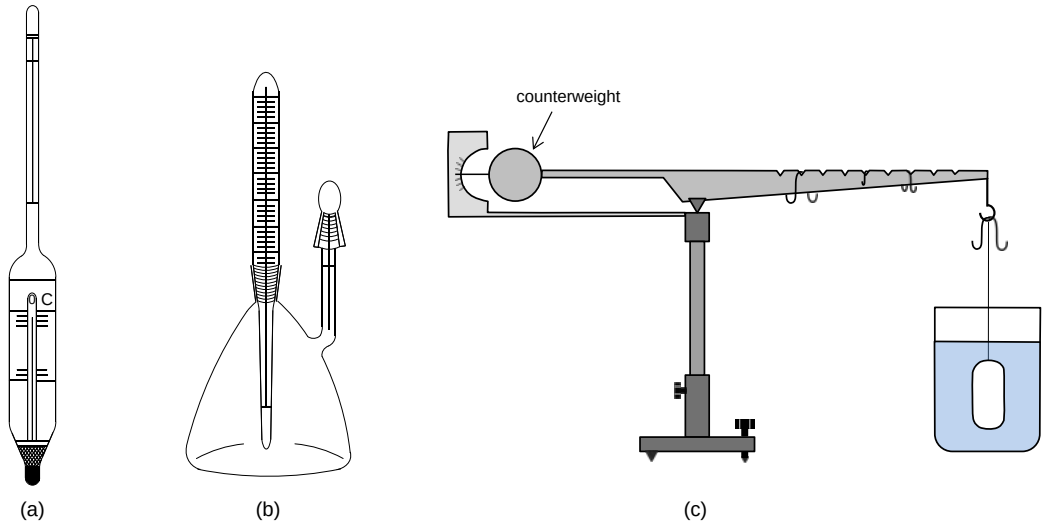
First the hydrometer is floated in the reference liquid and the displacement (the level of the liquid on the stalk) is marked. The reference could be any liquid, but in practice it is usually water. The hydrometer immerses into the liquid until the weight of the discharged liquid is equal with the weight of the hydrometer (*Archimedes' principle*).

The hydrometer is then floated in a liquid of unknown density. The change in displacement is noted. Application of simple physical principles allows the relative density of the unknown liquid to be calculated from the change in displacement.

It is, of course, necessary that the hydrometer floats in both liquids. A hydrometer can be applied only in a definite range of density. Accordingly, two types of hydrometers are used. "*Search hydrometers*" are applied for determination of the approximate density of the tested liquid to find the appropriate measuring range. For accurate measurements "*measuring hydrometers*" can be used, which are operating in the relevant (narrow) density range.

A *pycnometer* is a device used to determine the density of a liquid. Using pycnometers, measurement of density is based on measurement of mass and volume: mass of liquid of known volume is measured and the density is calculated from the measured data. A pycnometer is a bottle with a capacity of usually 10 ml to 100 ml, having a ground-glass stopper fitted with a thermometer, and a side inlet-tube with a marked line and a close-fitting ground glass stopper (Figure IV-6; b). This device enables a liquid's density to be measured accurately by reference to an appropriate working fluid, such as water, using an analytical balance.

Figure IV-6: Tools for density measurement.



Since density is the function of temperature, it is necessary to measure the temperature of the sample. After setting the meniscus into the proper position, the side inlet-tube can be closed with a glass stopper and practically there is no evaporation loss. If the flask is weighed empty, full of water, and full of a liquid whose relative density is desired, the relative density of the liquid can easily be calculated. The mass of the

empty pycnometer is subtracted from masses of the filled pycnometer, and because their volumes are the same, their ratio of density is the same as their ratio of masses.

Density measurement of liquids by hydrostatic method is based on *Archimedes' principle*. Determination is based on measurement of mass reduction of a reference glass body (plummet) of known volume in liquids with known and unknown densities. These measurements can be performed using a *hydrostatic* or a *Mohr-Westhphal balance*.

The *Mohr-Westphal balance* (Figure IV-6; c) is an unequal-arm balance designed for determining the density of liquids and solids by hydrostatic weighing. The heaviest unit of the counterweight series - a U shaped nickel-plated brass wire - has a weight equal to the reduced weight (to vacuum) of that volume of water of 4 °C which is equal to the volume of the plummet. The smaller counterweights (called *riders*) are the 0.1, 0.01 and 0.001 parts of weight of the main unit. If the weight loss of the plummet is measured by these series of counterweights, the density will be given directly as the weight loss of the plummet.

To operate a Mohr-Westphal balance care must be taken to first calibrate the balance by means of the levelling screw at the bottom of the body. With no weight on the arm of the balance the two pointers must be aligned before the balance can be used. Then the plummet is fully immersed into distilled water of 4 °C temperature. To reset the equilibrium position of the balance the heaviest counterweight have to hang on the No 10 position (tenth notch) of the bar; because the density of distilled water at 4 °C is 1.0000 g/cm^3. If the plummet is immersed into a liquid of density of 1.354 g/ml, one of the two largest weight units has to be placed to the end (first notch) of the bar, while the 0.1 unit counterweight is to be placed onto the third notch, and continuously, the 0.01 unit counterweight onto the fifth and the 0.001 unit counterweight have to be placed onto the fourth notch of the arm to balance the scale.

With the use of the Mohr-Westphal balance, the density can be determined conveniently with three-decimal-precision without performing calculations, but this method does not reach the accuracy of measurements with a pycnometer.

IV.1.7.1 Measurement of relative density (Ph. Hg. VIII.)

The *relative density* d_{t2}^{t1} of a substance is the ratio of the mass of a certain volume of a substance at temperature t_1 to the mass of an equal volume of water at temperature t_2.

Unless otherwise indicated, the relative density d_{20}^{20} is used. Relative density is also commonly expressed as d_4^{20}.

Density ρ_{20}, defined as the mass of a unit volume of the substance at 20 °C may also be used, expressed in kilograms per cubic meter or grams per cubic centimetre ($1\ kg \cdot m^{-3} = 10^{-3}\ g \cdot cm^{-3}$). These quantities are related by the following equations where density is expressed in grams per cubic centimetre:

$\rho_{20} = 998.202\ d_{20}^{20}$ or $d_{20}^{20} = 1.00180 \cdot 10^{-3}\ \rho_{20}$

$\rho_{20} = 999.972\ d_4^{20}$ or $d_4^{20} = 1.00003 \cdot 10^{-3}\ \rho_{20}$

$d_4^{20} = 0.998230\ d_{20}^{20}$

Relative density or density are measured with the precision to the number of decimals prescribed in the monograph using a density bottle (solids or liquids), a

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hydrostatic balance (solids), a hydrometer (liquids) or a digital density meter with an oscillating transducer (liquids and gases).

When the determination is made by weighing, the buoyancy of air is disregarded, which may introduce an error of 1 unit in the 3rd decimal place. When using a density meter, the buoyancy of air has no influence.

Experimental task: Determination of density and ethanol content of *Ethanolum* (*96 per centum*) Ph. Hg. VIII.

Measurement with pycnometer

The mass of the dry pycnometer (with its stopper) has to be weight accurately by an analytical balance. The pycnometer should be filled entirely with the liquid of which density is to be determined. Keep the pycnometer filled with the liquid in a water-bath at 20 °C ± 0.1 °C for 20 minutes before adjustment the meniscus. When closing the pycnometer, a special attention has to pay that there should not remain any air bubbles in the liquid and the any spilled fluid has to be wiped off from the outer side of the glassware.

The measurement can be achieved by three consecutive weighing. First, the mass of the clean and dry pycnometer has to be measured by an analytical balance (m_1), then, after taking off the stopper and the capillary of the pycnometer, it is to be filled with the liquid of which density is to be determined (*Ethanolum 96 per centum*). Keep the filled pycnometer in a water-bath at 20 °C ± 0.1 °C for 20 minutes before adjustment the meniscus. Then, adjust the meniscus, wipe off water from the outer side of the glassware and perform the weighing repeatedly (m_2). The mass of the test fluid (m_t;) is equal to:

$$m_t = m_2 - m_1$$

After the measurement, the pycnometer is emptied and rinsed thoroughly. Then, similar to the measurement with the test liquid, the dish is filled with *water R*. The properly thermostated and filled dish is weighed again (m_3). The mass of the liquid (*water R*) in the dish is equal to:

$$m_w = m_3 - m_1$$

Based on the mass of the test liquid (m_t) and the mass of the same volume of water (m_w) the relative density of the liquid related to 20 °C can be calculated as follows:

$$\rho_{20^\circ C} = \frac{m_t}{m_w} = \frac{m_2 - m_1}{m_3 - m_1} = \frac{m_2 - m_1}{m_3 - m_1} \cdot 0.997003 + 0.0012$$

According to the Pharmacopeia (Ph. Hg. VIII.) the relative density of the *Ethanolum 96 per centum* should fall into the region of 0.805 to 0.812.

Determination of ethanol content

The ethanol (C_2H_6O) content should be calculated on the basis of the alcoholimetric table of the Pharmacopeia (Ph. Hg. VIII.) (**Table IV-3**).

Table IV-3: Alcoholimetric table (Ph. Hg. VIII.).

%v/v	% m/m	ρ_{20}	%v/v	% m/m	ρ_{20}	%v/v	% m/m	ρ_{20}
94.0	91.01	0.8151	95.0	92.41	0.8113	96.0	93.84	0.8074
94.1	91.15	0.8148	95.1	92.55	0.8109	96.1	93.98	0.8070
94.2	91.29	0.8144	95.2	92.69	0.8106	96.2	94.13	0.8066
94.3	91.43	0.8140	95.3	92.83	0.8102	96.3	94.27	0.8062
94.4	91.56	0.8136	95.4	92.98	0.8098	96.4	94.42	0.8057
94.5	91.70	0.8133	95.5	93.12	0.8094	96.5	94.57	0.8053
94.6	91.84	0.8129	95.6	93.26	0.8092	96.6	94.71	0.8049
94.7	91.98	0.8125	95.7	93.41	0.8086	96.7	94.86	0.8045
94.8	92.13	0.8121	95.8	93.55	0.8082	96.8	95.01	0.8041
94.9	92.27	0.8117	95.9	93.69	0.8088	96.9	95.16	0.8037

According to the Pharmacopeia (Ph. Hg. VIII.) the C_2H_6O content of *Ethanolum 96 per centum* should fall into the region of 95.1-96.9 % V/V (92.6-95.2 % m/m).

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IV.2 IDENTIFICATION

IV.2.1 Identification reactions of ions (Ph. Eur. 8.0/Ph. Hg. VIII.) (Selection)

Aluminium

Dissolve about 15 mg of the substance to be examined in 2 ml of *water R* or use 2 ml of the prescribed solution. Add about 0.5 ml of *dilute hydrochloric acid R* and about 0.5 ml of *thioacetamide reagent R*. No precipitate is formed. Add dropwise *dilute sodium hydroxide solution R*. A gelatinous white precipitate is formed which dissolves on further addition of *dilute sodium hydroxide solution R*. Gradually add *ammonium chloride solution R*. The gelatinous white precipitate is re-formed.

In the first part of the experiment other amphoteric cations which form precipitates with sulphide in acid medium are excluded (e.g. Pb(II), Sn(II), Sb(III)). Addition of sodium hydroxide results in formation of aluminium hydroxide precipitate, wich dissolve in the excess of the reagent:

$$Al^{3+} + 3\ OH^- \longrightarrow \underline{Al(OH)_3}$$

$$\underline{Al(OH)_3} + OH^- \rightleftharpoons [Al(OH)_4]^-$$

Ammonium ions hydrolyse with the formation of protons, thus

$$[Al(OH)_4]^- + H^+ \rightleftharpoons \underline{Al(OH)_3} + H_2O$$

Ammonium salts

To the prescribed solution add 0.2 g of *magnesium oxide R*. Pass a current of air through the mixture and direct the gas that escapes just beneath the surface of a mixture of 1 ml of *0.1 M hydrochloric acid* and 0.05 ml of *methyl red solution R*. The colour of the indicator changes to yellow. On addition of 1 ml of a freshly prepared 100 g/l solution of *sodium cobaltinitrite R* a yellow precipitate is formed.

Adding magnesium oxide, the strong, non-volatile base to the solution liberates ammonia, which can be recognized by its characteristic smell.

$$MgO + 2\ NH_4^+ = Mg^{2+} + 2\ NH_3 + H_2O$$

Ammonia neutralizes the hydrochloric acid solution and changes the acid colour of the indicator to yellow. The formed ammonium ions form yellow precipitate with sodium-hexanitritocobaltate(III). The reaction is not selective, potassium ions also give a positive reaction.

$$2\ NH_4^+ + Na_3[Co(NO_2)_6] = \underline{(NH_4)_2Na[Co(NO_2)_6]} + 2\ Na^+$$

Arsenic

Heat 5 ml of the prescribed solution on a water-bath with an equal volume of *hypophosphorous reagent R*. A brown precipitate is formed.

Arsenite or arsenate ions are reduced to arsenic, which is a brown precipitate.

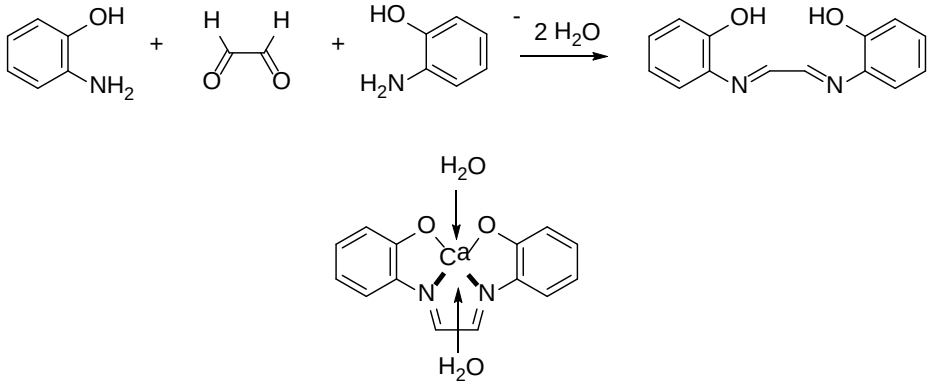
$$2\ AsO_3^{3-} + 3\ H_2PO_2^- + 9\ H^+ = 2\ \underline{As} + 3\ H_3PO_3 + 3\ H_2O$$

$$2\ AsO_4^{3-} + 5\ H_2PO_2^- + 11\ H^+ = 2\ \underline{As} + 5\ H_3PO_3 + 3\ H_2O$$

Calcium

a) To 0.2 ml of a neutral solution containing the substance to be examined in a quantity equivalent to about 0.2 mg of calcium (Ca^{2+}) per millilitre, or to 0.2 ml of the prescribed solution add 0.5 ml of a 2 g/l solution of *glyoxal-hydroxyanil R* in *ethanol (96 per cent) R*, 0.2 ml of *dilute sodium hydroxide solution R* and 0.2 ml of *sodium carbonate solution R*. Shake with 1 ml to 2 ml of *chloroform R* and add 1 ml to 2 ml of *water R*. The chloroform layer is coloured red.

Glyoxalhydroxyanil is the product of the reaction of hydroxyaniline and glyoxal, which forms a red chelate complex (λ_{max}= 520 nm) with calcium ions in alkaline medium. Other alkaline earth metal ions (Ba(II), Sr(II)), which also form complexes with glyoxalhydroxyanil are precipitated out with carbonate ions.



b) Dissolve about 20 mg of the substance to be examined or the prescribed quantity in 5 ml of *acetic acid R*. Add 0.5 ml of *potassium ferrocyanide solution R*. The solution remains clear. Add about 50 mg *ammonium chloride R*. A white, crystalline precipitate is formed.

Calcium ions do not react in acidic medium directly with hexacyanatoferrate(II) ions, but after addition of ammonium ions a white precipitate is formed. Magnesium ions also give positive reaction.

$$Ca^{2+} + 2\,NH_4^+ + [Fe(CN)_6]^{4-} = \underline{Ca(NH_4)_2[Fe(CN)_6]}$$

Carbonates and bicarbonates

0.1 g of the substance to be examined or 2 ml of the prescribed solution is placed into a test tube and suspended in 2 ml of *water R*. Add 3 ml of *dilute acetic acid R*. Close the tube immediately using a stopper fitted with a glass tube bent twice at right angles. The solution or the suspension becomes effervescent and gives off a colourless and odourless gas. Heat gently and collect the gas in 5 ml of *barium hydroxide solution R*. A white precipitate is formed that dissolves on addition of an excess of *hydrochloric acid R1*.

$$CO_3^{2-} + 2\,H^+ \longrightarrow CO_2 + H_2O$$

$$HCO_3^- + H^+ \longrightarrow CO_2 + H_2O$$

$$Ba(OH)_2 + CO_2 \longrightarrow \underline{BaCO_3} + H_2O$$

$$\underline{BaCO_3} + 2\,H^+ = Ba^{2+} + CO_2 + H_2O$$

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Chlorides

a) Dissolve a quantity of the substance to be examined equivalent to about 2 mg of chloride (Cl^-) in 2 ml of *water R* or use 2 ml of the prescribed solution. Acidify it with *dilute nitric acid R* and add 0.4 ml of *silver nitrate solution R1*. Shake it and allow it to stand. A curdled, white precipitate is formed. Centrifuge and wash the precipitate with three quantities, 1 ml each, of *water R*. Carry out this operation rapidly in subdued light, disregarding the fact that the supernatant solution may not become perfectly clear. Suspend the precipitate in 2 ml of *water R* and add 1.5 ml of *ammonia R*. The precipitate dissolves easily with the possible exception of a few large particles which dissolve slowly.

$$Ag^+ + Cl = \underline{AgCl}$$

$$\underline{AgCl} + 2\,NH_3 = [Ag(NH_3)_2]^+ + Cl^-$$

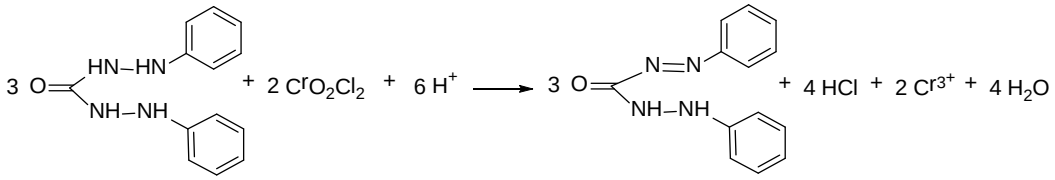
The pale yellow <u>AgBr</u> dissolves with difficulty, and the yellow <u>AgI</u> is insoluble in ammonia.

b) Place a quantity of the substance to be examined equivalent to about 15 mg of chloride (Cl^-) or the prescribed quantity into a test tube. Add 0.2 g of *potassium dichromate R* and 1 ml of *sulphuric acid R*. Place a filter-paper strip impregnated with 0.1 ml of *diphenylcarbazide solution R* over the opening of the test-tube. The paper turns violet-red. The impregnated paper must not come into contact with the potassium dichromate.

In concentrated sulphuric acid chloride ions react with dichromate ions to form volatile chromyl chloride.

$$4\,Cl^- + Cr_2O_7^{2-} + 6\,H^+ = 2\,CrO_2Cl_2 + 3\,H_2O$$

Chromyl chloride can oxidize diphenylcarbazide to diphenylcarbazone, which forms a violet 1:1 complex with the produced chromium(III) ions.



Iodides

a) Dissolve a quantity of the substance to be examined equivalent to about 4 mg of iodide (I^-) in 2 ml of *water R* or use 2 ml of the prescribed solution. Acidify it with *dilute nitric acid R* and add 0.4 ml of *silver nitrate R1*. Shake it and allow it to stand. A curdled, pale-yellow precipitate is formed. Centrifuge and wash it with three quantities, 1 ml each, of *water R*. Carry out this operation rapidly in subdued light disregarding the fact that the supernatant solution may not become perfectly clear. Suspend the precipitate in 2 ml of *water R* and 1.5 ml of *ammonia R*. The precipitate does not dissolve.

$$Ag^+ + I = \underline{AgI}$$

b) Add 0.5 ml of *dilute sulphuric acid R*, 0.1 ml of *potassium dichromate solution R*, 2 ml of *water R* and 2 ml of *chloroform R* to 0.2 ml of a solution of the substance to be examined containing about 5 mg of iodide (I^-) per millilitre, or to 0.2 ml of the

prescribed solution. Shake it for a few seconds and allow it to stand. The chloroform layer is coloured violet or violet-red.

The iodine produced in the reaction dissolves in chloroform with a violet or violet-red colour.

$$Cr_2O_7^{2-} + 6\,I^- + 14\,H^+ = 2\,Cr^{3+} + 3\,I_2 + 7\,H_2O$$

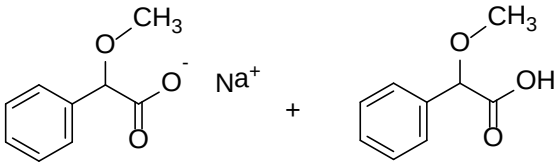
Sodium

a) Dissolve 0.1 g of the substance to be examined in 2 ml of *water R* or use 2 ml of the prescribed solution. Add 2 ml of a 150 g/l solution of *potassium carbonate R* and heat to boiling. No precipitate is formed. Add 4 ml of *potassium pyroantimonate solution R* and heat to boiling. Allow to cool in iced water and if necessary rub the inside of the test-tube with glass rod. A dense white precipitate is formed.

In the first part of the experiment the majority of cations are excluded by the reaction with carbonate ions.

$$Na^+ + [Sb(OH)_6]^- \rightleftharpoons \underline{Na[Sb(OH)_6]}$$

b) Dissolve a quantity of the substance to be examined equivalent to about 2 mg of sodium (Na^+) in 0.5 ml of *water R* or use 0.5 ml of the prescribed solution. Add 1.5 ml of *methoxyphenylacetic reagent R* and cool the reaction mixture in ice-water for 30 min. A voluminous, white, crystalline precipitate is formed. Place it in water at 20 ºC and stir for 5 min. The precipitate does not disappear. Add it to 1 ml of *dilute ammonia R1*. The precipitate dissolves completely. Add 1 ml of *ammonium carbonate solution R*. No precipitate is formed.



Sodium ions with α-methoxyphenylacetic acid form a precipitate of 1:2 ratio of sodium ions and the reagent, which crystallizes out of the cooled solution. The precipitate does not dissolve on addition of ammonium carbonate solution.

Sulphates

a) Dissolve about 45 mg of the substance to be examined in 5 ml of *water R* or use 5 ml of the prescribed solution. Add 1 ml of *dilute hydrochloric acid R* and 1 ml of *barium chloride solution R1*. A white precipitate is formed.

$$Ba^{2+} + SO_4^{2-} = \underline{BaSO_4}$$

b) Add 0.1 ml of *0.05 M iodine* to the suspension obtained during reaction (a). The suspension remains yellow (distinction from sulphites and dithionites), but is decolourised by adding *stannous chloride solution R* dropwise (distinction from iodates). Boil the mixture. No coloured precipitate is formed (distinction from selenates and tungstates).

Sulphite and dithionite ions reduce iodine to iodide ions, thus the solution becomes colourless (before addition of stannous ions). Iodate ions reoxidize iodide, formed in the reaction with stannous ions, to iodine, thus the solution will not become

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colourless. In the presence of selenate ions red elementary selenium would precipitate, while tungstates would form a blue precipitate.

$$SO_3^{2-} + I_2 + H_2O = SO_4^{2-} + 2\,I^- + 2\,H^+$$

$$S_2O_4^{2-} + 3\,I_2 + 4\,H_2O = 2\,SO_4^{2-} + 6\,I^- + 8\,H^+$$

$$Sn^{2+} + I_2 = Sn^{4+} + 2\,I^-$$

$$IO_3^- + 5\,I^- + 6\,H^+ = 3\,I_2 + 6\,H_2O$$

$$Sn^{2+} + I_2 = Sn^{4+} + 2\,I^-$$

IV.2.2 **Identification reactions of functional groups (Ph. Eur. 8.0./Ph. Hg. VIII.) (Selection)**

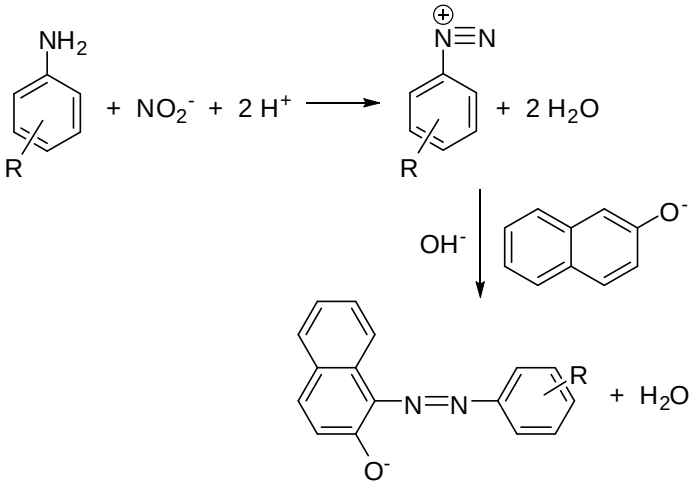
Alkaloids

Dissolve a few milligrams of the substance to be examined, or the prescribed quantity, in 5 ml of *water R*, add *dilute hydrochloric acid R* until an acid reaction occurs, then 1 ml of *potassium iodobismuthate solution R*. An orange or orange-red precipitate is formed immediately.

With large cations like protonated ammonium salts (HB^+) Dragendorff reagent forms a coloured precipitate in acid medium: $\underline{HB[BiI_4]}$. Weakly basic amines do not react. Typical reaction of alkaloids.

Amines, primary aromatic

Acidify the prescribed solution with *dilute hydrochloric acid R* and add 0.2 ml of *sodium nitrite solution R*. After 1 to 2 min, add 1 ml of *β-naphthol solution R*. An intense orange or red colour and usually a precipitate of the same colour are produced.

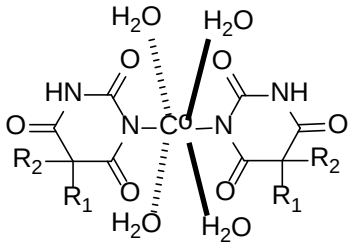


red azodye

First a diazonium cation is formed that reacts in alkaline medium with activated aromatic ring containing compounds, e.g. 2-naphthol and a red coloured azo dye is produced.

Barbiturates, non-nitrogen substituted

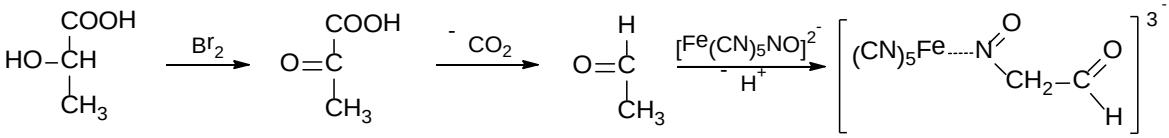
Dissolve about 5 mg of the substance to be examined in 3 ml of *methanol R*, add 0.1 ml of a solution containing 100 g/l of *cobalt(II) nitrate R* and 100 g/l of *calcium chloride R*. Mix and add, with shaking, 0.1 ml of *dilute sodium hydroxide solution R*. A violet-blue colour and precipitate are formed.



Parri-Zwicker reaction*: Dissolved in methanol the compounds form a violet-blue octahedral complex with cobalt(II) ions in alkaline solution. The base promotes deprotonation of barbiturates. The reaction is not selective, hydantoins, sulphonamides, a few purines, some pyridine and piperidine derivatives react silmilarly.*

Lactates

Dissolve a quantity of the substance to be examined equivalent to about 5 mg of lactic acid in 5 ml of *water R* or use 5 ml of the prescribed solution. Add 1 ml of *bromine water R* and 0.5 ml of *dilute sulphuric acid R*. Heat on a water-bath until the colour is discharged, stirring occasionally with a glass rod. Add 4 g of *ammonium sulphate R* and mix. Add dropwise and without mixing 0.2 ml of a 100 g/l solution of *sodium nitroprusside R* in dilute *sulphuric acid R*. Still without mixing add 1 ml of *concentrated ammonia R*. Allow to stand for 30 min. A dark green ring appears at the junction of the two liquids.



Lactic acid is oxidized by bromine to pyruvic acid that is decarboxylated to form acetaldehyde. Acetaldehyde is detected in the Legal reaction with pentacyanonitrosylferrate(II) anions.

Tartrates

a) Dissolve about 15 mg of the substance to be examined in 5 ml of *water R* or use 5 ml of the prescribed solution. Add 0.05 ml of a 10 g/l solution of *ferrous sulphate R* and 0.05 ml of *dilute hydrogen peroxide solution R*. A transient yellow colour is produced. After the colour has disappeared add *dilute sodium hydroxide solution R* dropwise. A violet or purple colour is produced.

Hydrogen peroxide oxidizes tartaric acid in the presence of iron(II) ions to dihydroxyfumaric acid and iron(II) ions to iron(III) ions. The two products form a violet-blue complex in alkaline medium.

$$H_2O_2 + Fe^{2+} = Fe^{3+} + OH^- + HO^{\cdot}$$

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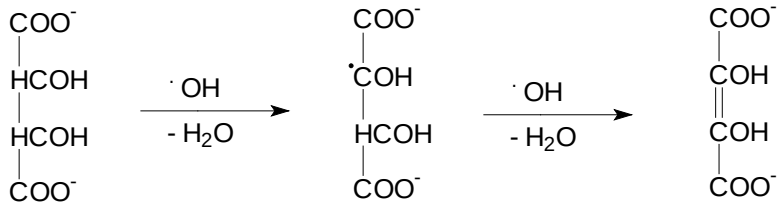
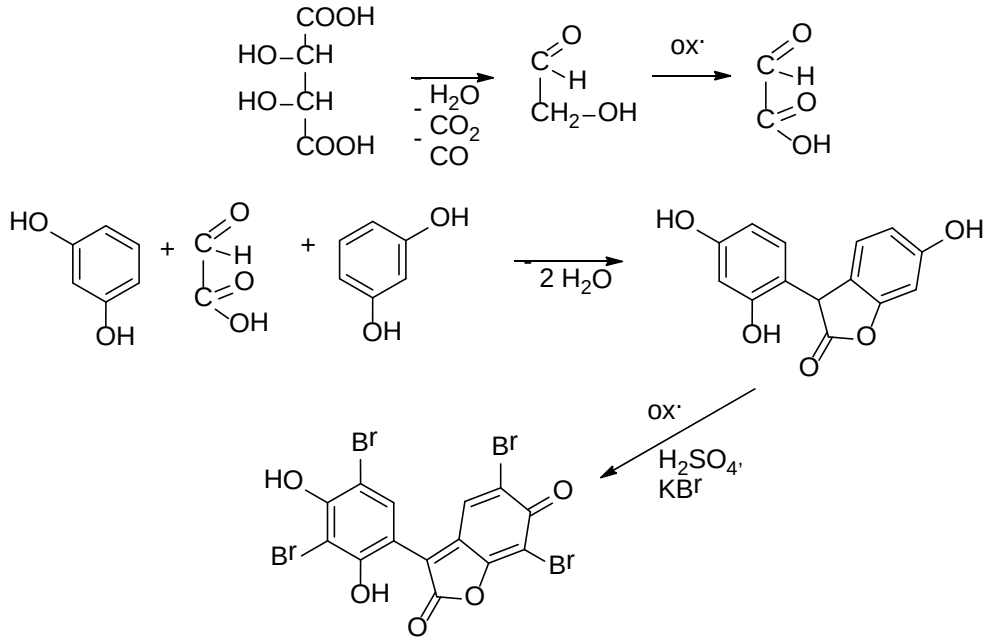


b) Add 0.1 ml of a 100 g/l solution of *potassium bromide R*, 0.1 ml of a 20 g/l solution of *resorcinol R* and 3 ml of *sulphuric acid R* to 0.1 ml of a solution of the substance to be examined containing the equivalent of about 15 mg of tartaric acid per millilitre or to 0.1 ml of the prescribed solution. Heat it on a water-bath for 5 min to 10 min. A dark-blue colour develops. Allow it to cool and pour the solution into *water R*. The colour changes to red.

Pesez reaction*: Tartaric acid – by losing carbon dioxide, carbon monoxide and water – is converted to glycolaldehyde, which is oxidized to glyoxylic acid. Glyoxylic acid, being an aldehyde, condenses with resorcinol to a diphenylmethane dye that immediately forms an intramolecular ester, a lactone. It is oxidized and substituted with bromine and the produced compound exists in strong sulphuric acid medium as an oxonium salt (blue). After dilution, the original colour of the product (red) is observed.*



IV.3 LIMIT TESTS (Ph. Eur. 8.0/Ph. Hg. VIII.)

Ammonium

METHOD A

Dissolve the prescribed quantity of the substance to be examined in 14 ml of *water R* in a test-tube, make the solution alkaline if necessary by the addition of *dilute sodium hydroxide solution R* and dilute it to 15 ml with *water R*. Add 0.3 ml of *alkaline potassium tetraiodomercurate solution R* to the solution. Prepare a standard by mixing 10 ml of *ammonium standard solution (1 ppm NH_4) R* with 5 ml of *water R* and 0.3 ml of *alkaline potassium tetraiodomercurate solution R*. Stopper the test-tubes.

After 5 min, any yellow colour in the test solution is not more intense than in the standard.

Small amounts of ammonium impurities are detected in the form of yellow colorization caused by addition of Nessler reagent. Due to the µg amount of ammonium ions precipitation can be observed as slight colorization.

$$NH_3 + 2\,K_2HgI_4 + 3\,KOH = \underline{HgO{\cdot}HgNH_2I} + 7\,KI + 2\,H_2O$$

$$NH_3 + 2\,K_2HgI_4 + KOH = \underline{HgI_2{\cdot}HgNH_2I} + 5\,KI + H_2O$$

Nessler reagent as a general reagent for alkaloids gives a positive reaction with organic tertiary amines, thus the reaction is not selective.

METHOD B

Place the prescribed quantity of the finely powdered substance to be examined in a 25 ml jar fitted with a cap, and dissolve or suspend it in 1 ml of *water R*. Add 0.30 g of *heavy magnesium oxide R*. Close the jar immediately after placing a piece of *silver manganese paper R* 5 mm square, wetted with a few drops of *water R*, under the polyethylene cap. Swirl, avoiding projections of liquid, and allow it to stand at 40 ºC for 30 min. If the silver manganese paper shows a grey colour, it is not more intense than that of a standard prepared at the same time and in the same manner using the prescribed volume of *ammonium standard solution (1 ppm NH_4) R*, 1 ml of *water R* and 0.30 g of *heavy magnesium oxide R*.

The basic magnesium oxide reacts with the ammonium ions to liberate volatile ammonia gas. Ammonia makes the wetted silver manganese paper basic and under the basic conditions manganese(II) ions reduce silver ions to elementary silver.

$$4\,NH_3 + Mn^{2+} + 2\,Ag^+ + 3\,H_2O = \underline{Mn(OH)_2} + \underline{2\,Ag} + 4\,NH_4^+$$

Arsenic

METHOD A

The apparatus consist of a 100 ml conical flask closed with a ground-glass stopper through which a glass tube about 200 mm long and 5 mm in internal diameter passes. The lower part of the tube is drawn to an internal diameter of 0.1 mm, and 15 mm from its tip is a lateral orifice 2 mm to 3 mm in diameter. When the tube is in position in the stopper, the lateral orifice should be at least 3 mm below the lower surface of the stopper. The upper end of the tube has a perfectly flat, ground surface at right angles to

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the axis of the tube. A second glass tube of the same internal diameter and 30 mm long, with a similar flat ground surface, is placed in contact with the first, and is held in position by two spiral springs. Into the lower tube insert 50 mg to 60 mg of *lead acetate cotton R*, loosely packed, or a small plug of cotton and a rolled piece of *lead acetate paper R* weighing 50 mg to 60 mg. Between the flat surfaces of the tubes place a disc or a small square of *mercuric bromide paper R* large enough to cover the orifice of the tube (15 mm x 15 mm).

In the conical flask dissolve the prescribed quantity of the substance to be examined in 25 ml of *water R*, or in the case of a solution adjust the prescribed volume to 25 ml with *water R*. Add 15 ml of *hydrochloric acid R*, 0.1 ml of *stannous chloride solution R* and 5 ml of *potassium iodide solution R*, allow it to stand for 15 min and introduce 5 g of *activated zinc R*. Assemble the two parts of the apparatus immediately and immerse the flask in a bath of water at a temperature such that a uniform evolution of gas is maintained. Prepare a standard in the same manner, using 1 ml of *arsenic standard solution (1 ppm As) R*, diluted to 25 ml with *water R*.

After not less than 2 h the stain produced on the mercuric bromide paper in the test is not more intense than that in the standard.

***Sanger-Black method**: Due to the effect of different reducing agents (KI, $SnCl_2$, Zn/HCl) arsenic will be reduced to AsH_3 (oxidation number -3) gas, which will flow up in the reagent tube. Detection is made by wet mercury(II) bromide paper put on the mouth of the test tube. Depending on the amount of arsenic different products with coloration from yellow to orange are formed. In the presence of higher levels of As contamination a brown colour can be observed. The test is evaluated after 2 hours, immersing the apparatus into a water-bath at a temperature that maintains a uniform evolution of gas.*

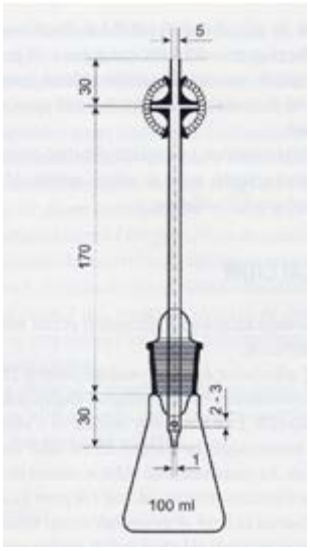
$$AsO_4^{3-} + 2\,I^- + 2\,H^+ = AsO_3^{3-} + I_2 + H_2O$$

$$AsO_3^{3-} + 3\,Zn + 9\,H^+ = AsH_3 + 3\,Zn^{2+} + 3\,H_2O$$

$AsH_3 + HgBr_2 \longrightarrow HBr + AsH_2(HgBr)$	yellow
$AsH_2(HgBr) + HgBr_2 \longrightarrow HBr + AsH(HgBr)_2$	orange
$AsH(HgBr)_2 + HgBr_2 \longrightarrow HBr + As(HgBr)_3$	orange
$AsH_3 + As(HgBr)_3 \longrightarrow 3\,HBr + As_2Hg_3$	brown

The role of KI in the reaction is to reduce As(V) to As(III). As(III) is reduced to elementary As by $SnCl_2$, and further reduced by nascence hydrogen to AsH_3 (with oxidation number -3).

A piece of lead acetate cotton is inserted into the reagent tube of the apparatus, which – by formation of PbS – can eliminate H_2S which may be formed from the possible sulphur contamination of the sample and would react with $HgBr_2$ as well.



METHOD B

Place the prescribed quantity of the substance to be examined into a test-tube containing 4 ml of *hydrochloric acid R* and about 5 mg of *potassium iodide R*, then add 3 ml of *hypophosphorous reagent R*. Heat the mixture on a water-bath for 15 min, shaking it occasionally. Prepare a standard in the same manner, using 0.5 ml of *arsenic standard solution (10 ppm As) R*.

After heating the mixture on the water-bath, any colour in the test solution is not more intense than that in the standard.

Thiele test. *Hypophosphite ions reduce arsenite and arsenate ions to elementary arsenic. Iodide ions reduce As(V) to As(III).*

$$2\ AsO_3^{3-} + 3\ H_2PO_2^- + 9\ H^+ = \underline{2\ As} + 3\ H_3PO_3 + 3\ H_2O$$

$$2\ AsO_4^{3-} + 5\ H_2PO_2^- + 11\ H^+ = \underline{2\ As} + 5\ H_3PO_3 + 3\ H_2O$$

Chlorides

Add 1 ml of *dilute nitric acid R* to 15 ml of the prescribed solution and pour the mixture as a single addition into a test-tube containing 1 ml of *silver nitrate solution R2*. Prepare a standard in the same manner using 10 ml of *chloride standard solution (5 ppm Cl) R* and 5 ml of *water R*. Examine the tubes laterally against a black background.

After standing for 5 min protected from light, any opalescence in the test solution is not more intense than that in the standard.

Chloride ions are detected in nitric acid in the form of <u>AgCl</u>. The colloidal precipitate results in formation of a slight opalescence.

The acid medium excludes phosphates but the reaction is not selective because other halides give a positive reaction as well. (The yellow colour of <u>AgI</u> can not be observed at such low concentration.)

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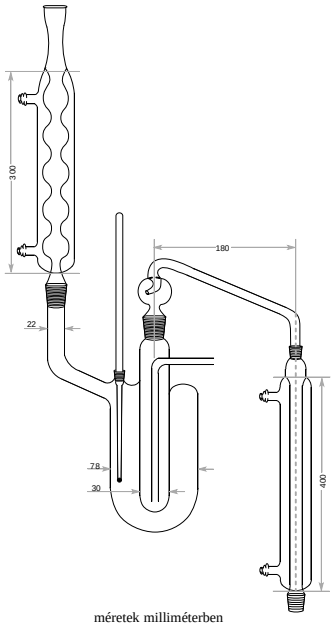
Fluorides

Place the prescribed quantity of the substance to be examined, 0.1 g of acid-washed *sand R* and 20 ml of a mixture of equal volumes of *sulphuric acid R* and *water R* into the inner tube of the apparatus. Heat the jacket containing *tetrachloroethane R* maintained at its boiling point (146 ºC). Heat the steam generator and distil, collecting the distillate in a 100 ml volumetric flask containing 0.3 ml of *0.1 M sodium hydroxide* and 0.1 ml of *phenolphthalein solution R*. Maintain a constant volume (20 ml) in the tube during distillation and ensure that the distillate remains alkaline, adding *0.1 M sodium hydroxide* if necessary. Dilute the distillate to 100 ml with *water R* (test solution).



méretek milliméterben

Prepare a standard in the same manner by distillation, using 5 ml of *fluoride standard solution (10 ppm F) R* instead of the substance to be examined. Into two glass-stoppered cylinders introduce 20 ml of the test solution and 20 ml of the standard and 5 ml of *aminomethylalizarindiacetic acid reagent R*.

After 20 min, any blue colour in the test solution (originally red) is not more intense than that in the standard.

Under acidic conditions fluoride ions are converted to volatile silicon tetrafluoride upon heating.

$$SiO_2 + 6\ H^+ + 6\ F^- = H_2[SiF_6] + 2\ H_2O$$

$$H_2[SiF_6] \xrightarrow{H_2O} SiF_4$$

Reaction of SiF_4 transferred into the solution of sodium hydroxide by steam distillation results in formation of silicic acid and non-complexed fluoride ions:

$$3\ SiF_4 + 2\ H_2O = SiO_2 + 2\ H_2[SiF_6]$$

$$H_2[SiF_6] + 6\ OH^- = H_2SiO_3 + 6\ F^- + 3\ H_2O$$

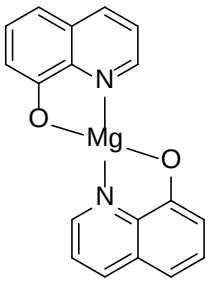
In the presence of fluoride ions the red colour of cerium(III)aminomethylalizarin acetic acid complex turns blue.

Magnesium

Add 0.1 g of *disodium tetraborate R* to 10 ml of the prescribed solution. Adjust the solution, if necessary, to pH 8.8 to pH 9.2 using *dilute hydrochloric acid R* or *dilute sodium hydroxide solution R*. Shake it with 2 quantities, 5 ml each, of a 1 g/l solution of *hydroxyquinoline R* in *chloroform R*, for 1 min each time. Allow it to stand. Separate and discard the organic layer. Add 0.4 ml of *butylamine R* and 0.1 ml of *triethanolamine R* to the aqueous solution. Adjust the solution, if necessary, to pH 10.5 to pH 11.5. Add 4 ml of solution of hydroxyquinoline in chloroform, shake it for 1 min, allow it to stand and separate. Use the lower layer for comparison. Prepare a standard in the same manner using a mixture of 1 ml of *magnesium standard solution (10 ppm Mg) R* and 9 ml of *water R*.

Any colour in the solution obtained from the substance to be examined is not more intense than that in the standard.

The method is suitable for the selective detection of low amounts of magnesium ions. Magnesium ion forms a complex with 8-hydroxyquinoline (oxin) which complex is insoluble in apolar solvent (like chlroform). However, if the medium contains a solubilizing material, for example aliphatic amines (butylamine in the test) the complex can be extracted into the organic phase from a pH 10.5-13.6 aqueous medium. The probable structure of the complex is:



First the pH is adjusted to 8.8-9.2, and the oxin complexes of other metal ions are extracted to chloroform and the organic phase is discarded. Adding butylamine to the aqueous phase containing the complex and adjusting the pH to 10.5-11.5 we perform another extraction with chloroform and the magnesium complex appears in the organic phase with yellow colour.

Heavy metals

METHOD A

Test solution. 12 ml of the prescribed aqueous solution of the substance is to be examined.

Reference solution (standard). A mixture of 10 ml of *lead standard solution (1 ppm Pb) R* or *lead standard solution (2 ppm Pb) R*, as prescribed, and 2 ml of prescribed aqueous solution of the substance to be examined.

Blank solution. A mixture of 10 ml of *water R* and 2 ml of the prescribed aqueous solution of the substance to be examined.

To each solution, add 2 ml of *buffer solution pH 3.5 R*. Mix and add to 1.2 ml of *thioacetamide reagent R*. Mix immediately. Examine the solutions after 2 min. The test is invalid if the reference solution does not show a slight brown colour compared to the blank solution. The substance to be examined complies with the test if any brown colour in the test solution is not more intense than that in the reference solution.

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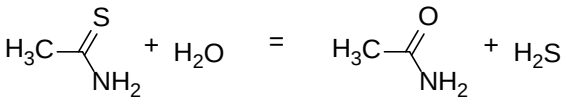
If the result is difficult to judge, filter the solutions through a membrane filter (pore size 3 µm). Carry out the filtration slowly and uniformly, applying moderate and constant pressure to the piston. Compare the spots on the filters obtained with the different solutions.

Heavy metals are detected in the form of sulphide precipitates in slightly acidic medium. Sulphide ions are formed by hydrolysis of thioacetamide reagent forming H_2S.



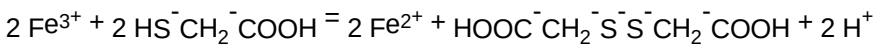
This is a general, non-selective reaction, in acidic medium most of the first, second and third class cations precipitate in $\underline{Me_xS_y}$ form. The change observed is a slight brownish coloration. R lead standard solution is used as reference.

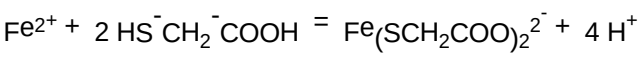
Iron

Dissolve the prescribed quantity of the substance to be examined in *water R* and dilute it to 10 ml with the same solvent or use 10 ml of the prescribed solution. Add 2 ml of a 200 g/l solution of *citric acid R* and 0.1 ml of *thioglycollic acid R*. Mix, make it alkaline with *ammonia R* and dilute it to 20 ml with *water R*. Prepare a standard in the same manner, using 10 ml of *iron standard solution (1 ppm Fe) R*.

After 5 min, any pink colour in the test solution is not more intense than that in the standard.

Iron contamination is detected in form of its complex with thioglycollic acid. In the acidic medium iron(III) ions are reduced to iron(II) ions. Making the pH alkaline with ammonia iron(II) ions form a colourless complex with the excess of the reagent, which is soon oxidized to pink on air.





V Pharmacopoeial qualification of inorganic substances (Selection)

V.1 Halogens

+ IODINE

Iodum

I_2

$M_r = 253.8$

DEFINITION

Content: 99.5 per cent to 100.5 per cent of I.

CHARACTERS

Appearance: greyish-violet, brittle plates or fine crystals with a metallic sheen.

Solubility: very slightly soluble in water, very soluble in concentrated solutions of iodides, soluble in ethanol (96 per cent), slightly soluble in glycerol.

It volatilises slowly at room temperature.

IDENTIFICATION

A. Heat a few fragments in a test-tube. Violet vapour is evolved and a bluish-black crystalline sublimate is formed.

B. To a saturated solution add *starch solution R*. A blue colour is produced. Heat until decolourised. On cooling the colour reappears.

Iodine forms a blue complex with starch solution. Stability of the complex is reduced on heating but the colour reappears on cooling.

SODIUM BROMIDE

Natrii bromidum

NaBr $M_r = 102.9$

DEFINITION

Content: 98.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, granular powder or small, colourless, transparent or opaque crystals, slightly hygroscopic.

Solubility: freely soluble in water, soluble in alcohol.

IDENTIFICATION

A. Bromides. Dissolve 0.1 g in 2 ml of *water R*. Acidify with *dilute nitric acid R* and add 0.4 ml of *silver nitrate solution R1*. Shake it and allow it to stand. A curdled,

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pale yellow precipitate is formed which dissolves in 1.5 ml of *ammonia R* with difficulty.

Bromide ions under acidic conditions form pale yellow AgBr precipitate, which easily dissolves in ammonia solution.

$$Ag^+ + Br^- = \underline{AgBr}$$

$$AgBr + 2\ NH_3 = [Ag(NH_3)_2]^+ + Br^-$$

B. Sodium. Dissolve 0.2 g in 2 ml of *water R*. Add 2 ml of a 150 g/l solution of *potassium carbonate R* and heat to boiling. No precipitate is formed. Add 4 ml of *potassium pyroantimonate solution R* and heat to boiling. Allow it to cool in iced water and if necessary rub the inside of the test-tube with a glass rod. A dense white precipitate is formed.

See Identification reactions: Sodium ions.

POTASSIUM IODIDE

Kalii iodidum

KI $M_r = 166.0$

DEFINITION

Content: 99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder or colourless crystals.

Solubility: very soluble in water, freely soluble in glycerol, soluble in ethanol (96 per cent).

IDENTIFICATION

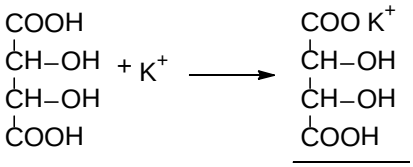
Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 10 ml with the same solvent.

A. Iodides. Use 2 ml of *Solution S*. Acidify with *dilute nitric acid R* and add 0.4 ml of *silver nitrate R1*. Shake it and allow it to stand. A curdled, pale-yellow precipitate is formed. Add 1.5 ml of *ammonia R*. The precipitate does not dissolve.

See Identification reactions for iodide ions.

B. Potassium Add 1 ml of *sodium carbonate solution R* to 2 ml of solution S and heat the reaction mixture. No precipitate is formed. Add 0.05 ml of *sodium sulphide solution R* to the hot solution. No precipitate is formed. Cool it in iced water and add 2 ml of a 150 g/l solution of *tartaric acid R*. Allow it to stand. A white crystalline precipitate is formed.

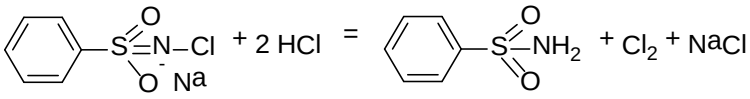
In the first part of the test the presence of alkaline earth metal ions is excluded (alkaline earth metals with sodium carbonate; heavy metals with sodium sulphide). Crystallization of potassium hydrogen tartrate can be initiated by scrubbing the internal wall of the test tube by a glass rod.



INFORMATIVE TESTS

Add 4 to 5 drops of *dilute hydrochloric acid R* and 2 ml of *chloroform R* to 1 ml of *Solution S*, and shake it with 1 to 2 drops of *chlorogen solution R*. The chloroform phase should be violet. When shaken with an adequate excess of *chlorogen solution R*, the chloroform phase should remain colourless.

Hypochlorite ion formed by hydrolysis of chlorogen in water reacts with hydrochloric acid to form chlorine gas, which oxidizes iodide ions into iodine (dissolves with violet colour in chloroform). Iodine is further oxidized by an excess of chlorine into the colourless iodate.



$$HOCl + HCl = Cl_2 + H_2O$$

$$Cl_2 + 2\,I^- = I_2 + 2\,Cl^-$$

violet

in chloroform

$$I_2 + 5\,Cl_2 + 6\,H_2O = 2\,IO_3^- + 10\,Cl^- + 12\,H^+$$

violet colourless

V.2 Oxygen group

WATER PURIFIED

Aqua purificata

H_2O $M_r = 18.02$

DEFINITION

Water for the preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised.

CHARACTERS

Appearance: clear and colourless liquid.

TESTS

Acidity or alkalinity. To 10 ml, freshly boiled and cooled in a borosilicate glass flask, add 0.05 ml of *methyl red solution R*. The solution is not coloured red.
To 10 ml, add 0.1 ml of *bromothymol blue solution R1*. The solution is not coloured blue.

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The amount of acidic and basic contaminations are limited by methyl red and bromothymol blue indicators, respectively.

Heavy metals: maximum 0.1 ppm.

Heat 200 ml in a glass evaporating dish on a water-bath until the volume is reduced to 20 ml. 12 ml of the concentrated solution complies with limit test A.

Test solution. 12 ml of the concentrated solution.

Reference solution (standard). A mixture of 10 ml of *lead standard solution (1 ppm Pb) R* and 2 ml of the test (concentrated) solution.

Blank solution. A mixture of 10 ml of *water R* and 2 ml of the test (concentrated) solution.

To each solution, add 2 ml of *buffer solution pH 3.5 R.*

Mix it and add it to 1.2 ml of *thioacetamide reagent R*. Mix immediately. Examine the solutions after 2 min. The test is invalid if the reference solution does not show a slight brown colour compared to the blank solution. The substance to be examined complies with the test if any brown colour in the test solution is not more intense than that in the reference solution.

See Limit tests: Heavy metals

Calcium and magnesium. To 100 ml add 2 ml of *ammonium chloride buffer solution pH 10.0 R*, 50 mg of *mordant black 11 triturate R* and 0.5 ml of *0.01 M sodium edetate*. A pure blue colour is produced.

The blue colour of mordant black 11 indicator turns red in presence of calcium or magnesium ions as a consequence of complex formation.

Ammonium: maximum 0.2 ppm.

To 20 ml add 1 ml of *alkaline potassium tetraiodomercurate solution R*. After 5 min, examine the solution down the vertical axis of the tube. The solution is not more intensely coloured than a standard prepared at the same time by adding 1 ml of *alkaline potassium tetraiodomercurate solution R* to a mixture of 4 ml of *ammonium standard solution R1 (1 ppm NH_4) R* and 16 ml of *ammonium-free water R*.

See Limit tests: Ammonium

Sulphates. To 10 ml add 0.1 ml of *dilute hydrochloric acid R* and 0.1 ml of *barium chloride solution R1*. The solution shows no change in appearance for at least 1 h.

See Limit tests: Sulfate

Chlorides. To 10 ml add 1 ml of *dilute nitric acid R* and 0.2 ml of *silver nitrate solution R2*. The solution shows no change in appearance for at least 15 min.

See Limit tests: Chloride

Nitrates: maximum 0.2 ppm.

Place 5 ml in a test-tube immersed in iced water. Add 0.4 ml of a 100 g/l solution of *potassium chloride R*, 0.1 ml of *diphenylamine solution R* and 5 ml of *nitrogen-free sulphuric acid R*, dropwise with shaking. Transfer the tube to a water-bath at 50 ºC. After 15 min, any blue colour in the solution is not more intense than that in a reference solution prepared at the same time in the same manner using a mixture of 4.5 ml of *nitrate-free water R* and 0.5 ml of *nitrate standard solution (2 ppm NO_3) R*.

SULPHUR FOR EXTERNAL USE

Sulfur ad usum externum

S $A_r = 32.07$

DEFINITION

Content: 99.0 per cent to 101.0 per cent.

CHARACTERS

Appearance: yellow powder.

Solubility: practically insoluble in water, soluble in carbon disulphide, slightly soluble in vegetable oils. Mp: about 120 ºC

IDENTIFICATION

A. Heated in the presence of air, it burns with a blue flame, emitting sulphur dioxide which changes the colour of moistened *blue litmus paper R* to red.

$$SO_2 + H_2O \longrightarrow HSO_3^- + H^+$$

B. Heat 0.1 g with 0.5 ml of *bromine water R* until decolourised. Add 5 ml of *water R* and filter. Add 1 ml of *dilute hydrochloric acid R* and 1 ml of *barium chloride solution R1*. A white precipitate is formed.

$$3\,Br_2 + S + 4\,H_2O \longrightarrow 6\,Br^- + SO_4^{2-} + 8\,H^+$$

$$SO_4^{2-} + Ba^{2+} \longrightarrow \underline{BaSO_4}$$

TESTS

Solution S. To 5 g add 50 ml *carbon dioxide-free water R* prepared from *distilled water R*. Allow it to stand for 30 min with frequent shaking and filter.

Sulphides.

To 10 ml of *Solution S* add 2 ml of *buffer solution pH 3.5 R* and 1 ml of a freshly prepared 1.6 g/l solution of *lead nitrate R* in *carbon dioxide-free water*. Shake. After 1 min any colour in the solution is not more intense than that in a reference solution prepared at the same time using 1 ml of *lead standard solution (10 ppm Pb) R*, 9 ml of *carbon dioxide-free water R*, 2 ml of *buffer solution pH 3.5 R* and 1.2 ml of *thioacetamide reagent R*.

Formation of the black lead(II) sulphide precipitate is indicative for presence of sulphides.

$$Pb^{2+} + S^{2-} = \underline{PbS}$$

Sulphates: maximum 100 ppm, determined on *Solution S*.

Add 1 ml of a 250 g/l solution of *barium chloride R* to 1.5 ml of *sulphate standard solution (10 ppm SO_4) R1*. Shake it and allow it to stand for 1 min. Add 15 ml of *Solution S* and 0.5 ml of *acetic acid R* to this solution. Prepare a standard in the same manner using 15 ml of *sulphate standard solution (10 ppm SO_4) R* instead of *solution S*.

After 5 min, any opalescence in the test solution is not more intense than that in the standard.

See Limit tests: Sulphate.

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Chlorides: maximum 100 ppm.

Dilute 5 ml of *Solution S* to 15 ml with *water R*. To this solution, add 1 ml of *dilute nitric acid R* and pour the mixture as a single addition into a test-tube containing 1 ml of *silver nitrate solution R2*. Prepare a standard in the same manner using 10 ml of *chloride standard solution (5 ppm Cl) R* and 5 ml of *water R*. Examine the tubes laterally against a black background.

After standing for 5 min protected from light, any opalescence in the test solution is not more intense than that in the standard.

See Limit tests: Chloride

V.3 Nitrogen group

POTASSIUM NITRATE

Kalii nitras

KNO_3 $M_r = 101.1$

DEFINITION

Content: 99.0 per cent to 101.0 per cent (dried substance).

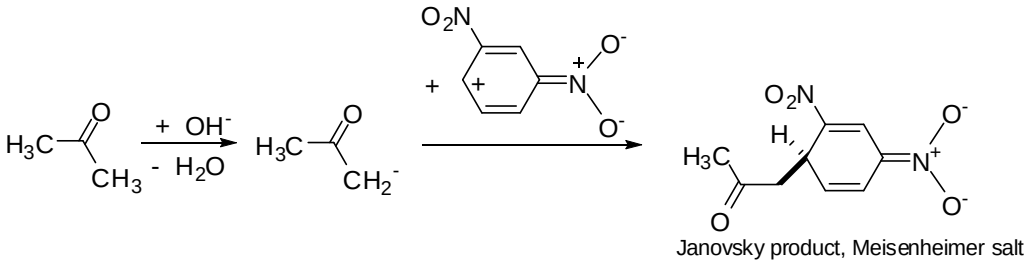
CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: freely soluble in water, very soluble in boiling water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Nitrates. Add 0.1 g to a mixture of 0.1 ml of *nitrobenzene R* and 0.2 ml of *sulphuric acid R*. Allow it to stand for 5 min. Cool it in iced water and add 5 ml of *water R* slowly with mixing, then 5 ml of *strong sodium hydroxide solution R*. Add 5 ml of *acetone R*. Shake it and allow it to stand. The upper layer is coloured deep violet.

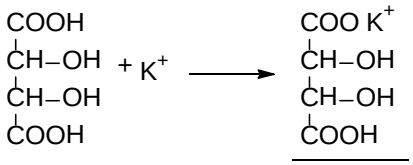


The reaction (Pesez reaction) is based on the Janovsky-Zimmermann reaction used for detection of active methyl and methylene groups. The nitrite ions formed

under the strong acidic conditions substitute nitrobenzene to form m-dinitrobenzene, which reacts with acetone under basic conditions to form the Janovsky product (Meisenheimer salt). The formed adduct is further oxidized to form the deep violet Zimmermann product. The reaction is specific even in the presence of nitrites.

B. Potassium. Dissolve 0.2 g in 2 ml of *water R*. Add 1 ml of *sodium carbonate solution R* to this solution, and heat it. No precipitate is formed. Add 0.05 ml of *sodium sulphide solution R* to the hot solution. No precipitate is formed. Cool it in iced water and add 2 ml of a 150 g/l solution of *tartaric acid R*. Allow it to stand. A white crystalline precipitate is formed.

In the first part of the test the presence of alkaline earth metal ions is excluded (alkaline earth metals with sodium carbonate; heavy metals with sodium sulphide). Crystallization of potassium hydrogen tartrate can be initiated by scrubbing the internal wall of the test tube by a glass rod.



+ SODIUM NITRITE

Natrii nitris

$NaNO_2$ $M_r = 69.0$

DEFINITION

Content: 98.5 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: colourless crystals or mass or yellowish rods, hygroscopic.
Solubility: freely soluble in water, soluble in alcohol.

IDENTIFICATION

Solution S1. Dissolve 0.5 g in *carbon dioxide-free water R* and dilute it to 10 ml with the same solvent.

A. Dilute 1 ml of *Solution S1* to 25 ml with *water R*. To 0.1 ml of the solution add 1 ml of *sulphanilic acid solution R1*. Allow it to stand for 2-3 min. Add 1 ml of *β-naphthol solution* and 1 ml of *dilute sodium hydroxide solution R*. An intense red colour develops.

Under acidic conditions sulphanylic acid reacts with nitrite ions to form the respective diazonium salt, which reacts with 2-naphtol under basic conditions yielding the red azo dye. The reaction is also applicable to detect amino substituents of aromatic compounds.

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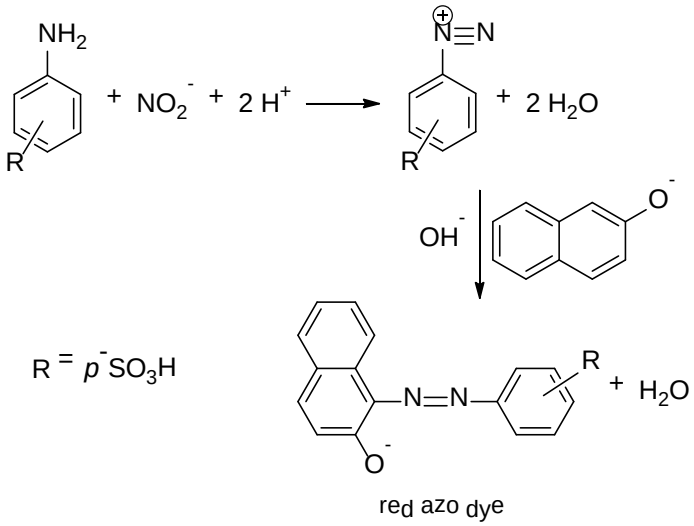
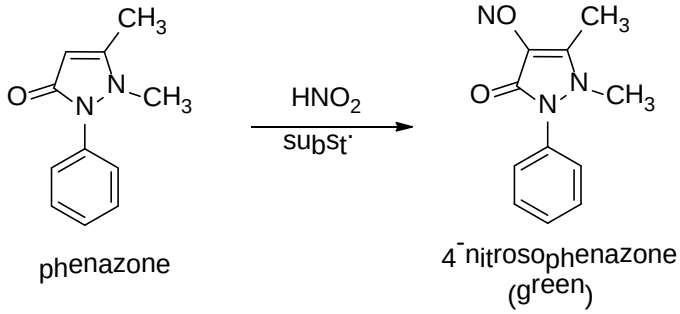


B. To 1 ml of the solution prepared for Identification test A add 3 ml of a 20 g/l solution of *phenazone R* and 0.4 ml of *dilute sulphuric acid R*. An intense green colour develops.



C. Sodium. To 0.15 ml of *Solution S1*, add 0.35 ml of *water R*. To this solution, add 1.5 ml of *methoxyphenylacetic reagent R*, and cool it in iced-water for 30 min. A voluminous, white, crystalline precipitate is formed. Place it in water at 20 ºC and stir it for 5 min. The precipitate does not disappear. Add it to 1 ml of *dilute ammonia R1*. The precipitate dissolves completely. Add 1 ml of *ammonium carbonate solution R*. No precipitate is formed.

See Identification reactions: Sodium ions.

V.4 Carbon group

CHARCOAL, ACTIVATED

Carbo activatus

C $A_r = 12{,}01$

DEFINITION

Obtained from vegetable matter by suitable carbonisation processes intended to confer a high adsorption power.

CHARACTERS

Appearance: black, light powder free from grittiness.

Solubility: practically insoluble in all usual solvents.

IDENTIFICATION

A. When heated to redness it burns slowly without a flame.
B. The matter should comply with the requirements specified in the paragraph "Adsorption Power".

TESTS

Adsorption power. To 3.000 g in a 100 ml ground-glass-stoppered conical flask. add 25.0 ml of a freshly prepared solution of 0.5 g of *phenazone R* in 50 ml of *water R*. Shake it thoroughly for 15 min. Filter and reject the first 5 ml of filtrate. To 10.0 ml of the filtrate add 1.0 g of *potassium bromide R* and 20 ml of *dilute hydrochloric acid R*. Using 0.1 ml of *methyl red solution R* as indicator, titrate it with *0.0167 M potassium bromate* until the red colour is discharged. Titrate slowly (1 drop every 15 s) towards the end of the titration. Carry out a blank titration using 10.0 ml of the phenazone solution.

Calculate the quantity of phenazone adsorbed per 100 g of activated charcoal from the following expression:

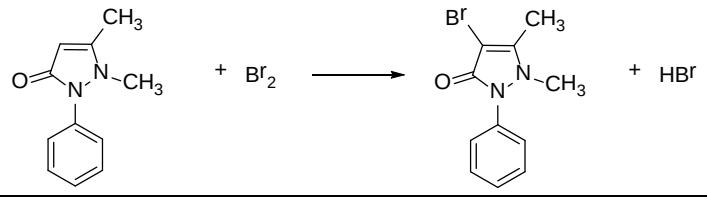
$$\frac{2.353\ (a-b)}{m}$$

a = number of millilitres of *0.0167 M potassium bromate* used for the blank,
b = number of millilitres of *0.0167 M potassium bromate* used for the test,
m = mass in grams of the substance to be examined.

Minimum 40 g of phenazone is adsorbed per 100 g of activated charcoal, calculated with reference to the dried substance.($M_{phenazone} = 188.23$)

The non-adsorbed amount of phenazone is measured by bromatometric titration. The endpoint of the titration is detected by oxidation of methyl red indicator by bromine. Accordingly, use of the prescribed amount of indicatior is essential.

$$BrO_3^- + 5\,Br^- + 6\,H^+ = 3\,Br_2 + 3\,H_2O$$



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SODIUM CARBONATE DECAHYDRATE

Natrii carbonas decahydricus

$Na_2CO_3 \cdot 10\ H_2O$ $M_r = 286.1$

DEFINITION

Content: 36.7 per cent to 40.0 per cent of Na_2CO_3.

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless, transparent crystals, efflorescent.

Solubility: freely soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 1 g in *water R* and dilute the solution to 10 ml with the same solvent. The solution is strongly alkaline.

The pH of aqueous solution of sodium carbonate is basic due to hydrolysis of the carbonate ions.

$$CO_3^{2-} + H_2O \rightleftharpoons HCO_3^- + OH^-$$

$$HCO_3^- + H_2O \rightleftharpoons H_2O + CO_2 + OH^-$$

The red color of phenolphthalein is indicative of the basic pH of the solution.

B. **Carbonates**. To 2 ml of solution prepared for identification test A add 3 ml of *dilute acetic acid R*. Close the tube immediately using a stopper fitted with a glass tube bent twice at right angles. The solution or the suspension becomes effervescent and gives off a colourless and odourless gas. Heat gently and collect the gas in 5 ml of *barium hydroxide solution R*. A white precipitate is formed that dissolves on addition of an excess of *hydrochloric acid R1*.

See Identification reactions: Carbonate and bicarbonate ions.

C. **Sodium.** To 2 ml of solution prepared for identification test A add 2 ml of a 150 g/l solution of *potassium carbonate R* and heat it to boiling. No precipitate is formed. Add 4 ml of *potassium pyroantimonate solution R* and heat the mixture to boiling. Allow it to cool in iced water and if necessary rub the inside of the test-tube with glass rod. A dense white precipitate is formed.

See Identification reactions: Sodium ions.

TESTS

Alkaline hydroxides and hydrogen carbonates. Dissolve 1.0 g in 20 ml *R water*. Add 20 ml *R1 barium chloride solution* and filter the precipitate. Add 0.1 ml *R phenolphthalein solution* to 10 ml portion of the filrate. The solution should not turn red. Rest of the filtrate is heated to boil for 2 minutes. The solution is clear.

Addition of barium chloride results in formation of barium carbonate precipitate, which can be filtered. The water soluble contaminations (hydroxides, hydrogen carbonates) could cause basic pH of the filtrate indicated by phenolphtalein. The

hydrogen carbonate contamination is converted to carbonate on boiling, which form barium carbonate precipitate.

$$Ba^{2+} + CO_3^{2-} = BaCO_3$$

$$2\,HCO_3^- \xrightarrow{\Delta} CO_3^{2-} + CO_2 + H_2O$$

V.5 Boron group

BORIC ACID

Acidum boricum

H_3BO_3 $M_r = 61.8$

DEFINITION

Content: 99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance: white or almost white, crystalline powder, colourless, shiny plates greasy to the touch, or white or almost white crystals.

Solubility: soluble in water and in ethanol (96 per cent), freely soluble in boiling water and in glycerol (85 per cent).

IDENTIFICATION

Solution S. Dissolve 0.3 g in 8 ml of boiling *distilled water R*, cool it and dilute it to 10 ml with *carbon dioxide-free water R* prepared from *distilled water R*.

A. Dissolve 0.1 g by gently heating in 5 ml of *methanol R*, add 0.1 ml of *sulphuric acid R* and ignite the solution. The flame has a green border.

The methyl ester of boric acid is formed, which is volatile and colorizes the flame.

$$H_3BO_3 + 3\,CH_3OH \rightleftharpoons B(OCH_3)_3 + 3\,H_2O$$

B. Solution S is acidic. To 10 ml of *Solution S* add 0.1 ml *methyl red solution R*. The color of the solution is orange or red.

Aqueous solution of boric acid is acidic indicated by the red color of the methyl red indicator.

$$H_3BO_3 + H_2O \longrightarrow B(OH)_4 + H^+$$

ASSAY

Dissolve 1,000 g with heating in 100 ml of *R water* containing 15 g of *mannitol R*. Titrate it with *1 M sodium hydroxide*, using 0.5 ml of *phenophthalein solution R* as indicator, until a pink colour is obtained.

Boric acid is weak enough (pK_a = 9.24) for direct titrimetric determination in water. Polyalcohols react with boric acid to form a monoprotic acid, which can be measured by titration with sodium hydroxide using phenolphthalein.

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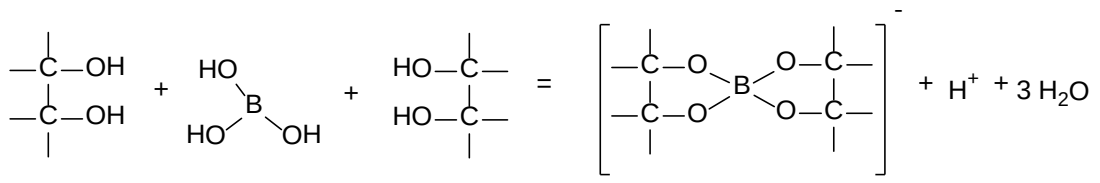


ALUM

Alumen

$AlK(SO_4)_2 \cdot 12\ H_2O$ $M_r = 474.4$

DEFINITION

Content: 99.0 per cent to 100.5 per cent of $AlK(SO_4)_2,12\ H_2O$.

CHARACTERS

Appearance: granular powder or colourless, transparent, crystalline masses.

Solubility: freely soluble in water, very soluble in boiling water, soluble in glycerol, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

Solution S. Dissolve 2 g in *water R* and dilute the solution to 40 ml with the same solvent.

A. Sulfates. To 5 ml of *Solution S* add 1 ml of *dilute hydrochloric acid R* and 1 ml of *barium chloride solution R1*. A white precipitate is formed.

$$Ba^{2+} + SO_4^{-} = \underline{BaSO_4}$$

B. Aluminium: To 2 ml of *Solution S* add about 0.5 ml of *dilute hydrochloric acid R* and about 0.5 ml of *thioacetamide reagent R*. No precipitate is formed. Add dropwise *dilute sodium hydroxide solution R*. A gelatinous white precipitate is formed which dissolves on further addition of *dilute sodium hydroxide solution R*. Gradually add *ammonium chloride solution R*. The gelatinous white precipitate is re-formed.

Aluminium ions do not form precipitate with hydrogen sulphide liberated from the thioacetamide reagent. Addition of sodium hydroxide results in formation of aluminium hydroxide precipitate, which dissolves in excess of the reagent.

$$Al^{3+} + 3\ OH^{-} \rightleftharpoons Al(OH)_3$$

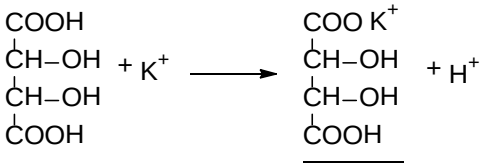
$$Al(OH)_3 + OH^{-} \rightleftharpoons [Al(OH)_4]^{-}$$

Additon of ammonium chloride to the solution reduces the hydroxide ion concentration and aluminium hydroxide precipitates again.

$$NH_4^{+} + OH \rightleftharpoons NH_3 + H_2O$$

C. Potassium. Shake 10 ml of *Solution S* with 0.5 g of *sodium bicarbonate R* and filter it. Add 1 ml of *sodium carbonate solution R* and heat. No precipitate is formed. Add to the hot solution 0.05 ml of *sodium sulphide solution R*. No precipitate is formed. Cool it in iced water and add 2 ml of a 150 g/l solution of *tartaric acid R*. Allow to stand. A white crystalline precipitate is formed.

The added sodium hydrogen carbonate results in formation of aluminium hydroxide precipitate. Potassium ions in the filtrate can be identified by tartaric acid.



TESTS

Ammonium: maximum 0.2 per cent.

To 0.4 ml of *Solution S* add 14 ml of *water R* in a test-tube, make alkaline if necessary by the addition of *dilute sodium hydroxide solution R* and dilute it to 15 ml with *water R*. Add 0.3 ml of *alkaline potassium tetraiodomercurate solution R*. Prepare a standard by mixing 10 ml of *ammonium standard solution (1 ppm NH_4) R* with 5 ml of *water R* and 0.3 ml of *alkaline potassium tetraiodomercurate solution R*. Stopper the test-tubes.

After 5 min, any yellow colour in the test solution is not more intense than that in the standard.

See Limit tests: Ammonium

Iron: maximum 100 ppm.

Dilute 2 ml of *Solution S* to 10 ml with *water R*. Add 2 ml of a 200 g/l solution of *citric acid R* and 0.3 ml of *thioglycollic acid R*. Mix, make it alkaline with *ammonia R* and dilute it to 20 ml *water R*. Prepare a standard in the same manner, using 10 ml of *iron standard solution (1 ppm Fe) R*.

After 5 min, any pink colour in the test solution is not more intense than that in the standard.

See Limit tests: Iron.

Heavy metals: maximum 20 ppm.

Test solution. 12 ml of *Solution S*.

Reference solution (standard): A mixture of 10 ml of *lead standard solution (1 ppm Pb) R*, and 2 ml of *Solution S*.

Blank solution: A mixture of 10 ml of *water R* and 2 ml of *Solution S*.

To each solution, add 2 ml of *buffer solution pH 3.5 R*. Mix and add it to 1.2 ml of *thioacetamide reagent R*. Mix immediately. Examine the solutions after 2 min. The test is invalid if the reference solution does not show a slight brown colour compared to the blank solution. The substance to be examined complies with the test if any brown colour in the test solution is not more intense than that in the reference solution.

See Limit tests: Heavy metals.

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V.6 Alkaline earth metals

MAGNESIUM OXIDE, LIGHT

Magnesii oxidum leve

MgO $M_r = 40.30$

DEFINITION

Content: 98.0 per cent to 100.5 per cent of MgO (ignited substance).

CHARACTERS

Appearance: fine, white or almost white, amorphous powder.

Solubility: practically insoluble in water. It dissolves in dilute acids with at most slight effervescence.

IDENTIFICATION

B. Magnesium. Dissolve about 15 mg in 2 ml of *dilute nitric acid R* and neutralise it with dilute *sodium hydroxide solution R*. Add 1 ml of *dilute ammonia R1*. A white precipitate is formed that dissolves on addition of 1 ml of *ammonium chloride solution R*. Add 1 ml of *disodium hydrogen phosphate solution R*. A white crystalline precipitate is formed.

The ($Mg(OH)_2$) precipitate formed on addition of ammonia solution does not dissolve in excess of the reagent.

$$Mg^{2+} + 2\ H_2O + 2\ NH_3 \rightleftharpoons \underline{Mg(OH)_2} + 2\ NH_4^+$$

Additon of ammonium chloride to the solution reduces the hydroxide ion concentration and the magnesium hydroxide dissolve. The obtained solution is called magnesia mixture. Addition of disodium hydrogen phosphate to the solution results in formation of magnesium ammonium phosphate precipitate.

$$Mg^{2+} + HPO_4^{2-} + NH_3 \rightleftharpoons \underline{MgNH_4PO_4}$$

TESTS

Solution S. Dissolve 5.0 g in a mixture of 30 ml of *distilled water R* and 70 ml of *acetic acid R*, boil it for 2 min, cool and dilute it to 100 ml with *dilute acetic acid R*. Filter it if necessary, through a previously ignited porcelain or silica filter crucible of a suitable porosity to give a clear filtrate.

Chlorides: maximum 0.15 per cent.

Dilute 0.7 ml of *Solution S* to 15 ml with *water R*. Add 1 ml of *dilute nitric acid R* and pour the mixture as a single addition into a test-tube containing 1 ml of *silver nitrate solution R2*. Prepare a standard in the same manner using 10 ml of *chloride standard solution (5 ppm Cl) R* and 5 ml of *water R*. Examine the tubes laterally against a black background.

After standing for 5 min protected from light, any opalescence in the test solution is not more intense than that in the standard.

See Limt tests: Chloride.

Calcium: maximum 1.5 per cent.

Dilute 1.3 ml of *Solution S* to 150 ml with *distilled water R*. To 0.2 ml of *alcoholic calcium standard solution (100 ppm Ca) R*, add 1 ml of *ammonium oxalate solution R*. After 1 min, add a mixture of 1 ml of *dilute acetic acid R* and 15 ml of the diluted *Solution S* and shake. Prepare a standard in the same manner using a mixture of 10 ml of aqueous *calcium standard solution (10 ppm Ca) R*, 1 ml of *dilute acetic acid R* and 5 ml of *distilled water R*.

After 15 min, any opalescence in the solution is not more intense than that in the standard.

Calcium oxalate precipitate is formed.

$$Ca^{2+} + (COO)_2^{2-} = \underline{Ca(COO)_2}$$

Arsenic: maximum 4 ppm, determined on 5 ml of Solution S.

In the conical flask dilute 5 ml of *Solution S* to 25 ml with water R. Add 15 ml of *hydrochloric acid R*, 0.1 ml of *stannous chloride solution R* and 5 ml of *potassium iodide solution R*, allow it to stand for 15 min and introduce 5 g of *activated zinc R*. Assemble the two parts of the apparatus immediately and immerse the flask in a bath of water at a temperature such that a uniform evolution of gas is maintained. Prepare a standard in the same manner, using 1 ml of *arsenic standard solution (1 ppm As) R*, diluted to 25 ml with *water R*.

After not less than 2 h the stain produced on the mercuric bromide paper in the test is not more intense than that in the standard.

See Limit tests: Arsenic

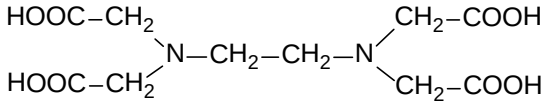
ASSAY

Dissolve 0.320 g in 20 ml of *dilute hydrochloric acid R* and dilute it to 100.0 ml with *water R*.

Introduce 20.0 ml of the solution into 500 ml conical flask and dilute it to 300 ml with *water R*. Add 10 ml of *ammonium chloride buffer solution pH 10.0 R* and about 50 mg of *mordant black 11 triturate R*. Heat the mixture to about 40 ºC then titrate it at this temperature with *0.1 M sodium edetate* until the colour changes from violet to full blue.

$$Mg^{2+} + H_2Y^{2-} = MgY^{2-} + 2\,H^+$$

H_4Y :



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BARIUM SULPHATE

Barii sulfas

$BaSO_4$ $M_r = 233.4$

CHARACTERS

Appearance: fine, white or almost white powder, free from gritty particles.

Solubility: practically insoluble in water and in organic solvents. It is very slightly soluble in acids and in solutions of alkali hydroxides.

IDENTIFICATION

A. Sulphates. Boil a suspension of 0.2 g with 5 ml of a 500 g/l solution of *sodium carbonate R* for 5 min, add 10 ml of *water R*, filter and acidify a part of the filtrate with *dilute hydrochloric acid R*. Add 1 ml of *barium chloride solution R1*. A white precipitate is formed.

A small amount of barium sulphate is converted into barium carbonate on heating in concentrated sodium carbonate solution.

$$BaSO_4 + CO_3^{2-} = \underline{BaCO_3} + SO_4^{2-}$$

The soluble sulphate ion can be detected in the filtrate by barium chloride; barium sulphate precipitate is formed.

B. Wash the residue collected in the preceding test with 3 successive small quantities of *water R*. To the residue add 5 ml of *dilute hydrochloric acid R*, filter it and add to the filtrate 0.3 ml of *dilute sulphuric acid R*. A white precipitate is formed that is insoluble in *dilute sodium hydroxide solution R*.

The solid barium carbonate dissolves in hydrochloric acid.

$$\underline{BaCO_3} + 2\,H^+ = Ba^{2+} + H_2O + CO_2$$

Barium ions form barium sulphate precipitate on addition of sulphuric acid.

$$Ba^+ + SO_4^{2-} = \underline{BaSO_4}$$

TESTS

Solution S: To 4.00 g add 8 ml of *distilled water R* and 12 ml of *dilute acetic acid R*. Boil it for 5 minutes, filter and dilute the cooled filtrate to 20 ml with *distilled water R*.

Soluble barium salts. To 10 ml *Solution S* add 1 ml of *dilute sulfuric acid R*. After one hour, any opalescence in the test solution is not more intense than that in the standard solution, which is prepared by addition of 1 ml of *distilled water R* to 10 ml of *Solution S*.

V.7 Alkaline metals

POTASSIUM PERMANGANATE

Kalii permanganas

$KMnO_4$ $M_r = 158.0$

DEFINITION

Content: 99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance: dark purple or brownish-black, granular powder or dark purple or almost black crystals, usually having a metallic lustre.

Solubility: soluble in cold water, freely soluble in boiling water.

It decomposes on contact with certain organic substance.

IDENTIFICATION

A. Dissolve about 50 mg in 5 ml *water R* and add 1 ml of *ethanol (96 per cent) R* and 0.3 ml of *dilute sodium hydroxide solution R*. A green colour develops. Heat to boiling. A dark brown precipitate is formed.

In the first step ethanol reduces permanganate ions to green coloured manganate ions. By boiling ethanol reduces manganate ions to manganese(IV) dioxide which is a brown precipitate.

$$2\ MnO_4^- + CH_3CH_2OH + 2\ OH^- = 2\ MnO_4^{2-} + CH_3CHO + 2\ H_2O$$

$$MnO_4^{2-} + CH_3CH_2OH = MnO_2 + CH_3CHO + 2\ OH^-$$

The formed acetaldehyde is further oxidized by permanganate.

$$2\ MnO_4^- + 3\ CH_3CHO + OH^- = 2\ MnO_2 + 3\ CH_3COO^- + 2\ H_2O$$

B. Potassium. Filter the mixture obtained in Identification test A. To 1 ml of the filtrate add 1 ml of *dilute acetic acid R* and 1 ml of a freshly prepared 100 g/l solution of *sodium cobaltinitrite R*. A yellow or orange-yellow precipitate is formed immediately.

Potassium ions react to form yellow precipitate.

$$2\ K^+ + Na^+ + [Co(NO_2)_6]^{3-} = \underline{K_2Na[Co(NO_2)_6]}$$

ASSAY

Dissolve 0.300 g in *water R* and dilute it to 100.0 ml with the same solvent. To 20.0 ml of the solution add 20 ml of *water R*, 1 g of *potassium iodide R* and 10 ml of *dilute hydrochloric acid R*. Titrate the liberated iodine with *0.1 M sodium thiosulphate*, using 1 ml of *starch solution R* as indicator.

Endpoint of titration is indicated by disappearance of the iodine-starch complex.

$$10\ I^- + 2\ MnO_4^- + 16\ H^+ = 5\ I_2 + 2\ Mn^{2+} + 8\ H_2O$$

$$I_2 + 2\ S_2O_3^{2-} = 2\ I^- + S_4O_6^{2-}$$

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VI General characterisation of organic compounds, principles of pharmaceutical investigation of organic drug compounds

VI.1 Hydrocarbons

Hydrocarbons are simple organic compounds that contain only carbon and hydrogen atoms. Linked carbon atoms form chains in *aliphatic hydrocarbons*, or rings in *cyclic hydrocarbons*.

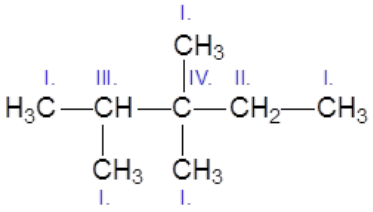
Saturated hydrocarbons with only sp^3-hybridized carbon atoms contain only single bonds, while hydrocarbons containing π bonds are called *unsaturated hydrocarbons*, which contain sp^2- or *sp*-hybridized carbon atoms.

VI.1.1 Aliphatic, saturated hydrocarbons

VI.1.1.1 Structure, nomenclature

Aliphatic saturated hydrocarbons are called *alkanes* or *paraffins*. Alkanes are the simplest representatives of hydrocarbons. Alkanes have the general formula: C_nH_{2n+2}. A uniform variation of this kind in a series of compounds is called *homologous*.

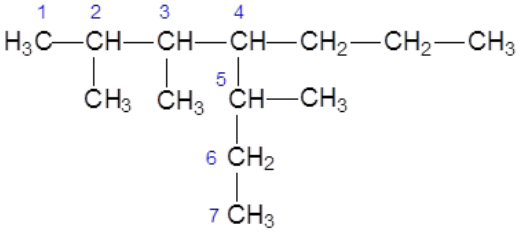
The *n*-alkanes are straight-chain or unbranched alkanes, which contain only *primary* (I) and *secondary* (II) carbon atoms, according to weather the carbon atom is linked with one or two other carbon atoms. The branched-chain alkanes contain *tertiary* (III) and/or *quaternary* (IV) carbon atoms as well, because these alkenes contain at least one carbon atom that is linked with three or four other carbon atoms.



The formal system of nomenclature used today has been proposed by the International Union of Pure and Applied Chemistry (IUPAC). The principle of naming alkanes is that the common "*ane*" suffix is linked to the stems of the names with Greek or Latin origin of alkanes. Nomenclature of branched chain paraffins are based on the following IUPAC rules:

1. Find the longest continous carbon chain, which determines the systematic basis name for the alkane. Determine the root name for this parent chain. When there are more longest chains of equal length, use the chain with the greater number of substituents.
2. Number the longest chain consecutively starting at the end nearest to a substituent group.
3. Determine the positions, identify and names of groups attached to this main chain.
4. Designate the location of the substituent group by an appropriate number and name. When two or more substituents are present, give each group a number corresponding to its location on the main chain.

5. Assemble the name, listing substituent groups in alphabetical order using the full name.
6. The prefixes *di-*, *tri-*, *tetra-*, *penta-* etc. are used to designate several groups of the same kind, but they are not considered when alphabetizing.



2,3,5-trimethyl-4-propylheptane

VI.1.1.2 Properties

Alkenes have no functional groups. Since there is not much difference in electronegativity between carbon and hydrogen, the C-H bond is almost purely covalent, the dipolmoment is zero. The molecules themselves also have very little polarity. A totally symmetrical molecule such as methane, for example, is completely non-polar.

Physical properties

The first four members of the homologous series of unbranched alkanes are gases at room temperature and under atmospheric condition (0.1 MPa). The C_5-C_{16} alkanes are liquids with low density, while those with 17 or more carbon atoms are solid.

The boiling points of the unbranched alkanes (pentane through decane) increase rather smoothly with their molecular weight. The explanation for this is that the only attractions among the molecules are based on the Van der Waals dispersion forces. With increasing of molecular weight, the size and the surface area of the molecules increase as well, so the Van der Waals forces get bigger. The more branched is the chain, however, the lower the boiling point tends to be. Van der Waals dispersion forces are smaller for shorter molecules (with lots of branching) due to them having a smaller surface area.

Alkanes are nonpolar compounds; therefore they are virtually insoluble in water, but dissolve in apolar organic solvents (benzene, acetone, carbon tetrachloride etc.). Liquid alkanes are good solvents for many other compounds.

Chemical reactions

Alkanes are – due to their apolar structure - relatively unreactive, stable molecules. Paraffins ordinarily do not react at room temperature with common acids and bases, or with oxidizing and reducing agents.

Alkanes burn in an excess of oxygen to form carbon dioxide and water. The combustion of alkanes is exothermic, it produces heat. These reactions are the bases for the utilization of natural hydrocarbons (natural gas and heating oil) as fuel and propellant in motors.

$$C_nH_{2n+2} + \frac{3n+1}{2} O_2 \longrightarrow n\,CO_2 + (n+1)\,H_2O$$

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The typical reaction of alkanes is halogenation catalyzed by light and/or heat. In this substitution process halogen atom(s) replace(s) one or more of the hydrogen atoms of the alkane. (*See* Alkyl halides)

Light absorption

Paraffins are optically fully transparent for light with wavelength over 170 nm, since only $\sigma \rightarrow \sigma^*$ excitation is possible. Hence, liquid aliphatic hydrocarbons can be used as solvents in UV spectrophotometric measurments.

VI.1.1.3 Preparation of alkanes

Paraffins can be prepared from natural sources, mainly from petroleum. Petroleum is a complex mixture of hydrocarbons, but it also contains small amounts of oxygen-, sulphur- and nitrogen-containing compounds.

Crude oil has to be refined by distillation, which means the separation of petroleum fractions based on the difference in the volatility of the components. Crude oil is heated to about 350 °C and the vapors rise through a fractionating column. Fractions with lower boiling points rise faster and higher in the column. By drawing off liquids at various levels of the column, petroleum is separated into fractions.

Common petroleum fractions

Boiling range	Name of the fraction	Number of carbon atoms	Use
below 20 °C	gases	C_1 - C_4	fuel, propellant, commodity
20 - 200 °C	gasoline	C_5 - C_{12}	fuel, industrial solvent
200 - 350 °C	kerosene	C_{12} - C_{18}	diesel oil, fuel oil
350 - 400 °C	nonvolatile liquids	C_{18} - C_{22}	lubricating oil, paraffin oil, vaseline
over 400 °C	nonvolatile solids	C_{22} -	asphalt

VI.1.1.4 Therapeutical applications

Paraffin-products applied in therapy are not uniform compounds, but mixtures of aliphatic hydrocarbones.

Paraffin and vaseline products are derivatives of the lubricating oil fraction. The products which are official in the Pharmacopoeia are mainly used as technological materials including in the preparation of externally applied medicaments (e.g. creams, ointments).

Hydrocarbon products official in the Ph. Eur. 8.0.

Name	Main hydrocarbon components	Physical index number
Paraffin, liquid (Paraffinum liquidum)	C_{10} - C_{20} (saturated hydrocarbons)	Boiling point: over 360 °C
Paraffin, hard (Paraffinum solidum)	C_{17} - C_{35} (saturated hydrocarbons)	Melting point: 50 - 61 °C
Paraffin, white soft (Vaselinum album)	C_{17} - C_{35} (n- and isoparaffines)	Drop point: 35 - 75 °C
Paraffin, yellow soft (Vaselinum flavum)	C_{17} - C_{35} (n- and isoparaffines)	Drop point: 40 - 60 °C

VI.1.1.5 Pharmacopoeial qualifications

The Ph. Eur. prescribes infrared absorption spectrophotometric methods - where the spectra needs to be compared with a reference spectra - as the first form of identifying hydrocarbons.

The adequacy of the composition also has to be controlled using physical methods. In the case of *Paraffinum liquidum*, for example, the determination of viscosity and relative density provides information about the composition. The appropriate composition of soft, unctuous *Vaselinum album* can be checked by measuring the drop point, while in the case of *Paraffinum solidum* the melting point has to be determined.

To controll the *polycyclic aromatic hydrocarbon* content of the mentioned substances the Pharmacopoeia prescribes the UV absorption spectrophotometric techniqe. The basis of this method is that paraffins show sign of absorption only in the short-wave UV range (below 200 nm), while the absorption of aromatic compounds can also be measured between the 200 and 400 nm UV range. The monitoring of polycyclic aromatic contaminants is particularly important because of their carcinogen effect.

PARAFFIN, LIQUID

Paraffinum liquidum

DEFINITION

Purified mixture of liquid saturated hydrocarbons obtained from petroleum.

CHARACTERS

Appearance: colourless, transparent, oily liquid, free from fluorescence in daylight.

Solubility: practically insoluble in water, slightly soluble in ethanol (96 per cent), miscible with hydrocarbons.

IDENTIFICATION

B. In a test-tube cautiously boil 1 ml with 1 ml of *0.1 M sodium hydroxide*, with continuous shaking, for about 30 s. On cooling it to room temperature, 2 phases separate. To the aqueous phase add 0.1 ml of *phenolphthalein solution R*. The solution becomes red.

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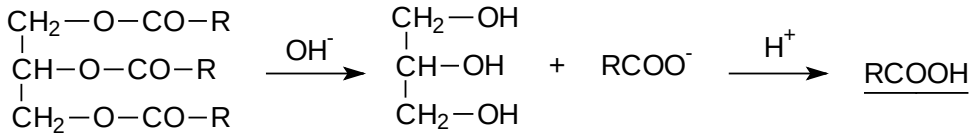
TESTS (Ph. Hg. VII.)

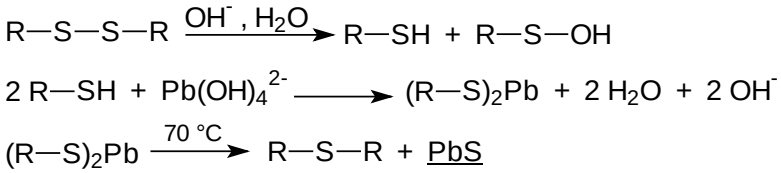
[9] Saponifiable matter. Immerse a 5 ml and 5 ml of *2 M sodium hydroxide solution* in a test tube into a boiling water-bath and heat it with frequent shaking for 10 minutes. The cooled aqueous layer must remain transparent. Filter the aqueous phase through a paper filter, previously wetted with water, and add 10 ml of *2 M hydrochloric acid* to the filtrate. No change must be produced.

The esters hydrolyse on heating with sodium hydroxide. The produced fatty acids and oleic acids precipitate after acidification.



[10]Sulphur compounds. To a 6 ml add 4 ml of dehydrated alcohol, 2 drops of *0.5 M lead acetate solution* and *2 M sodium hydroxide solution* until the initially formed precipitate dissolves. Heat the mixture under frequent agitation by immersion into a 70 ºC water-bath, for 10 minutes. The reaction mixture must remain colourless.

Organic contaminations containing sulphur (disulphides) decompose by adding sodium hydroxide. The produced thiols form in the persence of lead(II) ions lead mercaptids, from which lead(II) sulphide precipitate is formed after heating.



PARAFFIN, WHITE SOFT

Vaselinum album

DEFINITION

Purified and wholly or nearly decolorised mixture of semi-solid hydrocarbons, obtained from petroleum. It may contain a suitable antioxidant. White soft paraffin described in this monograph is not suitable for oral use.

CHARACTERS

Appearance: white or almost white, translucent, soft unctuous mass, slightly fluorescent in daylight when melted.

Solubility: practically insoluble in water, soluble in methylene chloride, practically insoluble in alcohol and in glycerol.

IDENTIFICATION

C. Melt 2 g and when a homogeneous phase is obtained, add 2 ml of *water R* and 0.2 ml of *0.05 M iodine*. Shake. Allow it to cool. The solid upper layer is violet-pink.

TESTS (PH. HG. VII.)

[4] Saponifiable matter. Heat a 5.0 g in a large test tube with 5.0 ml of *2 M sodium hydroxide solution* for 10 minutes, under frequent shaking. On cooling, filter the solution through a moistered paper filter. To the filtrate, add 6.0 ml of *2 M hydrochloric acid*. No change must occur.

See the monograph of Paraffin, liquid.

[5] Sulphur compounds. To a mixture of 6.0 g with 4.0 ml of P*-alcohol and 2 drops of *0.5 M lead acetate solution*, add *2 M sodium hydroxide solution* until the initially formed precipitate just dissolves. Heat the mixture for 10 minutes in a water-bath of about 70 ºC, under frequent shaking. No colour must be produced in the mixture.

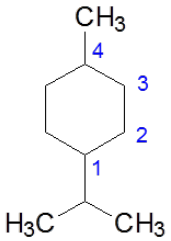
See the monograph of Paraffin, liquid.

VI.1.2 Cyclic, saturated hydrocarbons

VI.1.2.1 Structure, nomenclature

Saturated hydrocarbons in which the carbon skeleton forms a ring are called *cycloalkanes* or *cycloparaffins*. The general molecular formula of cycloalkanes is C_nH_{2n}.

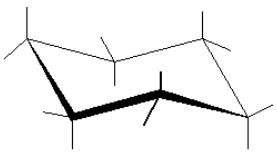
The name of cycloalkanes is formed from the name of the unbranched alkane with the same number of carbon atoms as the ring, but the prefix *cyclo-* is added to it. Substituents are identified in the ususal way.



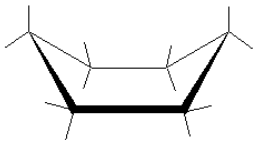
4-methyl-isopropylcyclohexane

Conformations of cyclohexane

The six-membered ring forms a stable conformation, free of angle strain, when the arrangement around all carbon atoms is tetrahedral, and the adjacent -CH_2- groups are in an open position. This conformation of cyclohexane is called the *chair* conformation, every second carbon atom is coplanar in it. The *boat* conformation of cyclohexane, however, is not very favorable, because it is not free of torsional strain, due to the eclipsed conformation of four carbon atoms.



chair



boat

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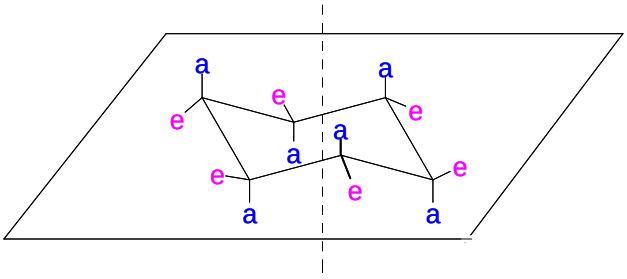
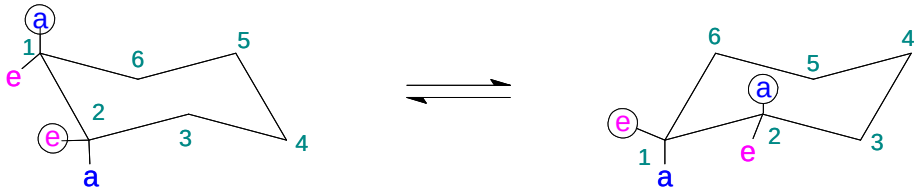
At room temperature the unsubstituted cyclohexane molecules change their conformation rapidly and reversibly. The energy barrier between the two conformations is too low to separate them. Because of the greater stability, more than 99 percent of the molecules are estimated to be in a chair conformation at room temperature.

On careful examination of a cyclohexane in the chair conformation, we find that the twelve hydrogens are not structurally equivalent. Six of them are oriented above and below the approximate plane of the ring (three in each location), and are termed *axial*. The other six hydrogens are located about the periphery of the carbon ring, and are termed *equatorial*.



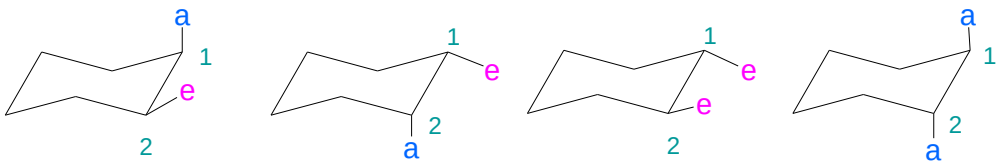
During the process known *chair-chair interconversion*, when one chair is converted to another chair, all the bonds that were axial become equatorial, and all that were equatorial become axial.



Disubstituted cyclohexane derivatives - *cis-trans* isomerism

In the case of 1,2-, 1,3- and 1,4-disubstituted cyclohexanes, when the substituents are different, 4-4 conformer may exist.

The 1,2-disubstituted derivatives:

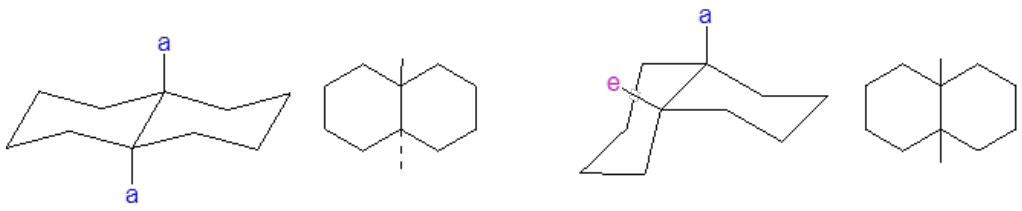


cis-1a,2e *cis*-1e,2a *trans*-1e,2e *trans*-1a,2a

When the substituents are the same, the maximum number of conformers is three (two *trans* and one *cis* conformer). The most stable isomer is the *trans* 1*e*,2*e*-isomer. The bigger substituents are usually located in this position.

The condensation of two cyclohexane rings leads to a bicyclic system, called *decalin*. Decalin shows *cis-trans* isomerism. In *trans*-decalin the two hydrogen atoms attached to the bridgehead atoms lie on the opposite side of the ring, therefore the two

rings form approximately one plane. In *cis*-decalin the two hydrogens lie on the same side of the ring, the molecule is curved.



trans-decalin *cis*-decalin

Both *cis* and *trans* conformations of decalin can be found in naturally occuring compounds. For example the condensation of three cyclohexane and one cyclopentane rings leads to the steroid skeleton, which is the substructure of many physiological and therapeutically important compounds.

VI.1.2.2 Properties

The physical properties of cycloalkanes (density, boiling point, melting point etc.) are very similar to that of the corresponding aliphatic hydrocarbons.

The very small ones are relatively reactive, because of the high angle strain that makes the bonds more easily breakable. The compounds with more than five carbon atoms are less reactive.

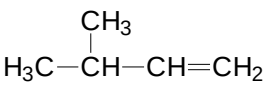
VI.1.3 Aliphatic, unsaturated hydrocarbons

Alkenes (*olefins*) are hydrocarbons that contain one or more carbon-carbon double bonds. Carbon-carbon triple bond(s) occur in *alkynes*.

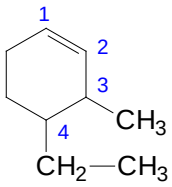
VI.1.3.1 Structure, nomenclature

Comparing alkenes to alkanes, we observe that the double bond reduces the number of hydrogen atoms by 2. Therefore the general formula of alkenes is: C_nH_{2n}. The *-ane* ending in the name of the corresponding alkane is replaced with *-ene* in the name of alkenes and with *-yne* in the name of alkynes, respectivelly.

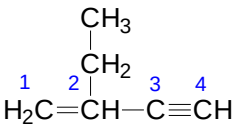
The longest continous chain that includes the double/triple bond forms the base name. The location of the double/triple bond has to be signed by numbers. The chain is numbered in that direction that gives the double(triple)-bonded carbons the lower numbers. If the chain contains double and triple bond as well, the double bond gets the lower number.



3-methylbut-1-ene



4-ethyl-3-methylcyclohexene



2-ethylbut-1-ene-3-yne

The double bond is formed from a σ and a π bond. While the σ bond has a cylindrical symmetry about the line connecting the two atoms, the π bond has a nodal

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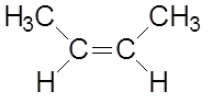
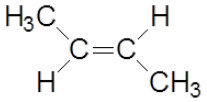
plane passing through the two bonded nuclei. Therefore, the strength of the π bond is a barrier to the rotation of the double bond. This causes *cis-trans (Z-E) isomerism* in alkenes, but only in cases when both of the carbon atoms in the double bond are substituted with two different groups.



Z-2-butene
cis-2-butene



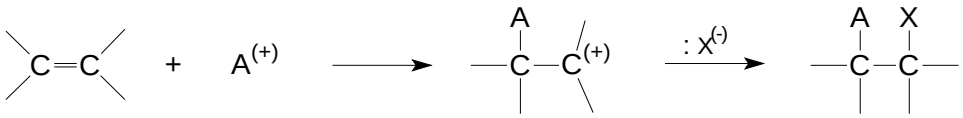
E-2-butene
trans-2-butene

The *trans* isomer is generally more stable than the *cis* one. The physical and chemical properties (e.g. solubility, melting point) of the stereoisomers may differ significantly.

VI.1.3.2 Reactions

The characteristic reaction of compounds with carbon-carbon double or triple bonds is the *addition*, including the addition with halogens, hydrogen or hydrogen halides.

The electrophilic reagent ($A^{(+)}$) causes activation of the double bond, which means the dislocation of the π electronpair, resulting formation of a carbocation, which can be attacked by a nucleophile ($:X^{(-)}$) to yield the new product. The two-step reaction is initiated by an electrophilic reactant, therefore the reaction is called *electrophilic addition*.



Addition of halogens

The rate of the addition follows the F > Cl > Br > I order. Taking an analytical viewpoint, the addition of bromine is the most important. This reaction takes place rapidly at room temperature, and is used as a way to identify double bonds in the Pharmacopoeia.

Addition of hydrogen halides

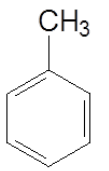
The relative reactivity of hydrogen halides is HI > HBr > HCl > HF in the addition process. In case of unsymmetrical alkenes, the addition of hydrogen halides follows the *Markovnikov's rule*, which states that the hydrogen adds to that carbon of the double bond that has the greater number of hydrogen atoms already attached to it. Selectivity of this sort is termed *regioselectivity*.

VI.1.4 **Aromatic hydrocarbons**

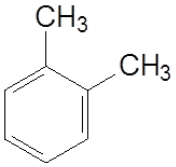
VI.1.4.1 Structure, nomenclature

The simplest compound of the aromatic hydrocarbons is *benzene*. In polycyclic benzenoid aromatic hydrocarbons two or more benzene rings are fused together, the simplest structure is *naphthalene*.

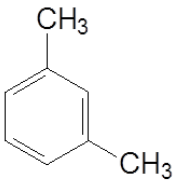
A majority of these compounds, however, are referred to by singular names that are unique.



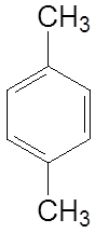
toluene
methylbenzene



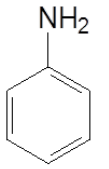
ortho-xylene
1,2-dimethylbenzene



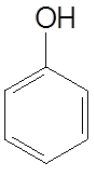
meta-xylene
1,3-dimethylbenzene



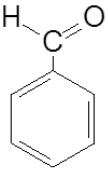
para-xylene
1,4-dimethylbenzene



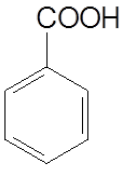
aniline
aminobenzene



phenol
hydroxybenzene

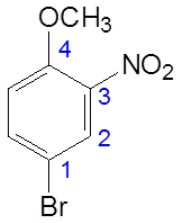


benzaldehyde

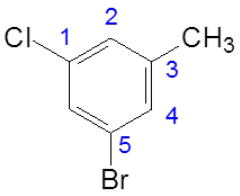


benzoic acid

The systematic name of an aromatic hydrocarbon is formed from benzene or the polycyclic aromatic compound, respectively. The ring is numbered in such a way that the lowest possible number is assigned to the substituents. Numbering starts at the carbon atom bearing the substituent with the highest priority. Substituents are listed alphabetically in the final name. If substitution is symmetrical, numbering corresponds to the alphabetical order.



3-nitro-4-methoxy-bromobenzene



5-bromo-3-methyl-chlorobenzene

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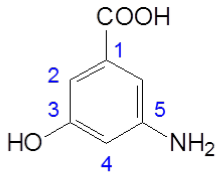
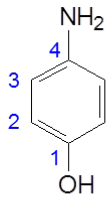


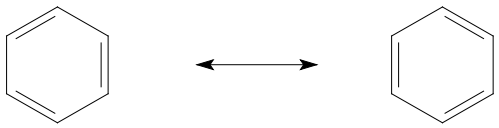
5-amino-3-hydroxybenzoic acid



4-aminophenol

When more than one substituent is present on a benzene ring, the relative locations of the substituents must be designated by numbering the ring carbons or by some other notation. In the case of trivial names of disubstituted benzenes, the prefixes *ortho*, *meta* and *para* are commonly used to indicate a *1,2*- or *1,3*- or *1,4*- relationship, respectively.

In benzene, the six carbon atoms form a symmetrical hexagon and one hydrogen atom is attached to each carbon atom. In the so-called *Kekulé structure* the carbon atoms are bonded to each other by altering single and double bonds.



The Kekulé structure of benzene cannot explain the different reactivities of a conjugated triene and the aromatic ring of benzene. Spectroscopic methods and X-ray diffraction techniques have revealed that the carbon-carbon bond lengths in benzene are equal. The π electrons are delocalized, which results in a cyclic π cloud. Aromaticity is attributed to this cyclic delocalization of the conjugated system of 6π electrons. Aromatic compounds are relative stable.

According to the *Hückel's rule*, any planar, monocyclic ring with (4n+2) π electrons should be aromatic, including isocyclic or heterocyclic derivatives. The delocalized π electrons in benzene can be represented by a simplified structural formula as a ring drawn in a hexagon. This formula also expresses that the bond lengths between the carbon atoms are all equal.

VI.1.4.2 Properties

Physical properties

Monocyclic aromatic hydrocarbons are colorless liquids with characteristic smell. They burn with smoky flame due to their high unsaturation. They are insoluble in water, but miscible with organic solvents. Their boiling point increases with their molecular weight.

Light absorption

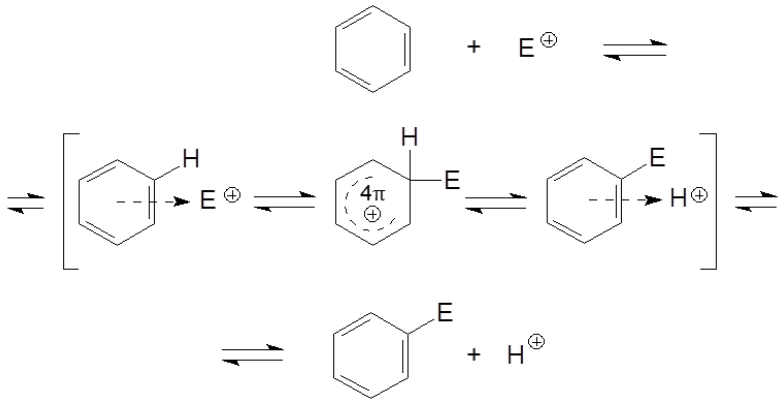
Due to its conjugated π bond system benzene shows intense absorption in the UV-range. At 254 nm a remarkable maximum can be perceived, which may be shifted under the effect of the substituents.

VI.1.4.3 Reactions

The nature of chemical reactions is fundamentally determined by the aromatic structure. The chemical reactivity of benzene contrasts with that of the alkenes in that substitution reactions occur in preference to addition reactions.

Electrophilic aromatic substitution

The most characteristic reactions of benzenoid aromatic compounds are the substitution reactions that occur when the nucleophil π electrons in the aromatic ring react with *electrophilic reagents* (e.g. Br_2, HNO_3, H_2SO_4). In the first step a complex is formed, next the electrophil reagent bounds to the aromatic ring leading to the formation of a cation (carboniumion). The reaction is facilitated by catalysts. The ion formed is stabilized by the removal of one proton. In the final step the aromatic nature is restored.



Since the six hydrogen atoms are equivalent, only one derivative can be formed in a monosubstitution reaction. In contrast, when substituted benzenes undergo electrophilic attack, the substituents already present on the ring influence both rate of the reaction and orientation of the substitution.

Subtituents can be grouped into two categories:

- *Ortho and para directors*:
  $-NH_2$, -NHR, $-NR_2$, -OH, -OR, -R, -Ar, -halogens
- *Meta directors*:
  $-NR_3^+$, $-NO_2$, -CN, $-SO_3H$, -CHO, -COR, -COOH, -COOR, $-CONR_2$

Substituents in the first group (except halogens) are also called *activating groups* since they cause the ring to be more reactive than benzene itself. The free electronpair of the substituent gets into conjugative interaction with the ring, increasing the electron density of it, hence the ring will be activated. The mentioned groups direct the electrophilic substitution primarily at the *ortho* and *para* position.

In the second category, the substituents are so-called *deactivating groups*, because they cause the ring to be less reactive than benzene. All of the members are powerful electron-withdrawing groups, therefore they effectively decrease the electron density of the ring, especially at *ortho* and *para* positions. In the *meta* position eletron density remains relatively large, hence substitution may take place, yet at a low rate.

For example, the relatively simple and rapid bromination of compounds possessing phenolic hydroxyl or aromatic amino group is a result of the activating effect. The reaction can be applied for identification and quantitative determination.

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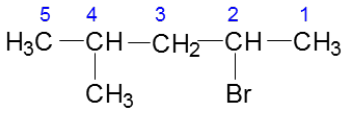
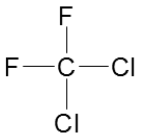
VI.2 Halogenoalkanes

VI.2.1.1 Structure, nomenclature

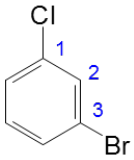
Halogenoalkanes are compounds in which one or more hydrogen atoms in an alkane have been replaced by halogen atoms (fluorine, chlorine, bromine or iodine). In the systematic nomenclature, the halogen is treated as a substituent to the alkane skeleton. They are named in a fashion very similar to that used for naming branched alkanes.



2-bromo-4-methylpentane



dichloro-difluoromethane



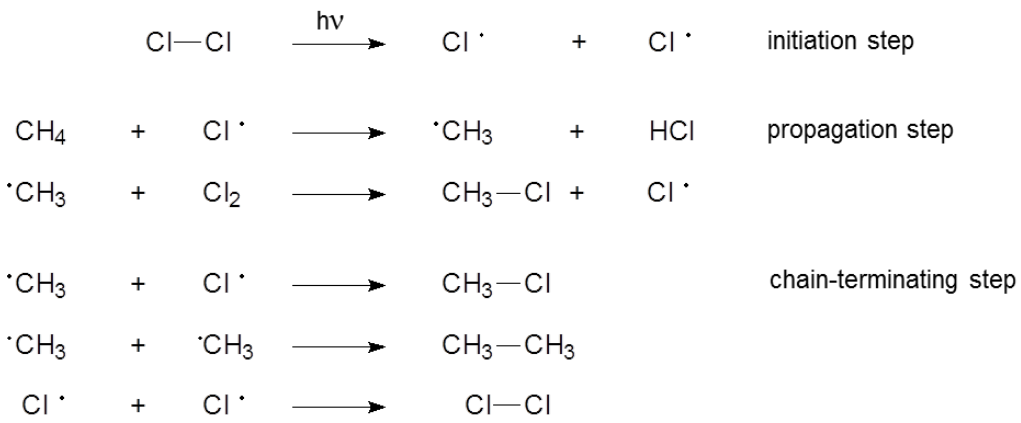
3-bromo-chlorobenzene

Many common alkyl halides also have trivial functional group names (e.g. propyl iodide, vinyl chloride, benzyl bromide). In these examples, the name of the alkyl group is given, followed by the name of the halide. Further trivial names are still in use, for example chloroform ($CHCl_3$), carbon tetrachloride (CCl_4).

VI.2.1.2 Preparation

The reaction of an alkane with a halogen is called *halogenation*, which is the replacement of one or more hydrogen atoms in the organic compound by a halogen (fluorine, chlorine, bromine or iodine). Among the substitution processes fluorination and chlorination occurs rapidly in sunlight and/or at high temperature, iodination requires specific conditions.

Halogenation reactions of alkanes occur through a *radical mechanism*. For example, the mixture of methane and chlorine reacts vigorously upon heat or irradiation with light. In the *initiation step* energy is required to break the covalent bond of the chlorine molecule. The chlorine atoms formed have unpaired electrons and are reactive radicals. In the *propagation step* chlorine atom abstract a hydrogen atom from the methane molecule, causing formation of a methyl radical, which attacks another chlorine molecule, and so on. During the propagation cycles free radicals are continuously formed, therefore the process is called *free radical chain reaction*. In the *chain-terminating step*s two radicals combine into a molecule.



Halogenation of most alkanes yields a mixture of mono-, di-, tri- etc. substituted derivatives and isomers, respectively. Since formation of each compound occurs with different rate, the ratio of products can be modified for example through the alteration of the temperature.

Halogenoalkanes can also be obtained in addition reactions of alkenes with halogens or hydrogen halides (See before).

VI.2.1.3 Properties

Physical properties

The halogen compounds are usually colorless. Alkyl-monohalogens with low carbon number (except the iodine compounds) are volatile liquids, compounds with higher carbon number are solid. Iodine derivatives are commonly solid.

The boiling point increases with molecular mass and with F < Cl < Br < I order. Most of halogenoalkanes are insoluble in water, but miscible with apolar solvents. Small molecules with more than one halogen atom are good solvents for other organic compounds as well.

Chemical properties

Since halogens are more electronegative than carbon, the C-X bond is polarized. The electron density along the C-X bond is displaced in the direction of the halogen, therefore the halogen possesses a partial negative charge and the carbon atom has a partial positive charge. The dipol moment is significant; it increases in C - I < C - Br < C - Cl < C - F order.

Beside bond polarity, polarizability of the bond also affects the reactivity. Polarizability, namely the ease of deformation of electron cloud caused by the reagent, increases in reverse direction of electronegativity: C - F < C - Cl < C - Br < C - I.

As a result, reactivity of alkyl halides increases from fluorine to iodine: C - F < C - Cl < C - Br < C - I.

VI.2.1.4 Reactions

Reactivity of halogenohydrocarbons may be influenced by further substituents. Therefore, the chemical properties of aliphatic and aromatic halogen compounds differ significantly.

Characteristic reactions of aliphatic halogen compounds:

- nucleophilic substitution
- elimination, in which hydrogen halide or a halogen molecule is eliminated

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- reactions with metals
- reduction to alkanes.

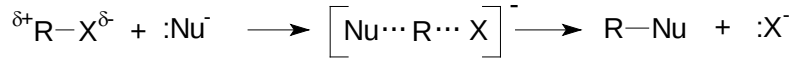
Characteristic reactions of aromatic halogen compounds:

- electrophilic substitution of the aromatic ring
- nucleophilic substitution, but only under specific conditions and/or by special structures
- reaction with metals.

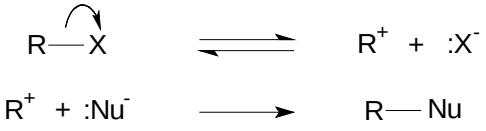
Nucleophilic substitution

It is the most frequent reaction of alkyl halides. An anion or other electron-rich species (e.g. a group with free electron pair) are able to attack the positively polarized carbon atom. The C-X covalent bond breaks, and a new covalent bond is formed between the carbon atom and the nucleophile. As a result the nucleophile replaces the halogen.

In general, there are two types of nucleophilic substitution mechanism. The *bimolecular nucleophilic substitution* ($S_{N}2$) is a one-step process. The nucleophile attacks the molecule, then at the transition state the nucleophile and the leaving group are both partly bound to the carbon, and finaly the halogen leaves. Increasing the nucleophile character of the reagent facilitates the reaction.



The monomolecular nucleophilic substitution ($S_{N}1$) is a two-step process: In the first step, there is polarization. In the second - rate-determining - step the carbon-halogen bond breaks. In this second, fast step the carbonium cation formed combines with the nucleophile to give the product.



The environment of the carbon atom is the most important determinant of the rate of the reaction. The more stable carbonium cation can be formed, the faster is the dissociation. Polar solvents facilitate the reaction.

In case of identification of halogen containing compounds the nucleophilic substitution reactions are frequent. The most common nucleophilic reagents are alkali hydroxides. During the reaction the covalently bound chlorine or bromine atom is released as an ion that is easily identified.

VI.2.1.5 Therapeutical applications

In the 19th century chloroform was widely used in surgery as a general anaesthetic. Because of the toxic side effects (e.g. severe liver damage, cardiotoxicity), which are attributable to phosgene formed from chloroform in the presence of light and oxygen. Nowadays, chloroform is not used as a narcotic but primarily as a solvent.

The inhaled general anaesthetics applied today, except nitrous oxide, are all alkyl halides or halogen derivatives of alkyl ethers, respectively. Among alkyl halides *halothane* ($ClBrCH\text{-}CF_3$), and among alkyl ether analogues *isoflurane*

(CF_3-CHCl-O-CHF_2) are official in Ph. Eur 8.0. They are volatile, colorless liquids, which get into the circulation and subsequently into the brain following inhalation. Their volatility and partition coefficient are the traits that mostly influence their effectiveness.

VI.2.1.6 Pharmacopoeial qualifications

HALOTHANE

Halothanum

$C_2HBrClF_3$ $M_r = 197.4$

DEFINITION

(*RS*)-2-Bromo-2-chloro-1,1,1-trifluoroethane to which 0.01 per cent *m/m* of thymol has been added.

CHARACTERS

Appearance: clear, colourless, mobile, heavy, non-flammable liquid.

Solubility: slightly soluble in water, miscible with anhydrous ethanol and with trichloroethylene.

IDENTIFICATION

A. Distillation range (see Tests).

B. Add 0.1 ml to 2 ml of *2-methyl-2-propanol R* in a test-tube. Add 1 ml of *copper edetate solution R*, 0.5 ml of *concentrated ammonia R* and mixture of 0.4 ml of *strong hydrogen peroxide solution R* and 1.6 ml of *water R* (solution A). Prepare a blank at the same time (solution B). Place both tubes in a water-bath at 50 °C for 15 min, cool and add 0.3 ml of *glacial acetic acid R*. To 1 ml of each of solutions A and B add 0.5 ml of a mixture of equal volumes of freshly prepared *alizarin S solution R* and *zirconyl nitrate solution R*. Solution A is yellow and solution B is red.

To 1 ml of each of solutions A and B add 1 ml of *buffer solution pH 5.2 R*, 1 ml of *phenol red solution R* diluted 1 to 10 with *water R* and 0.1 ml of *chloramine solution R*. Solution A is bluish-violet and solution B is yellow.

To 2 ml of each solutions A and B add 0.5 ml of a mixture of 25 volumes of *sulphuric acid R* and 75 volumes of *water R*, 0.5 ml of *acetone R* and 0.2 ml of a 50 g/l solution of *potassium bromate R* and shake. Warm the tubes in a water-bath at 50 °C for 2 min, cool and add 0.5 ml of a mixture of equal volumes of *nitric acid R* and *water R* and 0.5 ml of *silver nitrate solution R2*.
Solution A is opalescent and a white precipitate is formed after a few minutes; solution B remains clear.

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TESTS

Acidity or alkalinity. To 20 ml add 20 ml of *carbon dioxide-free water R*, shake for 3 min and allow to stand.
Separate the aqueous layer and add 0.2 ml of *bromocresol purple solution R*. Not more than 0.1 ml of *0.01 M sodium hydroxide* or 0.6 ml of *0.01 M hydrochloric acid* is required to change the colour of the indicator.

Relative density: 1.872 to 1.877.

Distillation range: it distils completely between 49.0 °C and 51.0 °C and 95 per cent distills within a range of 0.1 °C.

Volatile related substances. Gas chromatography.

Internal standard: trichlorotrifluoroethane CRS.

Test solution (a). The substance to be examined.

Test solution (b). Dilute 5.0 ml of *trichlorotrifluoroethane CRS* to 100 ml with the substance to be examined. Dilute 1.0 ml of this solution to 100.0 ml whit the substance to be examined. Dilute 1.0 ml of this solution to 10.0 ml with the substance to be examined.

Column:

- *size:* l = 2.75 m, ø = 5 mm;
- *stationary phase: silanised diatomaceous earth for gas chromatography R1* (180-250 µm), the first 1.8 m being impregnated with 30 per cent *m/m macrogol 400 R* and the remainder with 30 per cent *m/m* of *dinonyl phthalate R*;
- *temperature*: 50 °C.

Carrier gas: nitrogen for chromatography R.

Flow rate: 30 ml/min.

Detection: flame ionization.

Injection: 5 µl.

Limit: test solution (b):

- *total*: not more than the area of the peak due to the internal standard, corrected if necessary for any impurity with same retention time as the internal standard (0.005 per cent).

Thymol. Gas chromatography.

Internal standard solution. Dissolve 0.10 g of *menthol R* in *methylene chloride R* and dilute to 100.0 ml with the same solvent.

Test solution. To 20.0 ml of the substance to be examined add 5.0 ml of the internal standard solution.

Reference solution. Dissolve 20.0 mg of *thymol R* in *methylene chloride R* and dilute to 100.0 ml with same solvent. To 20.0 ml of this solution, add 5.0 ml of the internal standard solution.

Column:

- *material*: fused silica;
- *size:* l = 15 m, ø = 0.53 mm;
- *stationary phase*: *poly(dimethyl)siloxane R* (film thickness 1.5 µm).

Carrier gas: nitrogen for chromatography R.

Flow rate: 15 ml/min.

Temperature:

- *column*: 150 °C;
- *injection port*: 170 °C;
- *detector*: 200 °C.

Detection: flame ionization.

Injection: 1.0 µl.

Limit:

- *thymol*: 0.75 times to 1.15 times the area of the corresponding peak in the chromatogram obtained with the reference solution (0.008 per cent *m/m* to 0.012 per cent *m/m*).

Bromides and chlorides. To 10 ml add 20 ml of *water R* and shake for 3 min. To 5 ml of the aqueous layer add 5 ml of *water R*, 0.05 ml of *nitric acid R* and 0.2 ml of *silver nitrate solution R1*. The solution is not more opalescent than a mixture of 5 ml of the aqueous layer and 5 ml of water R.

Bromide and chlorine. To 10 ml of the aqueous layer obtained in the test for bromides and chlorides add 1 ml of *potassium iodide and starch solution R*. No blue colour is produced.

Non-volatile matter: maximum 20 mg/l.

Evaporate 50 ml to dryness on a water-bath and dry the residue in oven at 100-105 °C for 2 h. The residue weight a maximum of 1 mg.

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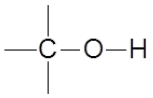
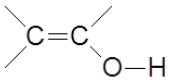
VI.3 Alcohols and phenols

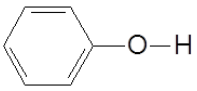
Compounds containing *hydroxyl functional groups* can be classified into three groups: alcohols, enols and phenols. In alcohols the hydroxyl group is attached to a saturated, sp^3-hybridized carbon atom, in enols to an unsaturated carbon atom, which is in sp^2 hybrid state. Compounds that have a hydroxyl group attached directly to a carbon atom of a benzene ring are called phenols.



alcohol



enol

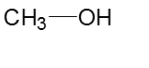


phenol

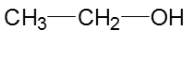
VI.3.1 **Alcohols**

VI.3.1.1 Structure, nomenclature

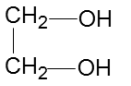
Alcohols are usually designated by an *-ol* suffix. Actually, alcohols are derivatives of alkanes, thus, an alkane is converted into an alkanol. If more than one hydroxyl group is attached to the chain, the ending *-diol*, *-triol* and so on, is used. Numerous alcohols have trivial names as well.



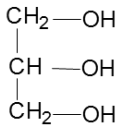
methanol
methyl alcohol



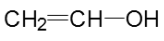
ethanol
ethyl alcohol



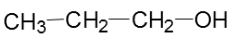
ethylene glycol
1,2-ethanediol



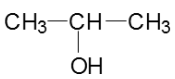
glycerol
1,2,3-propa netriol



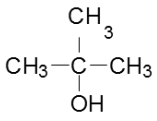
vinyl alcohol



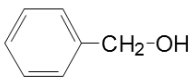
propyl alcohol
1-propanol



isopropyl alcohol
2-propanol

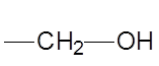


tert -butyl alcohol
2-methyl-2-propanol

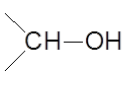


benzyl alcohol

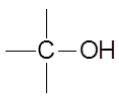
Alcohols may also be classified as *primary*, *secondary*, or *tertiary* alcohols. This terminology refers to alkyl substitution of the carbon atom bearing the hydroxyl group.



primary



secondary



tertiary

VI.3.1.2 Properties

Physical properties

The first eleven members (C_1-C_{11}) of the aliphatic alcohol series with one hydroxyl group are liquids with characteristic smell. Their density is lower than that of water. Alcohols over C_{12} are solid and odorless.

The boiling point of alcohols are unusually high, much higher than that of the alkane with the same number of carbon atoms. The reason for this is that the alcohol molecules can associate with each other through hydrogen bonding.

The small alcohols are completely soluble in water, which can be explained by the intermolecular hydrogen bondings between the alcohol and water molecules. However, solubility falls as the length of the hydrocarbon chain in the alcohol increases.

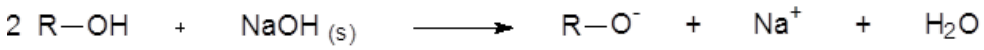
The small alcohols are very polar liquids with high dipole moments, therefore they are used as protic solvents.

Light absorption

The simple, aliphatic alcohols have around 180-190 nm absorption maximum, over 200 nm they are practically transparent, therefore they can be used as solvents in analytical investigations.

Chemical properties

Alcohols in aqueous solutions are very weak acids, they are practically neutral compounds. Under nonaqueous conditions the hydroxyl group of alcohols can act as a proton donor, but only in the presence of a strong base, resulting in the formation of an alkoxide (alcoholate anion) ion.

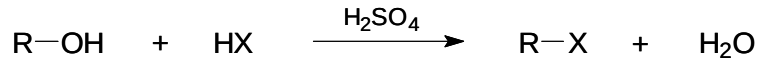


The acidic character of alcohols decreases with the length and branching of the carbon chain.

VI.3.1.3 Reactions

Substitution

The hydroxyl group can be replaced by halogens such as chlorine or bromine in the reaction with hydrogen chloride or hydrogen bromide, resulting in formation of alkyl halides. The reaction can be catalyzed by dehydrating agents.

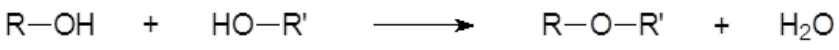


Elimination

Elimination of water from an alcohol (at high temperature and in the presence of a catalyst) is called *dehydration*, and leads to the formation of unsaturated alkenes.

Formation of ethers

Ethers can be prepared from alcohols in the presence of dehydrating agents, under appropriate conditions. During the intermolecular elimination of water, two alcohols form an ether molecule.



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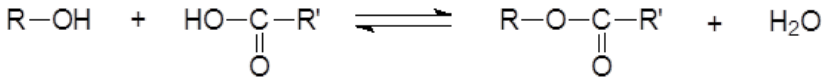
Formation of esters

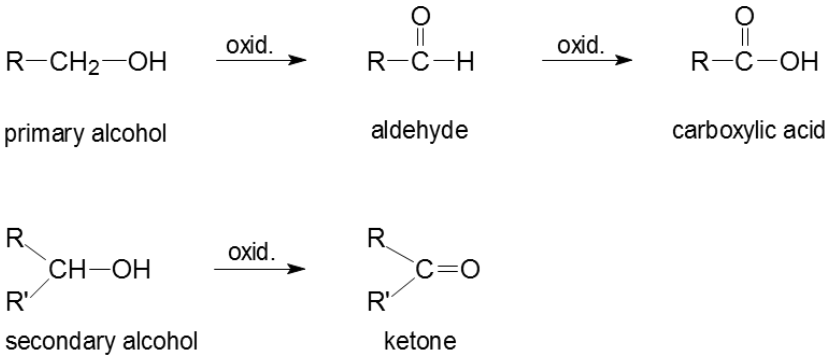
When an alcohol and a carboxylic acid are heated in the presence of an acid catalyst, an ester and water are formed.



Since the formed ester usually has a characteristic odor, formation of esters can be applied as identification reactions in pharmaceutical analysis. For example, in the Ph. Hg. VIII. the informative test of ethanol as follows: the mixture of ethanol and acetic acid has to be heated in the presence of concentrated sulphuric acid; the odor of the forming ethyl acetate is perceptible.

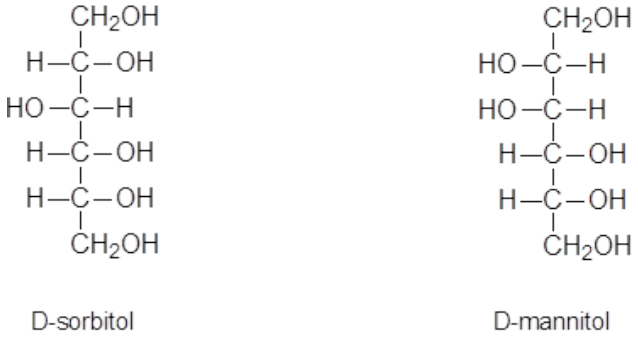
Oxidation

Primary alcohols can be oxidized with numerous oxidants ($K_2Cr_2O_7$, $KMnO_4$ etc.) to aldehydes, which can be further oxidized to carboxylic acids. Secondary alcohols form ketones due the oxidation. Tertiary alcohols do not undergo oxidation of this type; they can be oxidized under special conditions, which leads to the formation of smaller carboxylic acids after chain breaking.



VI.3.2 **Polyalcohols**

Polyalcohols contain more than one hydroxyl groups. Characteristic representatives are glycole, glycerol, sorbitol and mannitol. The latter two are widely used in therapy.



D-sorbitol

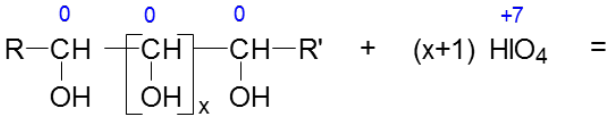
D-mannitol

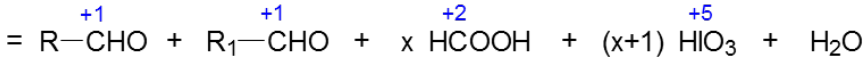
VI.3.2.1 Properties

Sorbitol and mannitol are white, crystalline, sweet, solid compounds. They are very soluble in water and insoluble in apolar solvents. Their aqueous solution is neutral.

VI.3.2.2 Analytics

Periodate is a selective oxidant of 1,2-diols and derivatives, which cleaves the bond between the two carbon atoms bearing the vicinal hydroxyl moiety, and oxidizes the hydroxyl groups (*Malaprade reaction*). The products are aldehyde and formic acid, respectively, depending on the structure of the polyol.

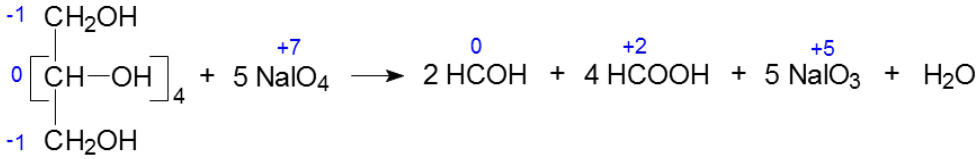




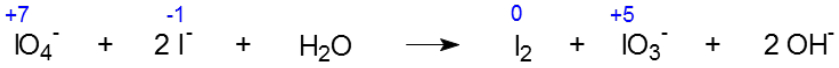
The reaction is applicable to investigate 1,2-diols selectively beside 1,3- and 1,4-diols. Based on the structure of the products, the primary or secondary character of the hydroxyl groups can be interpreted, since formaldehyde is formed from a primary alcohol group and formic acid from a secondary one, respectively.

Keeping the appropriate temperature and pH, the reaction can be quantitative, therefore it can be used for quantitative determinations.

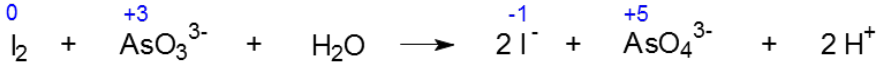
The reaction with periodate is the basis of the assay of polyalcohols in the Ph. Hg. VII. The aqueous solution of the polyalcohol is mixed and heated with a known amount of sodium periodate which is in excess. The reaction is quantitative.



Iodide ions added to the solution in the presence of potassium hydrogencarbonate, react with the excess of periodate to form iodine (the iodate ions do not react with iodide in this medium).



The formed iodine, which is equivalent to the excess of periodate, reacts with the known amount of arsenite ions added to the solution in excess. As a result, arsenate ions are formed:



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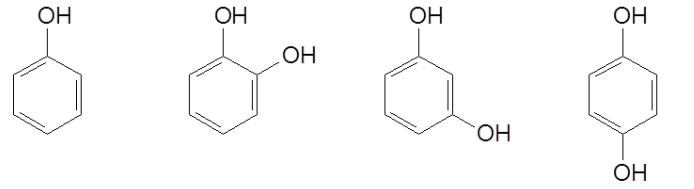
The excess of arsenite is back-titrated with iodine in the same, slightly alkaline medium.

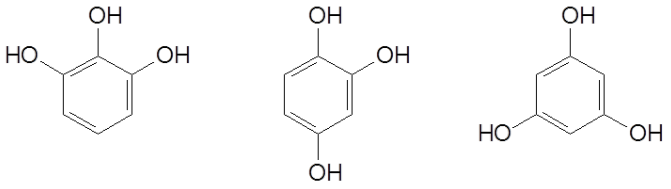
When a blank titration is performed simultanously, using the same volumes of periodate and arsenite solutions, the total amount of periodate changes to iodine, which oxidizes arsenite. So the excess of arsenite is smaller than before, therefore less iodine solution is needed in the titration.

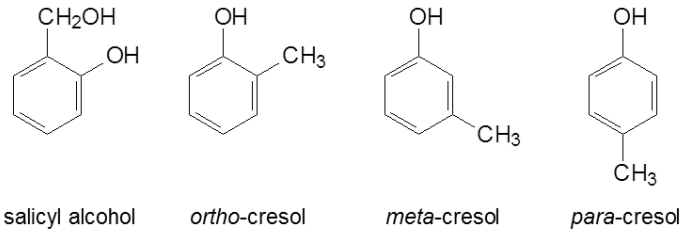
VI.3.3 **Phenols**

VI.3.3.1 Structure, nomenclature

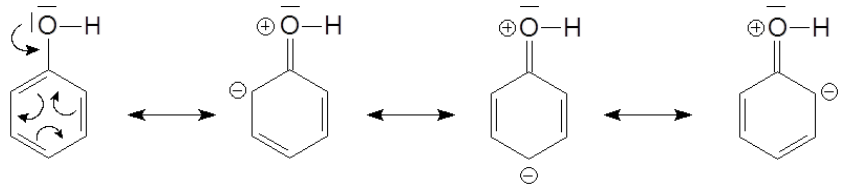
In phenols one or more hydrogens of benzene are replaced with hydroxyl function. Phenols are usually named as derivatives of the parent compound. Many phenols have common names, as well. A compound can be both an alcohol and a phenol at the same time, like salicyl alcohol.







The most important factor affecting the properties and reactivity of phenols is the interaction between the lone pairs of electrons of the hydroxyl group and the aromatic ring, which leads to activation of the ring and to participate in electrophile substitution reactions. (*See* Reactions of aromatic hydrocarbons)



VI.3.3.2 Properties

Physical properties

Phenols are usually solid crystalline compounds at room temperature, except for some alkyl phenols (e.g. *m*-cresol), which are liquids. Most of them have a characteristic odor.

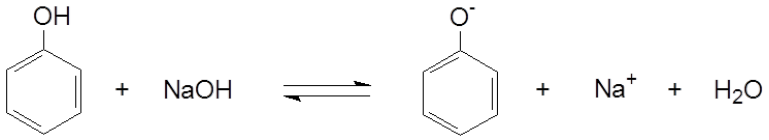
Their boiling point is higher than that of aromatic alkyl derivatives with similar molecular weight. The presence of the phenolic hydroxyl group increases the possibility of intermolecular interactions, therefore the solubilty in water also increases.

Light absorption

The interaction between the π electrons of oxygen and the aromatic ring is also perceptible in the UV spectrum of the components. The absorption maximum of benzene (254 nm) becomes more intense and shows a batochromic shift in the case of phenol (270 nm).

Chemical properties

Phenols are weak acids, their pK_a value is between 8 and 10. In the reaction with strong bases (e.g. alkali hydroxides) salt-like compounds (phenoxide (or phenolate) anions) are formed.



Phenols are stronger acids than alcohols. The main reason for this is that phenoxide ions are more stable than alkoxide ions due to the stabilization by resonance. Whereas the negative charge of an alkoxide ion is localized on the oxygen atom, the negative charge of a phenoxide ion can be localized both to the *ortho* and *para* positions of the benzene ring, through resonance. Further electron-withdrawing groups (like halogens or further hydroxyl group), increase the stability of phenoxide ions. The nitro-substituent increases acidity significantly, for example the acidity of picric acid (2,4,6-trinitrophenol) is comparable in strength to inorganic acids.

VI.3.3.3 Chemical reactions

Complex formation

Most phenolic compounds form a coloured complex with iron(III) chloride. Neutral or slightly acidic mediua promote the reaction. In the case of phenols bearing in *ortho*-position a further group which is also suitable for complex-formation (like salicylic acid), the formed complex is more stable, and its color is more intense. The colour of the complex is bluish-violet with a monovalent phenol, green with *o*-diphenols, blue with *m*-diphenols and bluish-black with triphenols. But the actual color may be influenced by the other parts of the molecule as well. Thymol does not form a complex with iron(III) due to the big substituent on the neighboring carbon atom.

The reaction with iron(III) chloride is a sensitive reaction, therefore applicable for identification of phenolic compounds, and it is widely used in the Pharmacopoeia as well. If the formation of the complex is quatitative, then it is usable for spectrophotometric quantitative determination as well. It is a disadvantage that the

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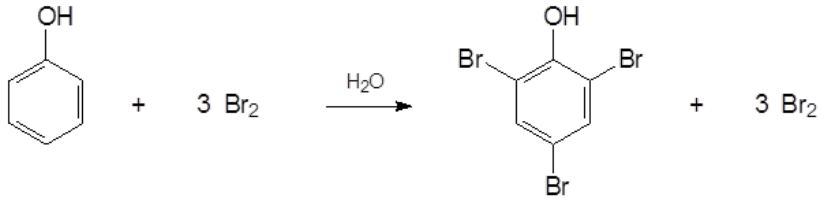
reaction is not specific, because beside phenols, some enols and other oxidizable components also react with iron(III) showing strong color.

Substitution reactions

Due to activating property of the hydoxyl group, electrophilic substitution reactions of phenols at *ortho*- and *para*-position occour relatively easily.

Bromination

In the reaction between phenol and bromine 2,4,6-tribromophenol is formed.



In the case of other phenolic compounds formation of mono-, di- or tribromo-derivatives depends on whether the activated positions are free or not. For example, salicylic acid - in which a carboxyl group can be found in *ortho*-position – undergoes decarboxylation as a result of its reaction with bromine, and bromine is replaced for the carboxyl function.

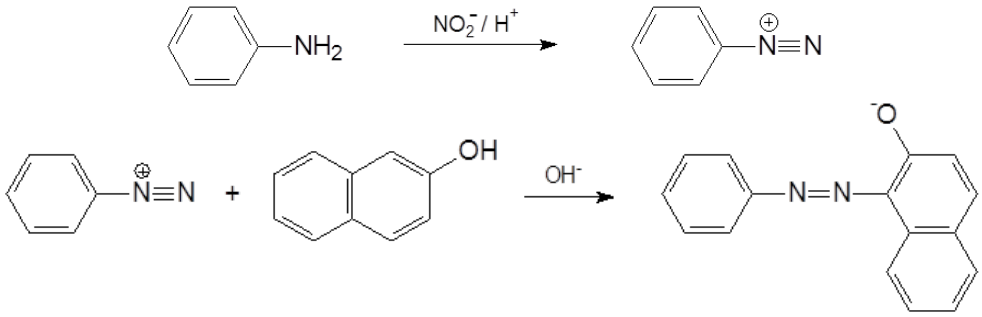
The bromine substituted products are usually less soluble than the initial compounds, therefore they commonly form precipitate.

The Ph. Hg. VIII. applies bromination reaction both for identification and quantitative determination.

Formation of azo dyes with diazonium salts.

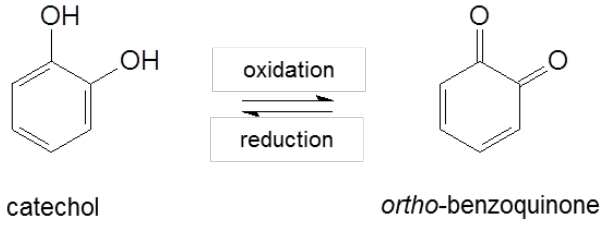
Phenolic compounds of which *ortho*- or *para*-position is free, easily react in alkaline medium with diazonium cations formed from aromatic primary amines, and an orange-red azo dye is produced.

The reaction is useful for identification of phenolic compounds, aromatic primary amines and nitrite ions as well. In the Ph. Hg. VIII. it represents a general identification reaction of aromatic primary amines. Giving sodium nitrite to the aromatic primary amine dissolved in hydrochloric acid results in the formation of diazonium cation, which reacts with *β*-naphthol in alkaline medium leading to the production of a red azo dye:

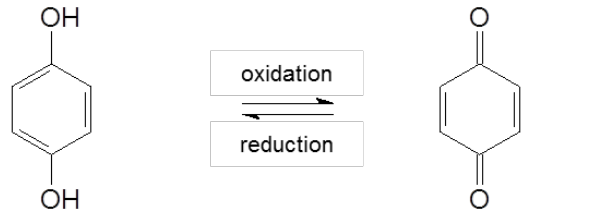


Oxidation reactions

Phenols are rather easily oxidized despite absence of a hydrogen atom on the hydroxyl bearing carbon atom. The colored product of oxidation of catechol is the dicarbonyl compound *ortho*-benzoquinone and the product formed from hydroquinone is called *para*-benzoquinone. (*Meta*-quinones having similar structures do not exist.)



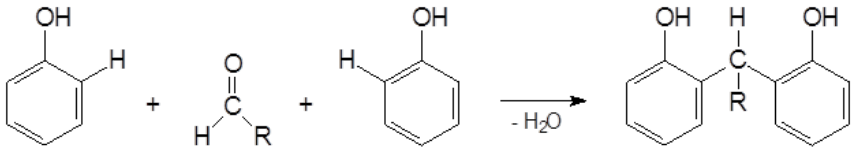
catechol *ortho*-benzoquinone



hydroquinone *para*-benzoquinone

Condensation with aldehydes

Phenols relatively easily undergo condensation reactions with aliphatic and aromatic aldehydes as well. As a result, coloured diarylmethane- or triarylmethane-type dyes are produced.



According to prescriptions in the Ph. Hg. VIII., the reaction provides the base of identification of formaldehyde formed from sugars after dehydration and decomposition. The produced formaldehyde reacts with resorcinol or thymol, respectively (e.g. *Selivanov reaction*).

Condensation with chloroform

Some phenols react in alkaline medium with chloroform. Hydrochloric acid and high coloured diarylmethane- or triarylmethane-type dyes are produced at the same time. The alkaline medium serves partly to deprotonate the phenol, partly to form the electrophilic dichlorocarbene from chloroform, which is subsequently condensed with the phenolic compound.

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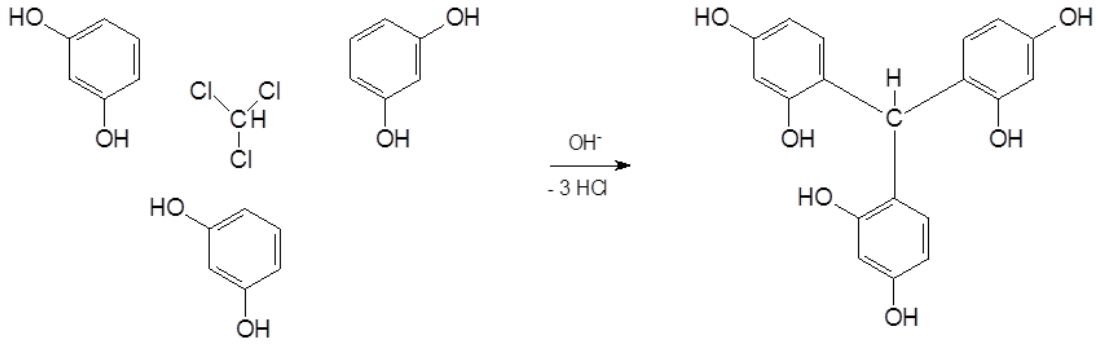

The reaction is applied as the identification reaction of resorcinol and thymol in the Pharmacopoeia.

VI.3.4 **Therapeutical application of alcohols and phenols**

Numerous alcohol and phenol derivatives are official in the Ph. Hg. VIII.

Alcohols and phenols officinal in the Ph. Hg. VIII.

Compound	Name in the Pharmacopoeia	Application
Alcohols		
Ethanol	Ethanolum (96 per centum) Ethanolum anhydricum	antiseptic, solvent
Propanol	Propanolum	antiseptic
Izopropyl alcohol	Alcohol isopropylicus	antiseptic
Cetyl alcohol	Alcohol cetylicus	technological material
Stearyl alcohol	Alcohol stearylicus	technological material
Benzyl alcohol	Alcohol benzylicus	antiseptic
Glycerol	Glycerolum	osmotic laxative, solvent
Propylene glycol	Propylenglycolum	technological material
Mannitol	Mannitolum	osmotic laxative, diuretic
Sorbitol	Sorbitolum	osmotic laxative, diuretic
Phenols		
Phenol	Phenolum	antiseptic
Resorcinol	Resorcinolum	antiseptic
Cresol	Cresolum crudum	antiseptic
Chlorocresol	Chlorocresolum	antiseptic
Hexylresorcinol	Hexylresorcinolum	antiseptic
Thymol	Thymolum	antiseptic

Aliphatic alcohols denatures proteins, hence they are antiseptics for external use. The antiseptic effect increases until 6-8 carbon atoms, for aliphatic alcohols with more carbon atoms the antiseptic effect decrases, because of the reduction of water solubility.

Phenol itself causes severe skin burns and is caustic, therefore the aqueous solution of phenol is used as a disinfectant. The antiseptic effect inreases with the incorporation of an alkyl chain and/or halogen atom, but the caustic effect decreases.

Mannitol and *sorbitol*, representatives of polyalcohols, are used on the one hand as osmotic laxatives, on the other hand as osmotic diuretics. *Mannitol* is used clinically in osmotherapy to reduce acutely raised intracranial pressure until more definitive treatment can be applied. *Sorbitol* is often used as sweetener in diet foods.

VI.3.5 **Pharmacopoeial qualifications**

ETHANOL (96 PER CENT)

Ethanolum (96 per centum)

C_2H_6O $M_r = 46.07$

CHARACTERS

Appearance: colourless, clear, volatile, flammable liquid, hygroscopic.
Solubility: miscible with water and with methylene chloride.
It burns with a blue, smokeless flame. Bp: about 78 ºC.

IDENTIFICATION

B. Mix 0.1 ml with 1 ml of a 10 g/l solution of *potassium permanaganate R* and 0.2 ml of *dilute sulphuric acid R* in a test tube. Cover the test tube immediately with a filter paper moistened with a freshly prepared solution containing 0.1 g of *sodium nitroprusside R* and 0.5 g of *piperazine hydrate R* in 5 ml of *water R*. After a few minutes, an intense blue colour appears on the paper which becomes paler after 10-15 minutes.

Potassium permanganate can oxidize ethanol under acidic conditions to form acetaldehyde, which reacts with piperazine to form N-vinylpiperazine. This latter compound reacts with the sodium nitroprusside reagent to form a blue coloured complex.

$$2\ MnO_4^- + 5\ CH_3CH_2OH + 6\ H^+ = 2\ Mn^{2+} + 5\ CH_3CHO + 8\ H_2O$$

D. To 0.5 ml add 5 ml of *water R*, 2 ml of *dilute sodium hydroxide solution R*, then slowly add 2 ml of *0.05 M iodine*. A yellow precipitate is formed within 30 min.

In the first step of the reaction acetaldehyde is formed, then iodal and in the end the yellow coloured precipitate iodoform.

$$CH_3CH_2OH + 2\ NaOH + I_2 = CH_3CHO + 2\ NaI + 2\ H_2O$$

$$CH_3CHO + 3\ NaOH + 3\ I_2 = I_3CCHO + 3\ NaI + 3\ H_2O$$

$$I_3CCHO + NaOH = \underline{CHI_3} + HCOONa$$

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TESTS (Ph. Hg. VII.)

Methanol. In a test tube digest 0.2 with 0.1 ml of *concentrated phosphoric acid,* and 0.2 ml of *0.3 M potassium permanganate solution*. After 10 minutes, dropwise add a *sodium hydrogen sulphite solution R* to the mixture until the liquid decolorizes.

To the reaction mixture add 15 ml of *chromotropic acid solution R* in small portions, and immerse the test tube with the liquid for 10 minutes in a water-bath of a temperature of 60 ºC to 70 ºC.

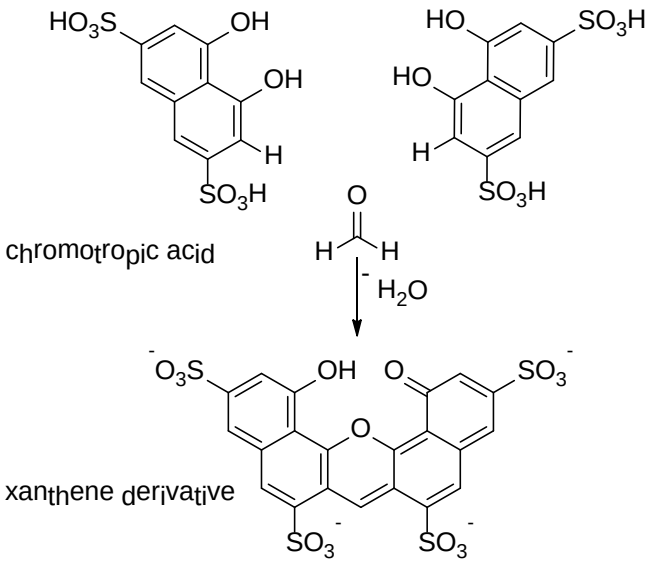
In another test tube, perform a refrence test with 0.20 ml of *hexamethylenetetramine limit solution.*

Lift both test tubes off the water-bath, keep them for one hour at room temperature and compare their colour in front view using a white background. A possible pale yellowish brown tint of the reaction mixture containing the alcohol sample may be neglected. When, however, a reddish violet colour appears, it must not exceed that of the comparasion test.

$$5\ CH_3OH + 2\ MnO_4^- + 6\ H^+ = 5\ CH_2O + 2\ Mn^{2+} + 8\ H_2O$$

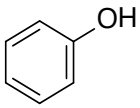
$$2\ MnO_4^- + 5\ HSO_3^- + 11\ H^+ = 2\ Mn^{2+} + 5\ SO_3 + 8\ H_2O$$

Permanganate ions can oxidize methanol to formaldehyde which forms with chromotropic acid a reddish-violet coloured xanthene derivative. The excess of permanganate ions is decomposed with sodium hydrogen sulphite solution.



PHENOL

Phenolum



C_6H_6O $M_r = 94.10$

DEFINITION

Content: 99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance: colourless or faintly pink or faintly yellowish, crystals or crystalline masses, deliquescent.

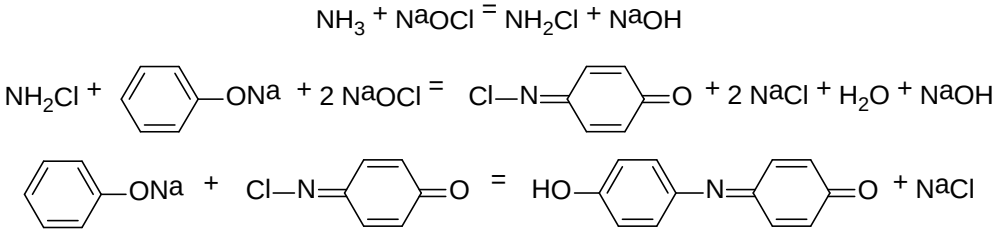
Solubility: soluble in water, very soluble in ethanol (96 per cent), in glycerol and in methylene chloride.

IDENTIFICATION

Solution S. Dissolve a 0.3 g sample in *water R* and dilute the solution to 5 ml with the same solvent.

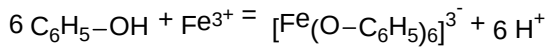
A. Dissolve a 0.5 g in 2 ml of *concentrated ammonia R*. The substance dissolves completely. Dilute the solution to about 100 ml with *water R*. To 2 ml of this solution add 0.05 ml of *strong sodium hypochlorite solution R*. A blue colour develops and becomes progressively more intense.

Berthelot reaction: Reaction of ammonia with sodium hypochlorite yields monochloramine, which reacts with two phenolate ions to form the blue indophenol.



B. To 1 ml of *Solution S* add 10 ml of *water R* and 0.1 ml of *ferric chloride solution R1*. A violet colour is produced which disappears on addition of 5 ml of *2-popanol R*.

Iron(III) ions reacts with phenolate ions to form a violet complex.



C. To 1 ml of *Solution S* add 10 ml of *water R* and 1 ml of *bromine water R*. A pale-yellow precipitate is formed.

The aromatic ring of phenol reacts with bromine to form 2,4,6-tribromophenol (white) and 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one (yellow). (See Assay.)

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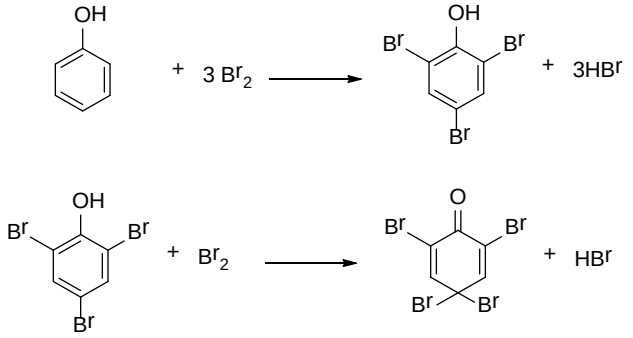
ASSAY

Dissolve a 2.000 g in *water R* and dilute the solution to 1000.0 ml with the same solvent. Transfer 25.0 ml of the solution to a ground-glass-stoppered flask and add 50.0 ml of *0.0167 M bromide-bromate* and 5 ml of *hydrochloric acid R*, close the flask, allow it to stand with occasional swirling for 30 min. Then allow it to stand for 15 min. Add 5 ml of a 200 g/l solution of *potassium iodide R*, shake and titrate with *0.1 M sodium thiosulphate* until a faint yellow colour remains. Add 0.5 ml of *starch solution R* and 10 ml of *chloroform R* and continue the titration with vigorous shaking. Carry out a blank titration.



The aromatic ring of phenol reacts with bromine to form 2,4,6-tribromophenol (white) and 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one (yellow). The fourth mole of bromine, however, can be back-titrated when the excess of bromine is determined by iodometry.

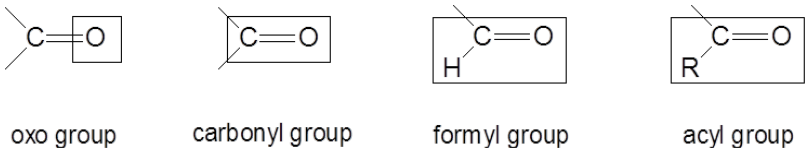
$$Br_2 + 2\ I^- = I_2 + 2\ Br^-$$

$$I_2 + 2\ S_2O_3^{2-} = 2\ I^- + S_4O_6^{2-}$$

Thus, the titration is based on the reaction of one mole of phenol and three moles of bromine.

VI.4 Aldehydes and ketones

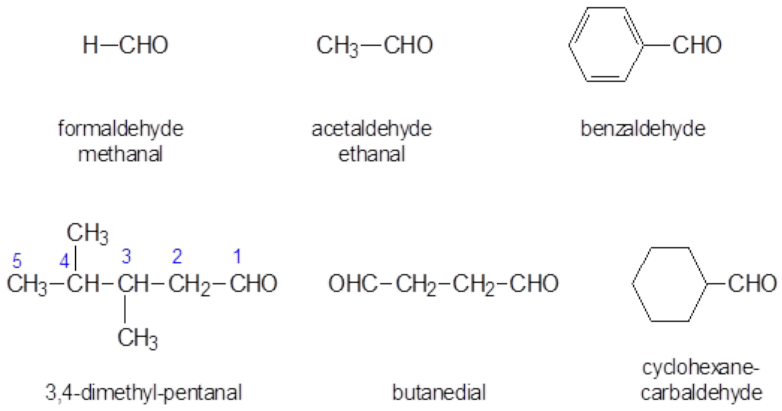
Aldehydes and ketones are simple compounds which contain a *carbonyl group*, where a carbon-oxygen double bond is found. The oxygen atom in a double bond is called *oxo group*. *Aldehydes* have at least one hydrogen attached to the carbon atom of the carbonyl. *Ketones* have two alkyl and/or aryl groups as substituents on the carbonyl carbon atom. The aldehyde group is also called *formyl* substituent.



VI.4.1 Structure, nomenclature

In the IUPAC system of nomenclature aliphatic aldehydes are named substitutively using the characteristic suffix *-al*. Since an aldehyde carbonyl group must always lie at the terminal of a carbon chain, it is position 1 by default, and therefore defines the numbering direction.

Many aldehydes also have common names derived from the common names of the corresponding carboxylic acid. In some cases the *carbaldehyde* suffix is used, in which case the carbonyl carbon atom do not form a part of the basic carbon chain.



Aliphatic ketones are named by replacing the final *-e* of the corresponding alkane with the suffix *-one*. A ketone carbonyl function may be located anywhere within a chain or ring, and its position is given by a locator number. Chain numbering normally starts from the end nearest the carbonyl group.

Common names of ketones are formed by adding the word ketone to the names of the alkyl or aryl groups attached to the carbonyl carbon atom.

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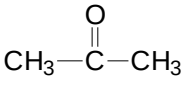
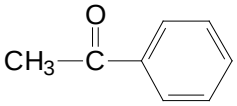
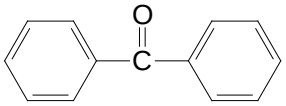


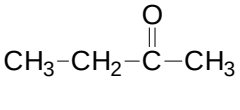
propanone
acetone
dimethyl ketone



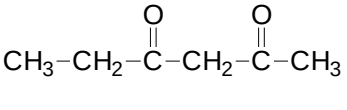
acetophenone
methyl phenyl ketone



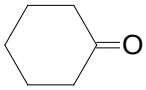
benzophenone
diphenyl ketone



butane-2-one
ethyl methyl ketone



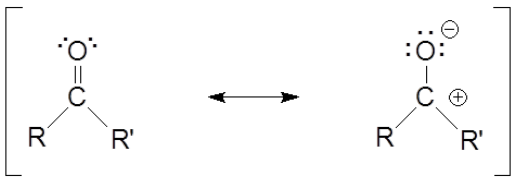
hexane-2,4-dione



cyclohexanone

The properties of the compounds are determined by the electron structure of the carbonyl group. The carbon atom of the carbonyl group is sp^2 hybridized; the oxygen and both atoms attached to the carbonyl carbon atom are in the same plane.

The greater electronegativity of oxygen results in polarization of the double bond, with partial positive charge on the carbon and partial negative charge on the oxygen. As a consequence, the carbon atom is electrophilic, the oxygen is nucleophilic.



VI.4.2 **Properties**

Physical properties

The simplest carbonyl compound - formaldehyde - is gaseous, but most aldehydes and ketones are liquids with characteristic odour.

Their boiling points are higher than those of the respective hydrocarbons with similar molecular mass because of the intermolecular dipole-dipole interactions. Nevertheless, their boiling point is lower than that of the corresponding alcohols since aldehydes and ketones cannot have strong hydrogen bonds between their molecules.

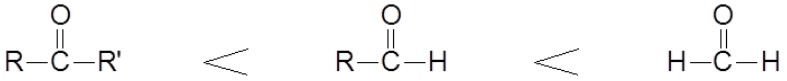
The small molecular weight aldehydes and ketones are freely soluble in water. Although aldehydes and ketones cannot form hydrogen bonds with themselves, they can with water molecules. Water solubility decreasing with increasing chain length due to the the increase of the apolar character of the whole molecules. Carbonyl compounds usually dissolve well in organic solvents.

Chemical properties

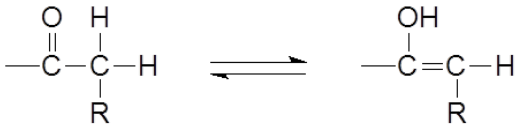
Polarization of the carbon-oxygen double bond is associated with reactivity of aldehydes and ketones. Substituents that enhance the positive character of the carbon atom increase its reactivity. The most reactive aldehyde is formaldehyde, since the hydrogen is only a weak electron-donating substituent vis-à-vis carbon, therefore the partial positive charge is higher in formaldehyde than in other aldehydes.

In aliphatic ketones two electron-donating alkyl substituents are bound to the carbonyl carbon atom, thus ketones are more stable and less reactive than aldehydes.

Hence, steric hindrance of the greater substituents decrease reactivity of the carbonyl carbon atom as well. The relative reactivity of carbonyl compounds develops as follows:



Polarization of the C=O bond influences that of the bonds of the adjacent atoms. Electrons of the neighbouring bonds are shifted towards the carbonyl group, whereupon the bond becomes less stable, and the hydrogen atom attached to the neighbour carbon atom is able to dissociate. This forms the basis of reversible *keto-enol tautomerism*.

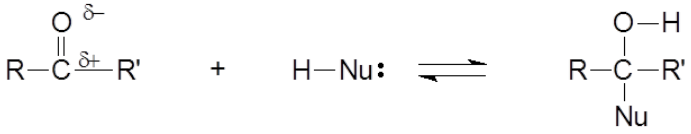


keto form enol form

VI.4.3 **Reactions**

Nucleophilic addition reactions

Nucleophiles attack the carbon atom of the polarized carbon-oxygen double bond because it has a partial positive charge; on the other hand the electrophilic reactants attack the oxygen atom.

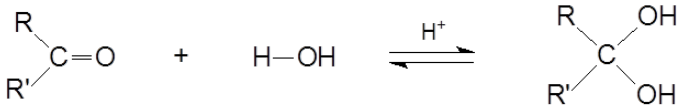


In the first step of the addition reactions the carbonyl carbon atom, which is trigonal and sp^2-hybridized, becomes tetrahedral and sp^3-hybridized. In the second step the oxygen atom, which carries a negative charge, accepts a proton and a hydroxyl group is formed.

The reaction is an equilibrium process. If it is needed, the electrophilic character of the carbonyl carbon atom can be increased with acid catalysis, accordingly the reaction rate becomes higher. However, a too acidic medium is unfavourable, because the basic H-Nu can be protonated losing its nucleophilic character. Therefore it is very important to find the optimal pH range of the reaction.

Hydration

Carbonyl compounds are able to form hydrates in aqueous solutions. Water adds rapidly to the carbonyl function of aldehydes and ketones, resulting in formation of germinal diols.



In most cases the resulting hydrate is unstable and cannot be isolated. Stability of the hydrate can be increased by electron-withdrawing substituents. For example, the

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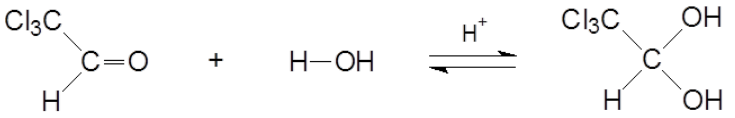
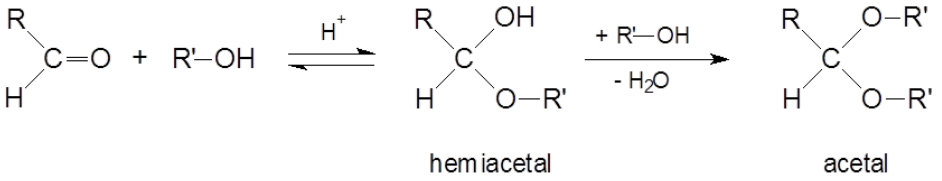
hydrate of chloral (trichloroacetaldehyde) - called chloral hydrate - can be isolated as a crystalline substance:



Reactions with alcohols

Alcohols also undergo addition to aldehydes and ketones. The adducts formed in the first step are called hemiacetals or hemiketals. In the next step the addition of a second alcohol occurs, which leads to the formation of an acetal or ketal.

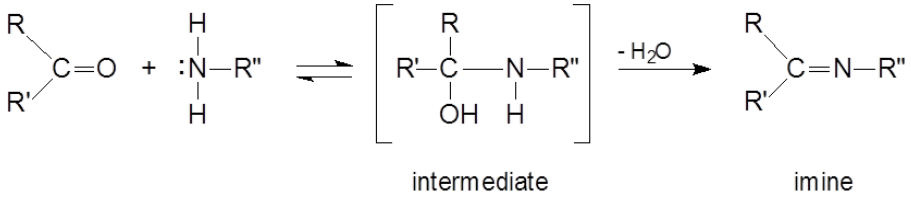


Hemiacetals and hemiketals are usually unstable, not isolable carbonyl derivatives. Exceptions are those formed by cyclization through intramolecular addition leading to the formation of stable rings. For example in case of carbohydrates five- or six-membered cyclic hemiacetals are formed, which structures are relatively stable.

Acetals are stable in alkaline solutions, but hydrolise easily by heating with acids.

Condensation reactions

Aldehydes and ketones react in an addition-elimination reaction with R"-NH_2 structures. The reaction is catalyzed by trace amounts of an acid. In the first, nucleophilic addition reaction an intermediate is formed, which is stabilized by elimination of water. The product of the condensation reaction is an *imine*.



Other primary amine derivatives react with carbonyl compounds as well, and various products are formed.

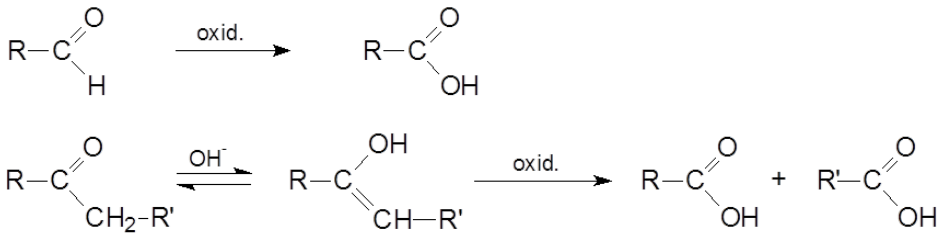
Condensation products of carbonyl compounds.

Reactant		Product	
Structure	Name	Structure	Name
R"-NH_2	Primary alkylamine	C=N–R"	imine (Schiff's base)
H_2N-NH_2	hydrazine	C=N–NH_2	hydrazone
HO-NH_2	hydroxylamine	C=N–OH	oxime
Ar-NH-NH_2	arylhydrazine	C=N–NH–Ar	arylhydrazone
H_2N–NH–C(=O)–NH_2	semicarbazide	C=N–NH–C(=O)–NH_2	semicarbazone

Imines are isolable, usually crystalline compounds, which can be identified relatively easily (e.g. by determination of their characteristic melting-point) and provide an opportunity to identify, and sometimes to quantitatively determine aldehydes and ketones.

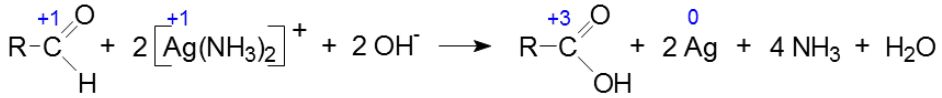
Oxidation reactions

Aldehydes are sensitive to oxidation, and can be oxidized easily to carboxylic acids. Ketones can be oxidized only with very strong oxidants (e.g. alkaline $KMnO_4$, hot concentrated HNO_3). Oxidation of ketones gives - through an enol intermediate - two carboxylic acids as well.

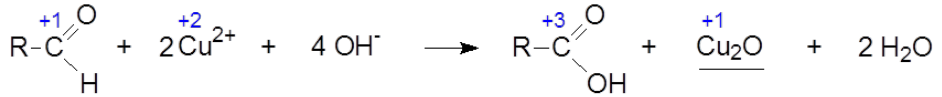


Several laboratory tests distinguish aldehydes from ketones based on their different behaviour toward oxidation.

Tollens' silver mirror test (the reagent contains silver-ammonia complex ion) is suitable to identify aldehydes, since the silver ions are readily reduced by aldehydes to metallic silver.



When the *Fehling's reagent* (which contains copper(II) ions complexed in alkaline solution of tartrate ions and is deep blue) reacts with aldehydes: copper(II) ions are reduced and a red precipitate of copper(I) oxide is formed.



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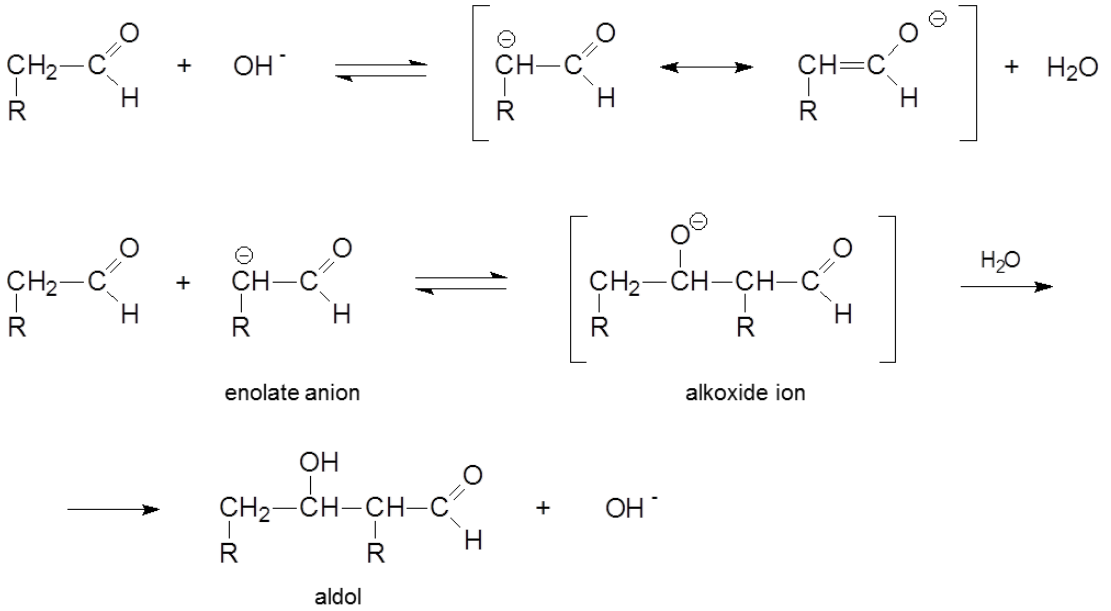
Aldol dimerisation

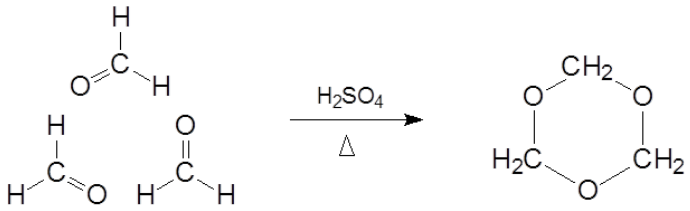
Those aldehydes and ketones in which a hydrogen is bound to the α carbon atom, can undergo dimerization in alkaline medium forming hydroxyaldehydes or hydroxyketones. Since the product is both an aldehyde and an alcohol, it has been given the common name *aldol*.

In the nucleophilic addition reaction the nucleophilic partner of the electrophilic carbonyl carbon is the enolate anion formed from another carbonyl molecule. The reaction mechanism illustrates the acidity of the α hydrogen atom and the tendency of the carbonyl groups to undergo nucleophilic addition.

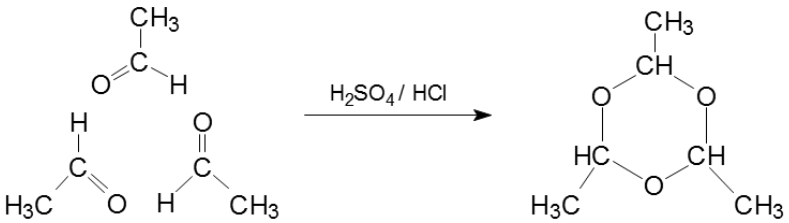


Polymerization

As an effect of a reaction with acids, polymerization can occur. Heating of formaldehyde with sulphuric acids leads to the formation of the trimeric cyclic *trioxane*, which can be isolated.



Anhydrous acetaldehyde - in the presence of sulphuric acid or hydrochloric acid - undergoes polimerization at room temperature to form *paraldehyde*.



VI.4.4 **Therapeutic applications of aldehydes and ketones**

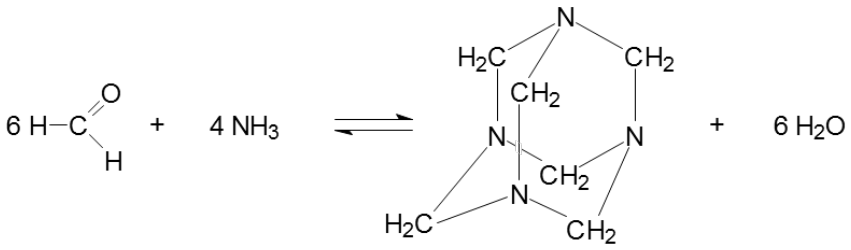
Numerous simple aldehydes with various effects are used in therapy, however the aldehyde function is rather rare in molecules with more complex structures. The keto group is a very common functional group in drug molecules. In the Ph. Hg. VIII. numerous aldehyde and ketone derivatives are official.

Aldehydes and ketons official in the Ph. Hg. VIII. (Selection).

Compound	Name in the Pharmacopoeia	Application
Aldehydes and analogues		
Formaldehyde	Formaldehydi solutio (35 per centum)	antiseptic
Paraldehyde	Paraldehydum	sedative and hypnotic
Chloral hydrate	Chlorali hydras	sedative and hypnotic
Methenamine	Methenaminum	antiseptic
Vanillin	Vanillinum	flavouring additive
Ketones and analogues		
Acetone	Acetonum	solvent

Formaldehyde, the simplest aldehyde, is a gas, very soluble in water. It is supplied as a 34% to 38% aqueous solution called *formalin*. Formalin is used as a disinfectant and preservative, since it denatures proteins and forms new bonds between the protein side chains.

Formaldehyde forms with ammonia a tricyclic condensation product called *methenamine* (hexamethylenetetramine).



Methenamine is used for the treatment of urinary tract infection: it decomposes at an acid pH to formaldehyde and ammonia, and the formed formaldehyde is bactericidal.

Acetaldehyde is a sweet smelling liquid with low melting point. It is used as an important intermediate in organic industrial syntheses. Its derivative, paraldehyde was once used as sedative and hypnotic drug.

Chloral hydrate (the hydrate of trichloroacetaldehyde) is a sedate-hypnotic drug as well.

Benzaldehyde is a colourless liquid with a characteristic pleasant almond-like odour. It is oxidizable on air and benzoic acid is formed from it. In fact, benzaldehyde is the primary component of bitter almond oil, which contains benzaldehyde not as an aglycon, but as a glycoside derivative called amygdalin. This glycoside breaks up under

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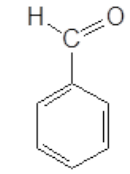
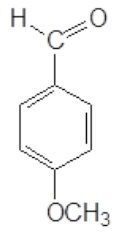
enzyme catalysis or in acetic medium into benzaldehyde, hydrocyanic acid and two molecules of glucose. Hydrocyanic acid causes the toxic effect of bitter almond.

The analogues of *benzaldehyde*: *anisaldehyde*, *vanillin* or *cinnamaldehyde* are mainly used in cosmetics, but also in drug formulation.

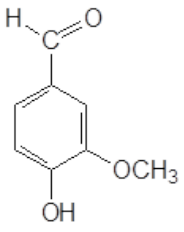
Glutaraldehyde is used to disinfect medical and dental equipment.



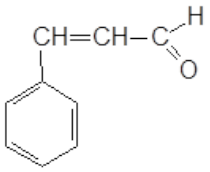
benzaldehyde



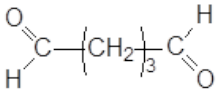
anisealdehyde



vanillin



cinnamaldehyde



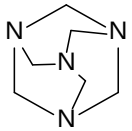
glutaraldehyde

Acetone is a volatile liquid with characteristic odour. Acetone is miscible with water and with most organic solvents as well. It is mainly used as a solvent and as a reagent in manufacturing other chemicals.

VI.4.5 **Pharmacepoeial qualifications**

METHENAMINE

Methenaminum



$C_6H_{12}N_4$ $M_r = 140.19$

DEFINITION

1,3,5,7-Tetraazatricyclo[3.3.1.1^{3,7}]decane.

Content: 99.0 per cent to 100.5 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

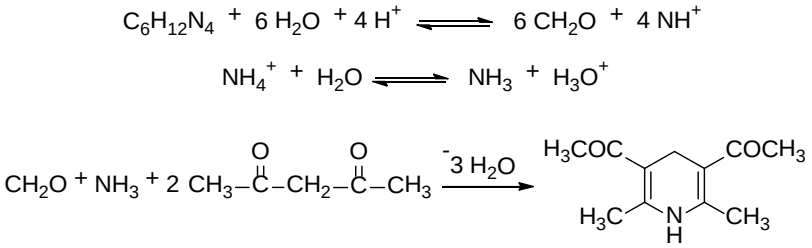
Solubility: freely soluble in water, soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

Solution S. Dissolve a 0.5 g sample in *carbon dioxide-free water R* prepared from *distilled water R* and dilute the solution to 5 ml with the same solvent.

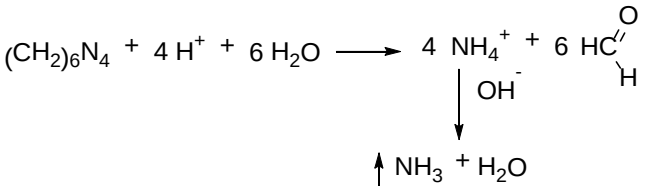
B. To 1 ml of *Solution S* add 1 ml of *sulphuric acid R* and immediately heat the mixture to boiling. Allow it to cool. To 1 ml of the solution add 4 ml of *water R* and 5 ml of *acetylacetone reagent R1*. Heat it on a water-bath for 5 min. An intense yellow colour develops.

Hantzsch reaction. Acid hydrolysis of methenamine yields ammonia and formaldehyde, which react with acetylacetone to give the yellow 3,5-diacetyl-2,5-dimethyl-1,4-dihydropyridine.



C. Ammonium salts and salts of volatile bases. To 1 ml of *Solution S* add 1 ml of *dilute sulphuric acid R* and immediately heat the mixture to boiling. Add 2 ml of *dilute sodium hydroxide solution R*. On heating, the solution gives off vapour that can be identified by its odour and by its alkaline reactions.

Acid hydrolysis of methenamine yields ammonium ions, which are quantitatively converted to ammonia by sodium hydroxide.



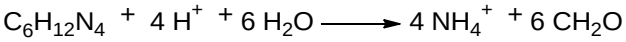
D. Dissolve a 10 mg in 5 ml of *water R* and acidify the solution with *dilute hydrochloric acid R*. Add 1 ml of *potassium iodobismuthate solution R*. An orange precipitate is formed immediately.

Dragendorff reaction. Tetraiodobizmutate ions react with large cations (e.g. protonated organic bases) to form orange/orange-red precipitate: $[C_6H_{13}N_4]^+BiI_4^-$.

ASSAY (Ph. Hg. VII.)

Dissolve a 0.350 g sample, accurately weigthed, in 50.0 ml of *water R*. To 10.00 ml solution add 25.00 ml of *0.1 M hydrochloric acid* and boil the solution for 15 minutes. After cooling, titrate the excess of hydrochloric acid with *0.1 M sodium hydroxide*. Indicator: 2 drops of *I-methyl red* solution.

Methenamine is hydrolyzed with known amount of hydrochloric acid used in excess yielding 4 moles of ammonia. The formed ammonia reacts with hydrochloric acid.



The excess of hydrochloric acid is backtitrated by sodum hydroxide standard solution.

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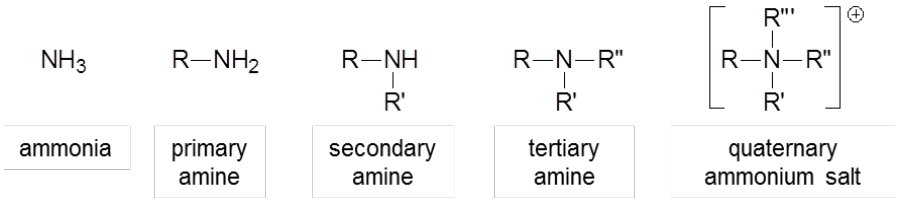
VI.5 Amines

Amines are organic derivatives of ammonia in which one or more of the hydrogens has been replaced by an alkyl or aryl group.

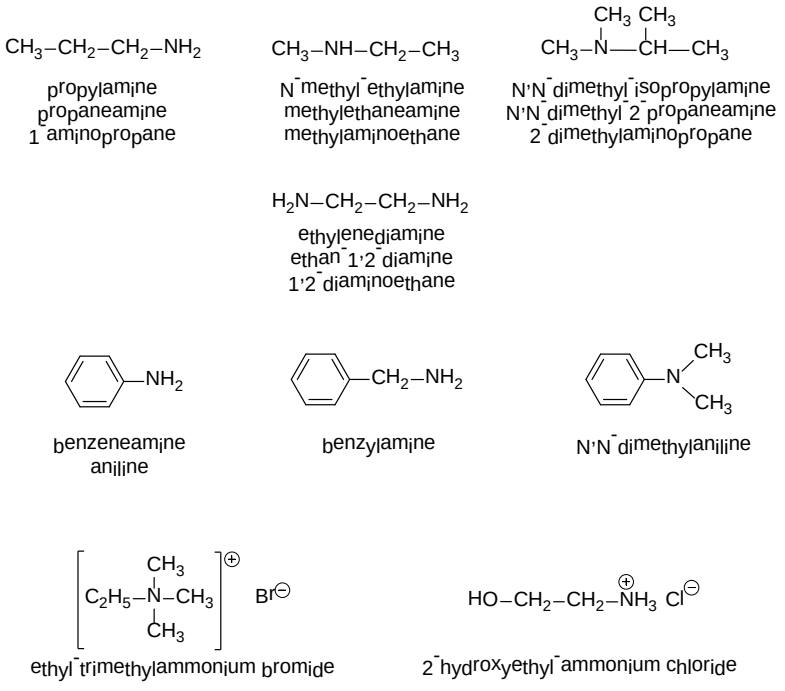
VI.5.1 Classification, nomenclature of amines

The nitrogen atom of amines is bound to carbon atom(s). Amines are classified as *primary*, *secondary* or *tertiary* amines according to the number of carbon atoms bound directly to the nitrogen atom. So the terms primary, secondary and tertiary are used to classify amines in a completely different manner than they were used for alcohols or alkyl halides, where they refer to the nature of an alkyl group. Therefore, the nitrogen atom of a primary amine has one substituent, the nitrogen atom of a secondary amine bears two substituents, and the nitrogen of a tertiary amine has three substituents. The quaternary ammonium salts are substituted ammonium ion analogues, in which all hydrogens are replaced by substituents.



According to the nature of the substituents *aliphatic*, *aromatic* and *aromatic-aliphatic* amines can be specified. *Mono-*, *di-* or *polyamines* can be defined based on the number of amino groups in a molecule.

A common system for naming simple amines to list each alkyl substituent of the nitrogen atom in alphabetical order, followed by the suffix *-amine*.



The IUPAC system names amine functions as substituents on the largest alkyl group. The simple -NH_2 substituent found in primary amines is called an *amino group*. For secondary and tertiary amines a compound prefix includes the names of all but the root alkyl group. Many aromatic and heterocyclic amines are known by unique common names.

The quaternary ammonium compounds are named as salts.

VI.5.2 **Structure, properties**

In amines the nitrogen atom takes part in the formation of three covalent bonds and has a nonbonding electron pair. It forms an approximately tetrahedral structure, similar to ammonia.

Physical properties

Low molecular weight amines are gases or volatile liquids with characteristic, usually unpleasant odour. The higher molecular weight representatives are solids.

The N-H bond in amines is partially polarized, therefore amines with low molecular weight can participate both in dipole-dipole interactions and hydrogen bonding. Because of the intermolecular interactions between the amine molecules their boiling point is much higher than that of hydrocarbons with similar molecular mass. But a lower boiling point is observed for an amine when compared to an alcohol of similar molecular weight. The reason for this observation is that the N-H bond is less polar than the O-H bond in alcohols and therefore the hydrogen bond is weaker as well.

Formation of hydrogen bonds is possible in the case of primary and secondary amines, but is not between molecules of tertiary amines. This results in the fact that the boiling point of amines with similar molecular weight is the highest in the case of primary amines and the lowest in the case of tertiary amines.

Low molecular weight amines are well soluble in water, but the solubility decreases with the increase of the alkyl chain, in which case the hydrophobic character dominates. Amines are soluble in organic solvents. Because of the ionic structure of ammonium salts and quaternary ammonium salts of amines, they have rather low solubility in water, but they are insoluble in apolar organic solvents.

Chemical properties

The characteristic part of amines is the nitrogen atom with the nonbonding pair of electrons. Most of the amines, like ammonia, are Bronsted bases, since they are able to bind a proton by means of the nonbonding pair of electrons. Amines are Lewis bases as well, because they can act as electronpair donors to form coordinative bonds with electron acceptor ions or molecules.

Amines are relatively weak bases. When an amine dissolves in water, an equilibrium is established, and the equilibrium constant characterizes the basicity.

$$R_3N: + H{-}OH \rightleftharpoons [R_3NH]^+ + OH^-$$

$$K_b = \frac{[R_3NH^+]\,[OH^-]}{[R_3N]}$$

$$pK_b = -\log K_b$$

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In order to compare basicity of amines with the acid-base character of other organic compounds, it is expedient to take the pK_a value of the conjugated acids (the appropriate ammonium ions) into consideration. The pK_a value can be easily calculated, since the sum of the pK_a and pK_b values of a conjugated acid-base pair is 14 (at 25 °C). Therefore, the stronger a base the larger the pK_a value of the conjugated acid.

In gas phase, basicity of amines is only influenced by the substituents. Electron-donating substituents increase basicity since they increase the electron density of the nitrogen atom. In gas phase the order of basicity as follows: ammonia < primary amine < secondary amine < tertiary amine.

In aqueous solutions basicity of amines is influenced by dipole-dipole interactions and hydrogen bonding as well. The alkyl substituents have a dual effect on the stability of the formed ammonium ions. The alkyl groups hinder interaction of water molecules with amines, hence the solvation. Since absence of solvation is a destabilizing factor, primary amines are the strongest bases. However, alkyl groups promote delocalization of the positive charge by their electron-donating property; thus they stabilize the ions. Accordingly, tertiary amines are supposed to be the strongest bases. The opposite effects deteriorate the basicity of primary and tertiary amines, and as result, the secondary amines are in fact the strongest bases.

Aromatic amines are much weaker bases than their aliphatic counterparts. The reason for this is that the nonbonding pair of electrons of the nitrogen atom conjugates with the π electrons of the aromatic ring, hence protonation of the nitrogen atom is less favoured.

The order of basicity of amines in aqueous solutions is the following:

$$Ar\text{–}NH_2 \ll NH_3 < R_3N < R\text{–}NH_2 < R_2NH$$

Comparison of basicity of ammonia and amines.

Name	Structure	pK_a (in aqueous solution)
aniline	Ar-NH_2	4.63
ammonia	NH_3	9.24
trimethylamine	$(CH_3)_3N$	9.80
methylamine	CH_3-NH_2	10.63
dimethylamine	$(CH_3)_2NH$	10.78

VI.5.3 **Reactions**

Reactions of amines are based on the basic and nucleophilic characters of the nitrogen atom, which are the most pronounced when small-size electron-donating substituents are attached to the nitrogen.

Formation of salts

When amines act as bases and react with acids, ammonium salts are formed. The salts of strong acids are relatively stable compounds.

$$R_3N: + H\text{—}Cl \longrightarrow R_3NH^+\ Cl^-$$

The pH of the solution of salts of amines formed with strong acids is acidic due to the hydrolysis.

Strong bases release amines from the solution of their salts. In the case of aliphatic homologues with small side chains the reaction can be used as identification reaction as well. The formed volatile bases can be recognized by their characteristic odour; furthermore their alkaline character (See *Chemical properties*) can be observable in the vapour space.

It is characteristic for solutions of salts of aliphatic and aromatic amines with higher molecular weight that the released base precipitates from the solution, because it is insoluble in water. When the free base is isolated, it can be identified by determination of its melting point. The free base can also be identified and measured quantitatively when its extraction with an organic solvent can be accomplished.

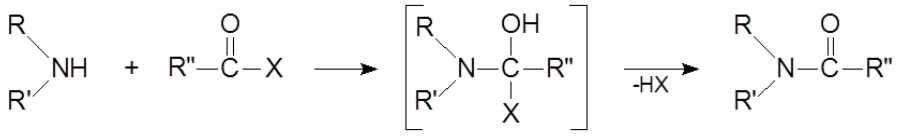
Quaternary ammonium salts are well soluble in water, their hydroxides are strong bases. The quaternary ammonium hydroxides cannot be extracted by organic solvents since they have a permanent positive charge. This characteristics provides possibility to separate tertiary amines and quaternary ammonium salts.

Nucleophilic reactions of amines

Amines exhibit characteristics of both bases and nucleophiles.

Acylation of amines

In acylation reactions of primary and secondary amines the hydrogen attached to the nitrogen atom is replaced by an acyl group. Accordingly, mono- or disubstituted amides are formed. Acyl halides, esters and acid anhydrides can be used as reagents.



Potassium carbonate added to the reaction mixture reacts with the released acid preventing salt formation of the original amine.

Secondary amines are more reactive than primary amines, while tertiary amines cannot be acylated. This can be the basis of the selective determination of tertiary amines. If a primary/secondary amine and a tertiary amine are in the same solution, they can be measured unless they disturb the determination of each other. For example the primary/secondary amine can be acylated with acetic anhydride. The formed amide is neutral and does not disturb titration of the tertiary amine with perchloric acid.

Acylation performed with sulphonic acid chloride leads to formation of the respective sulphonamide. This is an excellent test for distinguishing primary, secondary and tertiary amines (*Hinsberg reaction*). The sulphonamide formed in a reaction of a primary amine is soluble in alkaline medium, while the sulphonamide of a secondary amine is insoluble and precipitates. Tertiary amines do not react with benzenesulphonic acid chloride.

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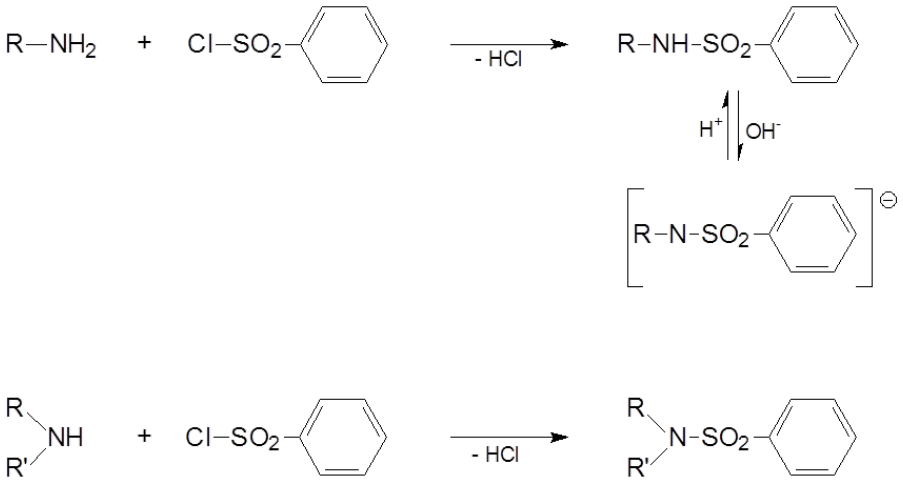
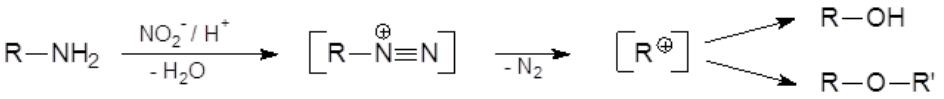


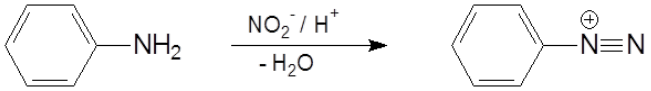
Reaction of amines with nitrous acid

Since nitrous acid is very unstable, usually the reagent is formed *in situ* from sodium nitrite and hydrochloric acid. Nitrous acid reacts with all classes of amines.

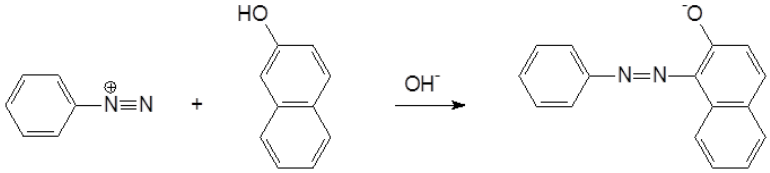
Primary aliphatic amines react with nitrous acid to form highly unstable diazonium salts, which decompose spontaneously by losing nitrogen to form carbocations. The reactive carbocations produce alcohols, ethers, esters or olefins. The formation of nitrogen is quantitative; it can be measured using the *Van Slyke method.*



Primary aromatic amines react with nitrous acid to give relatively stable diazonium salts.

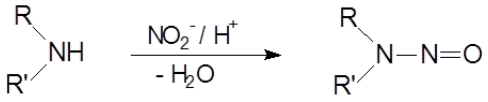


Diazonium cations react with activated aromatic rings. For example, *β*-naphthol yields coloured azo dyes:



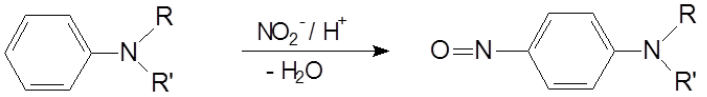
The reaction is widely used for identification of primary aromatic amines in the Pharmacopoeias. The reaction - conversely - is appropriate to identify phenols or nitrite ions, respectively.

Both *secondary aliphatic and aromatic amines* react with nitrous acid to yield N-nitrosoamines.



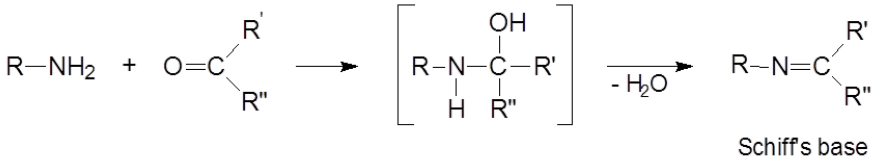
N-nitrosoamines are usually oily yellow liquids, which can be extracted from aqueous solutions with organic solvents. Nitrosoamines are very potent carcinogens.

Tertiary aliphatic amines form salts with nitrous acid, and the *tertiary aromatic amines* form nitroso-substituted derivatives.

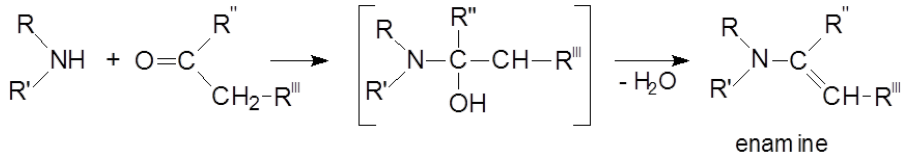


Reactions with aldehydes and ketones

Primary and secondary amines react with carbonyl compounds to form an unstable adduct in the first step, which is stabilized by an elimination reaction. In the case of primary amines the product is a Schiff's base, while in the case of secondary amines, if the carbonyl compound contains a hydrogen in α-position, it is an enamine.

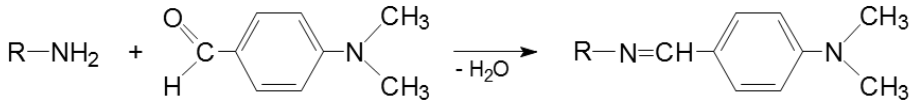


Schiff's base



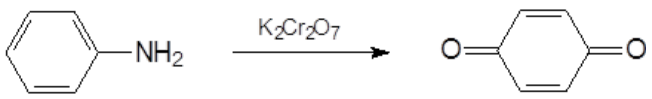
enamine

To identify primary amines usually aromatic aldehydes are used as reagent, because the formed Schiff's bases are coloured and/or insoluble, therefore can be easily identified. The most frequently used reagent is *p*-dimethylaminobenzaldehyde, which reacts with primary amines to yield orange or red condensation products.



Oxidation of amines

Amines, especially aromatic amines, are sensitive to oxidation. Most of them is oxidized even in the open air; their colour becomes darker. Aniline is oxidized to *p*-benzoquinone in the presence of potassium dichromate.



Usually, more products are formed during the oxidation. Oxidation of tertiary amines leads to a uniform product: *N*-oxides are formed.

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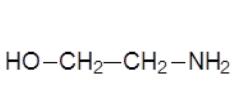
VI.5.4 **Important amines**

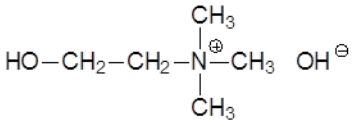
A large number of therapeutic and biological important compounds are amines, such as naturally occurring and even synthetic drugs, or chemical messengers in the body.

Biologically important amines

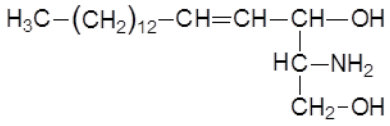
Phosphatidyl-ethanolamine is a major component of eukaryotic cells, which also contains *cholamine* and phosphatidyl-choline. *Choline* is a quaternary ammonium derivative of *cholamine*. *Sphingosine,* an unsaturated aminoalcohol, is involved in the construction of sphingolipides.



cholam ine

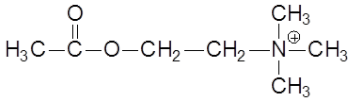


choline



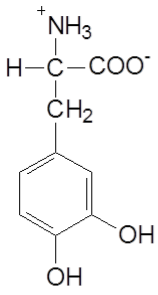
sphingosine

The most important biological aliphatic quaternary ammonium compound is *acetylcholine*, the neurotransmitter of the parasympathetic and central nervous system, and the neuromuscular synapses. It is synthesized by the reaction of choline and acetyl CoA.

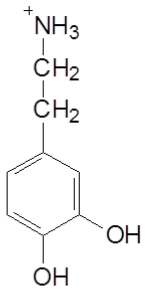


acethylcholine

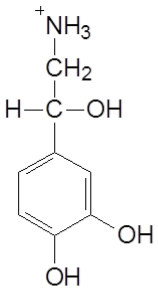
Cathecolamines and their analogues are major components in our body. 3',4'-dihydroxyphenylalanine (DOPA), formed from 4'-hydroxyphenylalanine (*tyrozine*), for example, is an intermediate in biosynthesis of *dopamine*. Dopamine takes part in signal transmission. *Noradrenaline*, synthetised from dopamine, is also a neurotransmitter. *Adrenaline*, formed from noradrenalin after methylation, has numerous biological functions.



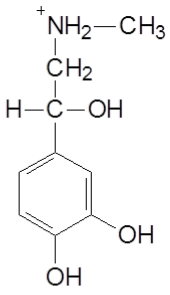
DOPA



dopamine

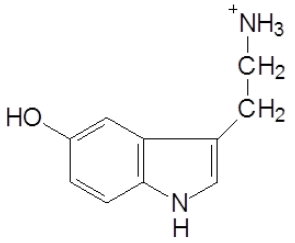


noradrenaline

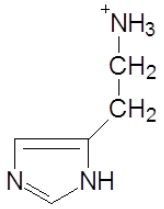


adrenaline

Biosynthesis of *serotonine* (5-hydroxytryptamine) also linked to an amino acid, called *tryptophane*. The last step of biosyynthesis of *histamine* is also a decarboxylation reaction of an amino acid, called *histidine*.



serotonine

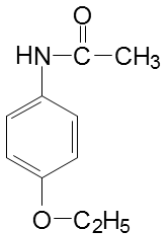


hystamine

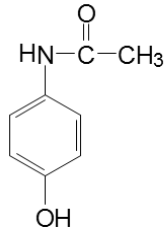
Drugs containing amino groups

Amines are very common derivatives among active pharmaceutical ingredients. Here only a few representatives with relatively simple structure are listed:

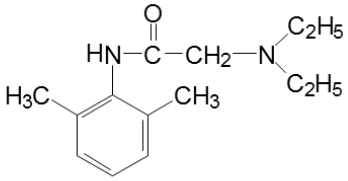
Phenacetin is not official in the Ph. Hg. VIII., only its active metabolite, called *paracetamol*. The derivatives of acetanilide are antipyretics and analgetics. *Lidocaine*, containing a diethylamino group is a medicine having both local anaesthetic and antiarrhythmic effect.



phenacetin

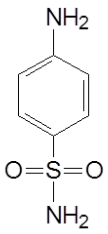


paracetamol



lidocaine

Sulphonamide derivatives are important members of chemotherapeutic drugs. The basic structure is *p*-aminobenzenesulphonamide. Benzenesulphonamide derivatives can also be found among diuretics.



sulphanylam ide

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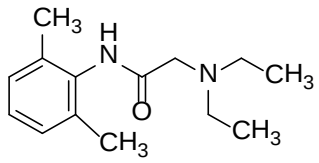
VI.5.5 **Pharmacopoeial qualifications**

✚ LIDOCAINE

Lidocainum



$C_{14}H_{22}N_2O$ $M_r = 234.3$

DEFINITION

2-(Diethylamino)-N-(2,6-dimethylphenyl)acetamide.
Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

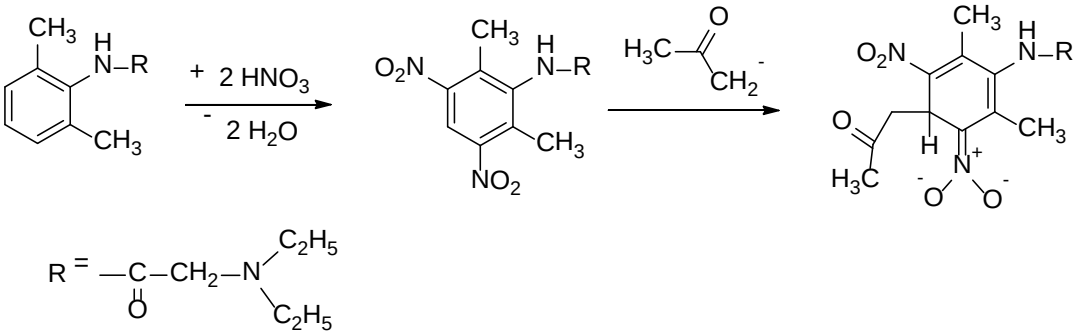
CHARACTERS

Appearance: white or almost white, crystalline powder.
Solubility: practically insoluble in water, very soluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

D. To about 5 mg add 0.5 ml of *fuming nitric acid R*. Evaporate to dryness on a water-bath, cool and dissolve the residue in 5 ml of *acetone R*. Add 0.2 ml of *alcoholic potassium hydroxide solution R*. A green colour is produced.

Vitali-Morin reaction: The dinitro derivative formed by nitration gives a green Meisenheimer-complex with the anion of acetone. Tetracaine gives the reaction with a violet-red colour; the other local anaesthetics react with a brown colour.



E. Dissolve about 0.1 g in 1 ml of *ethanol (96 per cent) R* and add 0.5 ml of a 100 g/l solution of *cobalt nitrate R*. A bluish-green precipitate is formed.

In alkaline conditions the cobalt(II) iones form colourful complexes with amides, but the precipitate produced in this reaction is probably cobalt(II) hydroxide chloride: Co(OH)Cl.

TESTS

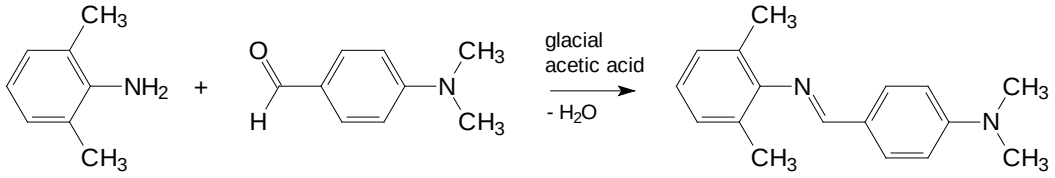
Appearance of solution. The solution is clear and colourless.

Dissolve a 1.0 g in 3 ml of *dilute hydrochloric acid R* and dilute the solution to 10 ml with *water R*.

2,6-Dimethylaniline: maximum 100 ppm.

Dissolve a 0.25 g in *methanol R* and dilute the solution to 10 ml with the same solvent. To 2 ml of the solution add 1 ml of a freshly prepared 10 g/l solution of *dimethylaminobenzaldehyde R* in *methanol R* and 2 ml of *glacial acetic acid R* and allow the reaction mixture to stand for 10 min. Any yellow colour in the solution is not more intense than that in a standard prepared at the same time and in the same manner using 2 ml of a 2.5 mg/l solution of *2,6-dimethylaniline R* in *methanol R*.

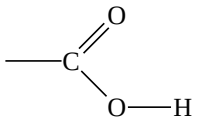
A Schiff's base is formed:



VI.6 Carboxylic acids

VI.6.1 Structure, nomenclature

The *carboxyl group*, -COOH, is one of the most widely occurring functional group in chemistry and biochemistry. The carboxyl group is formally a combination of carbonyl and hydroxyl groups, but the properties of carboxylic acids are distinct from the properties of either of these group. The -COOH group is *acidic*, and gives rise to the name of the series.



carboxyl group

The systematic (IUPAC) names for carboxylic acids are derived from the alkane having the same number of carbon atoms as the longest hydrocarbon chain of the compound containing the carboxyl group. The *-e* ending of the alkane is replaced by *-oic acid*, as shown in the parentheses below. Substituents are located by numbering from the carboxyl group.

A number of carboxylic acids are known by their common names and these are acceptable alternatives to the systematic names of these compounds. The common names usually come from Greek or Latin words that indicate the original sources of the acids. Methanoic acid, for example, is called formic acid after the Latin name of ant, *formica*. Butanoic acid is one of the compound responsible for the odor of rancid butter, thus its common name is butyric acid (from the Latin *butyrum*, or butter). Many of the acids were first obtained from fats, so they are sometimes referred to as *fatty acids*.

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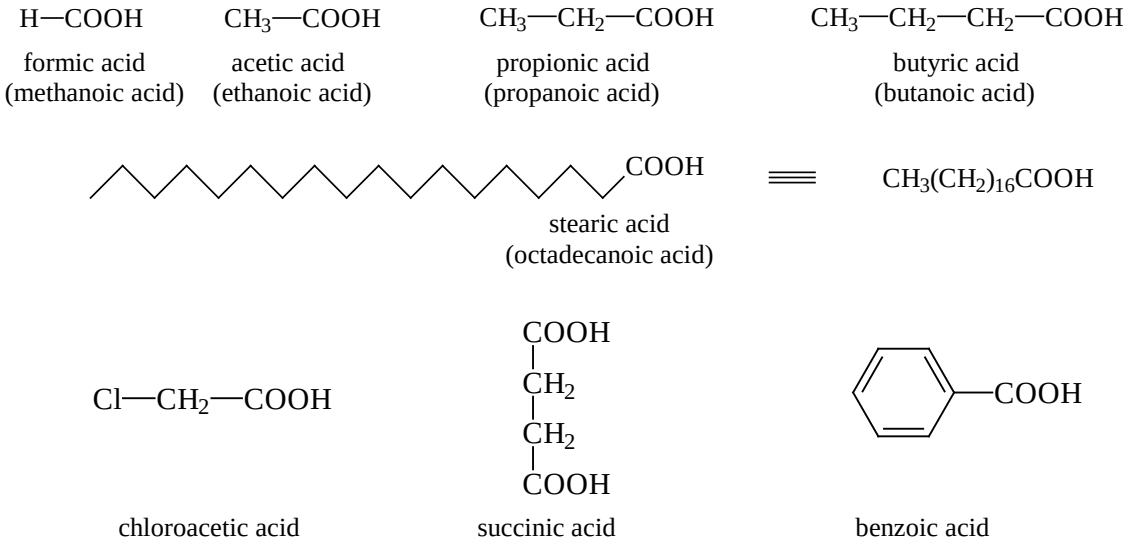
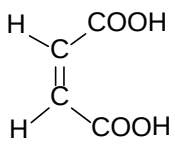
Dicarboxylic acids are named as alkanedioic acids in the IUPAC system. Most simple dicarboxylic acids have common names (e.g., succinic acid).

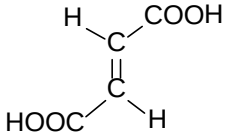
Aromatic carboxylic acids are named by attaching the suffix *-oic* or *-ic acid* to an appropriate prefix derived from the aromatic ring (e.g., *benzoic acid*).



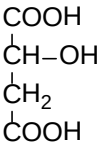
The name and structure of some further carboxylic acids of pharmaceutical importance as follows.



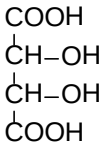
(*Z*)-butenedioic acid
maleic acid



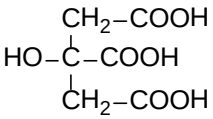
(*E*)-butenedioic acid
fumaric acid



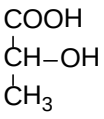
hydroxysuccinic acid
malic acid



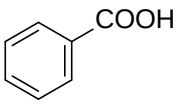
2,3-dihydroxy-
succinic acid
tartaric acid



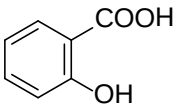
2-hydroxy-1,2,3-
propanetricarboxylic acid
citric acid



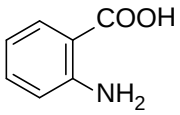
2-hydroxy-
propionic acid
lactic acid



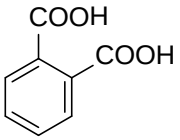
benzenecarboxylic acid
benzoic acid



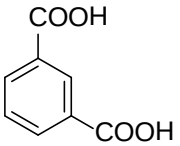
2-hydroxybenzoic acid
salicylic acid



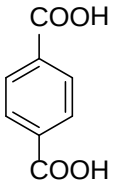
2-aminobenzoic acid
anthranilic acid



benzene-1,2-dicarboxylic acid
ortho-phthalic acid

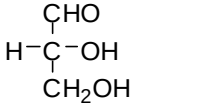


benzene-1,3-dicarboxylic acid
meta-phthalic acid

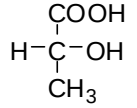


benzene-1,4-dicarboxylic acid
para-phthalic acid

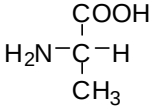
One of the most important carboxylic acid derivatives with substituents on the alkyl chain is represented by the genetically coded 2-aminocarboxylic acids (α-aminoacids). In the case of such compounds, having substituents at one of the side chain carbon atoms, the substituted carbon atom is an asymmetric center of the molecules. Accordingly, each asymmetric carbon atom can have two configurations. The two configurations are nonsuperimposable mirror images of each other. Configuration of asymmetric carbon atoms of substituted carboxylic acids (eg. amino- and hydroxy-substituted carboxylic acids) is generally characterized by the "D" and "L" (relative) configurational prefixes. Use of these prefixes is based on the structural relation of the asymmetric carbon atom of the particular compound with that of the glyceraldehyde enantiomer (D-(+)-glyceraldehyde) with clockwise direction of optical activity. The below structures are examples of use of the "D"/"L" prefixes. (Also see Chapter VI.7.; Carbohydrates)



D-(+)-glyceraldehyde



D-(-)-lactic acid



L-(+)-alanine

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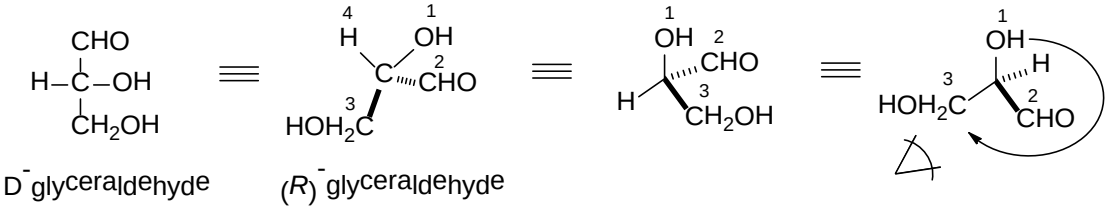
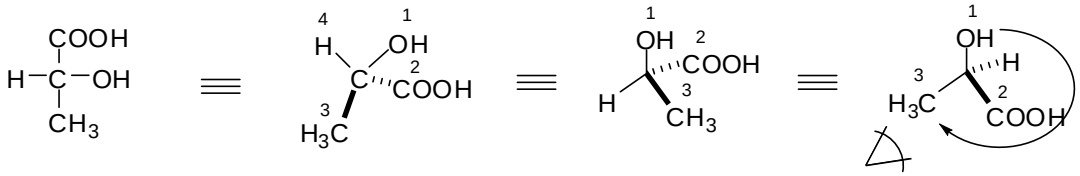
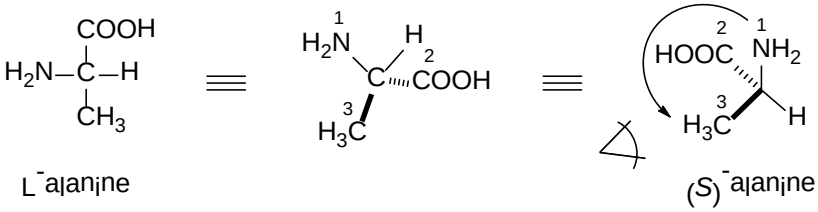
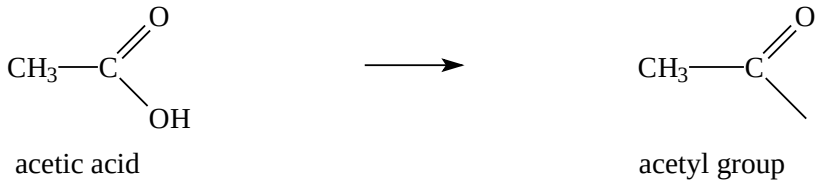
Configuration of asymmetric carbon atoms can be assigned by use of the "D" and "L" (relative), and the (*R*) and (*S*) (absolute) configurational prefixes. Without detailed description of determination of the (*R*)/(*S*) configuration of an asymmetric carbon atom, the relationship between the two configurational notation systems is demonstrated by comparison of the respective prefixes for the assymetric carbon atoms of the above three compounds:





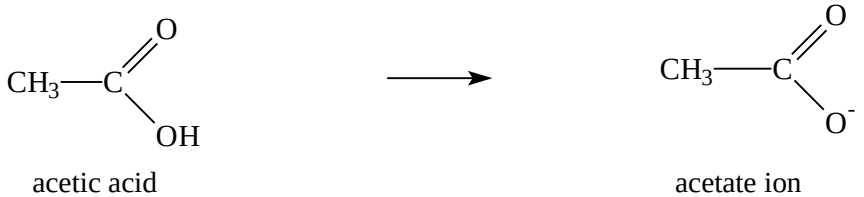


It is sometimes convenient to refer the $R-\overset{\overset{O}{\|}}{C}-$ group as an *acyl group*. Acyl groups are named by replacing the ending *-ic acid* by *-yl*. For example, the acyl group derived from acetic acid is the *acetyl group*.



(For further examples see Table below.)

The name of anion derived from a carboxylic acid (by removal of the proton from the carboxyl group) is called *carboxylate anion*. Carboxylate anions are named by replacing the ending *-ic acid* by *-ate*. Thus, the anion of acetic acid is the acetate ion.



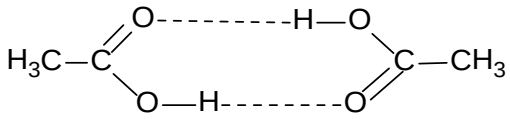
(For further examples see Table below.)

VI.6.2 **Physical properties**

Carboxylic acids are *polar molecules*. Like alcohols, they form hydrogen bonds with themselves or other molecules. The first four carboxylic acids are miscible with water in all portions. As the length of the carbon chain increases, however, water solubility declines.

Aliphatic carboxylic acids up to eight carbons are liquids with pungent, unpleasant odors. Aromatic acids are usually solids with high melting point.

Acetic acid, H_3C-COOH, the sour component of vinegar, is a typical carboxylic acid. Its boiling point (118 ºC) is 20 ºC higher than that of propanol, $CH_3CH_2CH_2OH$, which has the same molecular weight, showing that the acid is much more highly associated than the alcohol. Even in the gas phase the acid molecules are associated by *two* hydrogen bonds.



hydrogen-bonded acetic acid

The physical properties of all carboxylic acids reflect the presence of such hydrogen bonds between the molecules. Their melting points and boiling points are relatively high (see Table below).

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Homologous series of fatty acids.

Name and number of carbon atoms	Name of the carboxylate anion	Name of the acyl group	Melting point (°C)	Boiling point (°C)
formic acid [C_1]	formate	formyl	8	101
acetic acid [C_2]	acetate	acetyl	17	118
propionic acid [C_3]	propionate	propionyl	-20	141
butyric acid [C_4]	butyrate	butyryl	-6	164
valeric acid [C_5]	valerate	valeryl	-35	186
myristic acid [C_{14}]	myristate	myristyl	54	*
palmitic acid [C_{16}]	palmitate	palmityl	63	*
stearic acid [C_{18}]	stearate	stearyl	70	*

*No boiling points are available, because the solid carboxylic acids are degrading under heating at atmospheric pressure.

Acidity

Carboxylic acids are *weak acids* compared to inorganic acids such as HCl or H_2SO_4. The strength of an acid refers to the extent to which its ionization equilibrium lies to the side of the dissociated acid, expressed by the magnitude of the equilibrium constant, K_a. (The larger the K_a, the stronger the acid.)

$$R\text{-}COOH + H_2O \rightleftharpoons R\text{-}COO^- + H_3O^+$$

$$K_a = \frac{[R\text{-}COO^-]\,[H_3O^+]}{[R\text{-}COOH]}$$

(Since the concentration of water remains essentially constant, $[H_2O]$ does not appear in the equation for K_a.)

From the above equation we see that the greater the degree of ionization - that is, the stronger the acid - the larger the K_a. Simple carboxylic acids such as acetic acid have K_a values of 10^{-4} to 10^{-5}. Just as $[H_3O^+]$ is normally expressed as pH, it is convenient to use the negative logarithm of K_a or pK_a in discussing these very small numbers.

$$pK_a = -\log K_a$$

For acetic acid, with $K_a = 1.8 \times 10^{-5}$, the pK_a value is $-\log(1.8 \times 10^{-5}) = 4.7$. Note that while pK_a values provide convenient numbers for discussion and comparison, two points must be kept in mind when using negative logarithms. (1) The *larger* the pK_a, the *smaller* the K_a; and (2) the numbers are exponents and represent powers of 10; an acid with $pK_a = 3$ is *10 times more dissociated* (ionized) than an acid with $pK_a = 4$. Most of the unsubstituted carboxylic acids have pK_a values in the range of 4-5 (see Table below).

The Table below shows that carboxylic acids bearing only alkyl or aryl substituents are similar in acidity. Electronegative (electron-withdrowing) substituents (e.g., chlorine), however, particularly when they are attached to the α-carbon (carbon atom next to the carboxyl group), significantly increase the acidity of a carboxylic acid. As it is shown, multiple chlorine substitutions further increases the acidity.

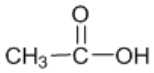
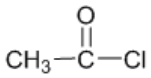
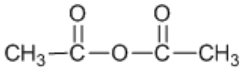
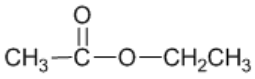
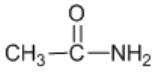
Acid strengths of carboxylic acids.

Name of acid	Structure	pK_a	K_a
Formic acid	H-COOH	3.75	$1.78x10^{-4}$
Acetic acid	CH_3-COOH	4.74	$1.82x10^{-5}$
Propionic acid	CH_3-CH_2-COOH	4.87	$1.35x10^{-5}$
Butyric acid	CH_3-CH_2-CH_2-COOH	4.82	$1.51x10^{-5}$
Benzoic acid	C_6H_5-COOH	4.18	$6.61x10^{-5}$
Chloroacetic acid	$ClCH_2$-COOH	2.82	$1.51x10^{-3}$
Dichloroacetic acid	Cl_2CH-COOH	1.30	$5.01x10^{-2}$
Trichloroacetic acid	Cl_3C-COOH	0.70 (!)	$2.00x10^{-1}$

VI.6.3 **Derivatives of carboxylic acids**

Several series of compounds with the general formula R- C(O) -X can be derived directly or indirectly from carboxylic acids, and can be converted to the acids by hydrolysis. The most important are those in which X = OR, NH_2, Cl, Br, or OC(O)R. These series of compounds, with the derivatives of acetic acid as examples, are illustrated in the Table below.

Derivatives of acetic acid.

Name of series	Structure	Name	Boiling point
Acid		Acetic acid	118 °C
Acid chloride		Acetyl chloride	52 °C
Anhydride		Acetic anhydride	139 °C
Ester		Ethyl acetate	77 °C
Amide		Acetamide	220 °C

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VI.6.4 **Reactions**

Reactions of carboxylic acids can be divided into two main grups:
reactions of the carboxyl group, and
reactions of the carbon skeleton.

VI.6.4.1 Reactions of the carboxyl group

Salt formation

Carboxylic acids react with bases to form salts. For example,

$$\underset{\text{acetic acid}}{CH_3\text{-}COOH} + NaOH \rightleftharpoons \underset{\text{sodium acetate}}{CH_3\text{-}COONa} + H_2O$$

An organic salt has many of the physical properties of its inorganic counterpart. These metal salts of carboxylic acids are named by giving the metal name preceding the carboxylate anion. Carboxylate ions are named by replacing the ending *-ic acid* by *-ate*. For example, lead acetate, sodium benzoate, and potassium sodium succinate. For more see Table above.

The reaction serves as basis of titrimetric assay of several carboxylic acids listed in the Pharmacopoeias. The pH at the equivalence point is basic due to the hydrolysis of the formed salts (carboxylate ions):

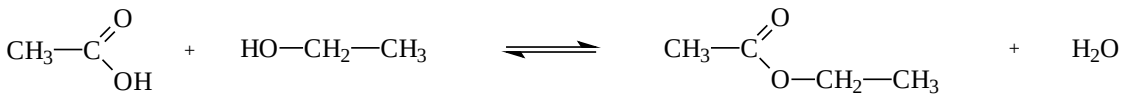
$$R-COOH + NaOH = R-COONa + H_2O$$

$$R-COONa + H_2O \rightleftharpoons R-COOH + Na^+ + OH$$

Accordingly, acid-base indicators with basic color change interval e.g. pholphthalein, phenol red) should be used.

Ester formation

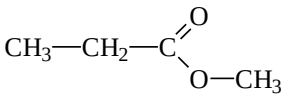
Esters can be obtained by direct esterification of carboxylic acids with alcohols and phenols. This reaction is catalyzed by a strong acid, such as sulfuric acid, H_2SO_4. The reaction is an equilibrium process and is carried to completion by removal of the water as it is formed by distillation.



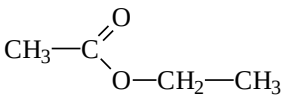
acetic acid ethanol ethyl acetate water

Esters are the most important and interesting series of acid derivatives. They are polar molecules but cannot form hydrogen bonds to each other. As a result, esters have boiling points that are lower than those of carboxylic acids and alcohols of comparable molecular masses. Consequently, esters have lower solubilities in water than acids and alcohols.

Esters are named as derivatives in which the hydrogen of the carboxyl group of the acid is removed to give R-COO- and then replaced by an alkyl group. The name of the ester is two words, with the alkyl group first and then the R-COO- group name, which is formed by changing the *-ic acid* ending of the acid to *-ate*.

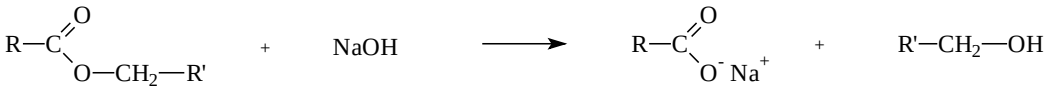


methyl propionate



ethyl acetate

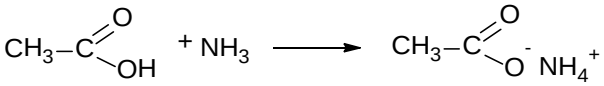
Esters are readily attacked by strong nucleophiles such as the hydroxide ion. Alkaline hydrolysis of esters is called *saponification* (from the Latin sapon, soap), because this type of reaction is used to make soaps from fats. Hydrolysis of an ester yields a salt of a carboxylic acid and an alcohol.



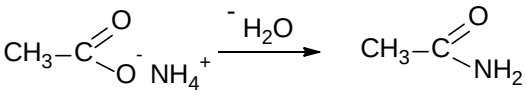
ester — salt of a carboxylic acid — alcohol

Formation of acid amides

Reaction of carboxylic acids and ammonia or organic amino compounds results in formation of ammonium salts. E.g. acetic acid reacts with ammonia to form ammonium acetate:

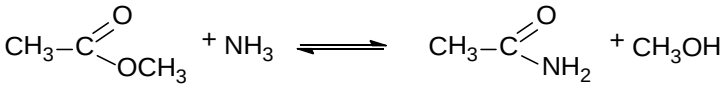


Thermal decomposition of the ammonium salts yields the respective acid amides:

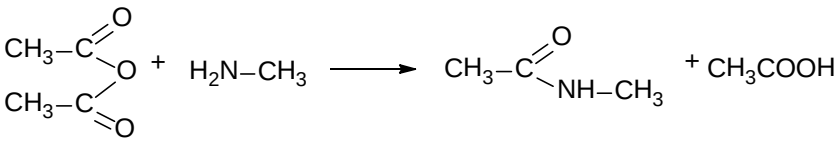


Acid amides can also be obtained in reaction of

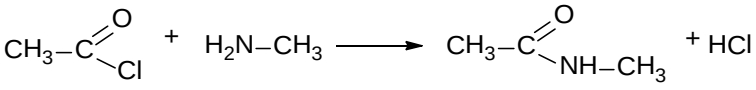
a.) esters and ammonia



b.) acid anhydrides and ammonia or organic amines



c.) acid chlorides and ammonia or organic amines



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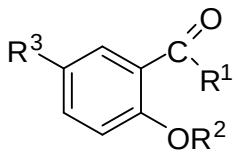
VI.6.5 **Important carboxylic acids (Selection)**

Acetic acid (CH_3-COOH) occurs naturally, for example, in vinegar, being produced by bacterial oxidation of ethanol. In its pure form it is called glacial acetic acid. The term glacial arise from the fact that pure acetic acid is a viscous liquid with a melting point of 17 ^oC. Below 17 ^oC it solidifies into an ice-looking solid. Acetic acid obtained commercially either by the catalytic oxidation of ethanol, or hydration of acetylene to acetaldehyde followed by oxidation to acetic acid. It is miscible with water yielding an acidic solution.

Benzoic acid (C_6H_5-COOH) is a white crystalline substance with limited solubility in water. Its sodium salt, sodium benzoate (C_6H_5-COONa), is water soluble and can be used as food preservative due to its bactericidal effect.

A number of commonly used drugs are carboxylic acids or carboxylic acid derivatives. Among others, the group of the widely used non-steroidal antiinflammatory drugs (NSAIDs) compromise several carboxylic acid derivatives. The prototype of this group of pharmacologically active compounds is *acetylsalicylic acid* (ASA). Several of the compounds are derivatives of acetic acid, propionic acid or salicylic acid.

Salicylic acid (SA) and salicylic acid derivatives have complex (antipyretic, antianalgesic and anti-inflammatory) pharmacological effects. Structure of salycilic acid derivatives of pharmacological importance is summarized in the in the Table below.



Pharmacologically active derivatives of salycilic acid

R^1	**R^2**	**R3**	**Név**
OH	H	H	salicylic acid
ONa	H	H	sodium salicylate
$ONH_2(CH_2CH_3)_2$	H	H	diethylammonium salicylate
OH	$OCCH_3$	H	acetylsalicylic acid
OCH_3	H	H	methyl salicylate
$O(CH_2)_2OH$	H	H	hidroxyethyl salicylate
OC_6H_5	H	H	phenyl salicylate
NH_2	H	H	salicylamide

VI.6.6 **Pharmacepoeial characterizations**

ACETIC ACID, GLACIAL

Acidum aceticum glaciale

CH_3COOH

$C_2H_4O_2$ Mr = 60.1

DEFINITION

Glacial acetic acid contains not less than 99.0 per cent *m/m* and not more than the equivalent of 100.5 per cent *m/m* of $C_2H_4O_2$.

CHARACTERS

A crystalline mass or a clear, colourless, volatile liquid, miscible with water, with alcohol and with methylene chloride.

IDENTIFICATION

A. A 100 g/l solution is strongly acid.

B. To 0.03 ml add 3 ml of *water R* and neutralise with *dilute sodium hydroxide solution R*. The solution gives reaction (b) of acetates.

TESTS

Solution S. Dilute 20 ml to 100 ml with *distilled water R*.

Appearance. It is clear and colourless.

Freezing point. Not less than 14.8 °C.

Reducing substances. To 5.0 ml add 10.0 ml of *water R* and mix. To 5.0 ml of the solution add 6 ml of *sulphuric acid R*, cool and add 2.0 ml of *0.0167 M potassium dichromate*. Allow to stand for 1 min and add 25 ml of *water R* and 1 ml of a freshly prepared 100 g/l solution of *potassium iodide R*. Titrate with *0.1 M sodium thiosulphate*, using 1.0 ml of *starch solution R* as indicator. Not less than 1.0 ml of *0.1 M sodium thiosulphate* solution is required.

Under acidic conditions dichromate ions can oxidize the reducing contaminants of the sample and the added iodide ions. The amount of the formed iodine is measured by sodium thiosulphate standard solutions.

$$Cr_2O_7^{2-} + 6\ I^- + 14\ H^+ = 2\ Cr^{3+} + 3\ I_2 + 7\ H_2O$$

$$I_2 + 2\ S_2O_3^{2-} = 2\ I^- + S_4O_6^{2-}$$

Chlorides. 10 ml of *Solution S* diluted to 15 ml with *water R* complies with the limit test for chlorides (25 mg/l).

Sulphates. 15 ml of *Solution S* complies with the limit test for sulphates (50 mg/l).

Iron. 5.0 ml of solution (a) obtained in the test for heavy metals diluted to 10.0 ml with *water R* complies with the limit test for iron (5 ppm).

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Heavy metals. Dissolve the residue obtained in the test for residue on evaporation by heating with two quantities, each of 15 ml, of *water R* and dilute to 50.0 ml (solution (a)). 12 ml of solution (a) complies with limit test A for heavy metals (5 ppm). Prepare the standard using *lead standard solution (2 ppm Pb) R*.

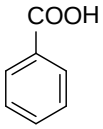
ASSAY

Weigh accurately a conical flask with a ground-glass stopper containing 25 ml of *water R*. Add 1.0 ml of the substance to be examined and weigh again accurately. Add 0.5 ml of *phenolphthalein solution R* and titrate with *1 M sodium hydroxide*.

Acetic acid can be titrated by using phenolphthalein in aqueous solution as monoprotic acid.

BENZOIC ACID

Acidum benzoicum



$C_7H_6O_2$ $M_r = 122.12$

DEFINITION

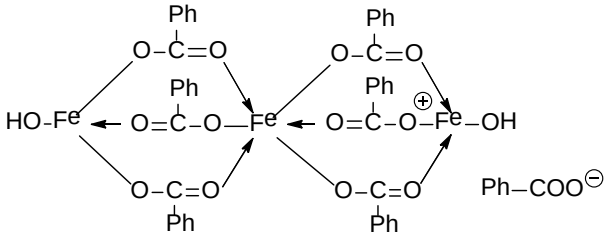
Benzenecarboxylic acid.
Content: 99.0 per cent to 100.5 per cent.

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.
Solubility: slightly soluble in water, soluble in boiling water, freely soluble in ethanol (96 per cent) and in fatty oils.

IDENTIFICATION

B. Benzoates. Dissolve a 0.1 g in *ethanol (96 per cent) R* and dilute the solution to 2 ml with the same solvent. Add 0.5 ml of *ferric chloride solution R1*. A dull-yellow precipitate, soluble in *ether R*, is formed.



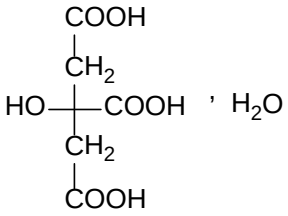
TESTS

Carbonisable substances. Dissolve a 0.5 g with shaking in 5 ml of *sulphuric acid R*. After 5 min, the solution is not more intensely coloured than *reference solution* Y_5.

Oxidisable substances. Dissolve a 0.2 g in 10 ml of *boiling water R*. Cool, shake and filter the solution. To the filtrate add 1 ml of *dilute sulphuric acid R* and 0.2 ml of *0.02 M potassium permanganate*. After 5 min, the solution is still coloured pink.

CITRIC ACID MONOHYDRATE

Acidum citricum monohydricum



$C_6H_8O_7 \cdot H_2O$ $M_r = 210.1$

DEFINITION

2-Hydroxypropane-1,2,3-tricarboxylic acid monohydrate.
Content: 99.5 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

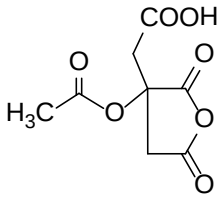
Appearance: white or almost white, crystalline powder, colourless crystals or granulates, efflorescent.
Solubility: very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

A. Dissolve 0.5 g in 5 ml of *water R*. The solution is strongly acidic.

C. Add about 5 mg to a mixture of 1 ml of *acetic anhydride R* and 3 ml of *pyridine R*. A red colour develops.

The product is probably acetylcitric acid-γ-anhydride, it shows red colour in pyridine.



D. Dissolve 0.5 g in 5 ml of *water R*, neutralise it using *1 M sodium hydroxide* (about 7 ml), add 10 ml of *calcium chloride solution R* and heat the reaction mixture to boiling. A wite precipitate is formed.

Calcium citrate is formed.

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TESTS

Appearance of solution.

Dissolve 2.0 g in *water R* and dilute the solution to 10 ml with the same solvent. The solution is clear and not more intensely coloured than *reference solution Y_7*, *BY_7* or *GY_7*.

Sulphates: maximum 150 ppm.

Dissolve 2.0 g in *distilled water R* and dilute the solution to 30 ml with the same solvent.

Add 3 ml of a 250 g/l solution of *barium chloride R* to 4.5 ml of *sulphate standard solution (10 ppm SO_4) R1*. Shake the mixture and allow it to stand for 1 min. To 2.5 ml of this solution, add 15 ml of the solution to be examined and 0.5 ml of *acetic acid R*. Prepare a standard in the same manner using 15 ml of *sulphate standard solution (10 ppm SO_4) R* instead of the solution to be examined.

After 5 min, any opalescence in the test solution is not more intense than that in the standard.

See Limit tests: Sulphate

Heavy metals: maximum 10 ppm.

Dissolve 5.0 g in several portions in 39 ml of *dilute sodium hydroxide solution R* and dilute the solution to 50 ml with *distilled water R*.

Test solution. 12 ml of the solution.

Reference solution (standard). A mixture of 10 ml of *lead standard solution (1 ppm Pb) R* and 2 ml of prescribed aqueous solution of the substance to be examined.

Blank solution. A mixture of 10 ml of *water R* and 2 ml of the prescribed aqueous solution.

To each solution, add 2 ml of *buffer solution pH 3.5 R*.

Mix and add to 1.2 ml of *thioacetamide reagent R*. Mix immediately.

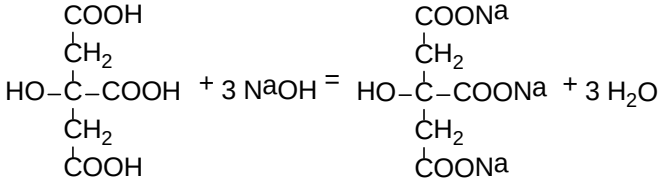
Examine the solutions after 2 min. The test is invalid if the reference solution does not show a slight brown colour compared to the blank solution. The substance to be examined complies with the test if any brown colour in the test solution is not more intense than that in the reference solution.

See Limit tests: Heavy metals.

ASSAY

Dissolve 0.550 g in 50 ml of *water R*. Titrate the solution with *1 M sodium hydroxide*, using 0.5 ml of *phenolphthalein solution R* as indicator.

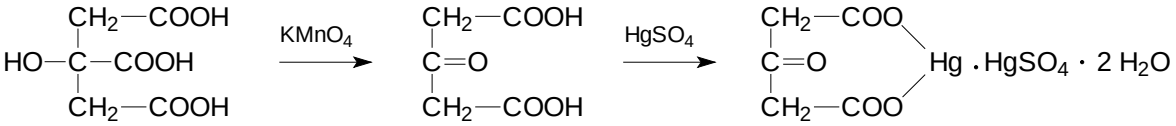
Citric acid can be titrated by using phenolphthalein in aqueous solution as triprotic acid.



INFORMATIVE TESTS

3. A 1 g sample dissolves in 10 ml of *water R* producing a clear, colourless and acid solution. To 0.5 ml of this solution add 5 ml of *water R* and 2 ml of *mercury(II) sulphate solution R* and boil. Add dropwise 2 ml of *0.02 M potassium permanganate solution* to the hot solution; the solution decolourizes and a white precipitate forms.

Denigés reaction:



VI.7 Carbohydrates

Carbohydrates, a very important class of naturally occurring chemicals, give structure to plants, flowers, vegetables, and trees. In addition, carbohydrates function as chemical energy-storage systems; they are metabolized to water, carbon dioxide, and heat or other energy. As such, they constitute an important source of food. Finally, they serve as the building units of fats and nucleic acids. Cellulose, starch, and ordinary table sugar are typical carbohydrates. All are said to be *polyfunctional*, because they possess multiple functional groups. Like glucose, $C_6(H_2O)_6$, many of the simple building blocks of complex carbohydrates have the general formula $C_n(H_2O)_n$, which is equivalent to hydrated carbon. This is one of the reasons why the compounds in this class are called carbohydrates.

Several classifications of carbohydrates have proven useful, and are outlined in the following table.

Complexity	**Simple Carbohydrates**		**Complex Carbohydrates**		
Size	**Tetrose**	**Pentose**	**Hexose**	**Heptose**	
	C_4 sugars	C_5 sugars	C_6 sugars	C_7 sugars	etc.
C=O Function	**Aldose** sugars having an aldehyde function or an acetal equivalent. **Ketose** sugars having a ketone function or an acetal equivalent.				
Reactivity	**Reducing** sugars oxidized by Tollens' reagent (or Benedict's or Fehling's reagents). **Non-reducing** sugars not oxidized by Tollens' or other reagents.				

Carbohydrate is the general name for the monomeric (*monosaccharides*), dimeric (*disaccharides*), trimeric (trisaccharides), oligomeric (*oligosaccharides*), and polymeric (*polysaccharides*) forms of sugar (saccharum, Latin, sugar). A monosaccharide, or simple sugar, is an aldehyde or ketone containing at least two additional hydroxyl groups. Thus, the two simplest members of this class of compounds are 2,3-dihydroxypropanal (glyceraldehyde) and 1,3-dihydroxypropanone (1,3-dihydroxyacetone). Complex sugars are those formed by linking simple sugars, with the elimination of water.

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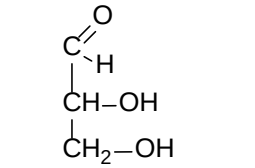
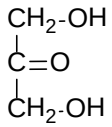
Aldehydic sugars are classified as *aldoses*; those with a ketone function are called *ketoses*. On the basis of their chain length, we call sugars *trioses* (3 carbons), *tetroses* (4 carbons), *pentoses* (5 carbons), *hexoses* (6 carbons), and so on. Therefore, 2,3-dihydroxypropanal (glyceraldehyde) is an aldotriose, whereas 1,3-dihydroxypropanone is a ketotriose.



2,3-dihydroxypropanal
(glyceraldehyde)



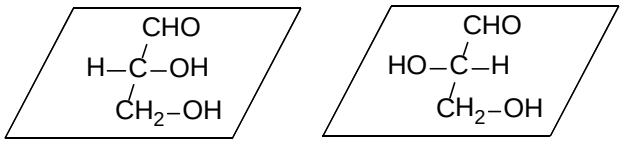
1,3-dihydroxypropanone
(1,3-dihydroxyacetone)

VI.7.1 **Monosaccharides**

Although they are not sugars, glyceraldehyde and 1,3-dihydroxypropanone can be considered as the simplest aldose and ketose, respectively. The homologous series can build up by introducing one or more (CH-OH) units into the carbon chains of the parent compounds.

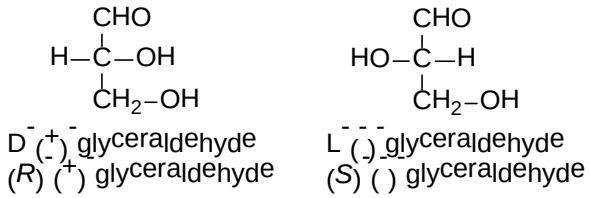
The carbon atom of each (CH-OH) unit is a chiral (asymmetric) center, which can have (*R*) or (*S*) configuration. Thus, glyceraldehyde has 1, aldotetroses have 2, aldopentoses have 3, and aldohexoses have 4 asymmetric centers. The respective ketoses have one less asymmetric carbon atoms.

The two enantiomeric (nonsuperimposable mirror image) structures and two dimensional Fisher projections of glyceraldehyde are shown below:

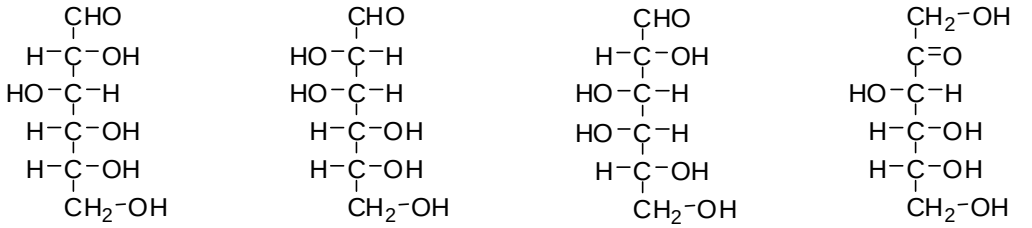


All the physico-chemical properties but direction of optical activity in aqueous solution of the two glyceraldehyde enantiomers are very much the same. The enantiomer on the left has optical activity of clockwise (+) direction, while that of on the right rotate the plain polarized light in counterclockwise (-) direction.

According to Emil Fischer's proposal the the configuration of the chiral carbon atom of (+) glyceraldehyde is designated "D", while that of the other enantiomer is called "L". Besides the "D" and "L" prefixes, configuration of the two carbon atoms can also be designated by means of the (*R*) and (*S*) prefixes. (see Chapter VI.6.; Carboxylic acids.) Accordingly, the two dimensional projected structures and nomenclature of the two glyceraldehyde enantiomers as follows.



In the pharmaceutical practice hexoses are the most common monosaccharides. Aldohexoses possess 4 and ketohexoses have 3 asymmetric carbon atoms. Accordingly, they can be found in 16 and 8 isomeric forms, respectively. Each monosaccharide can be found either in D form or L form; in D form the hydroxyl group at the penultimate carbon (the carbon before the last carbon) is on the right side while in L form the hydroxyl group at penultimate carbon is on the left side of the open-chain projected structures. The open-chain projected structure and name of the most common monosaccharide enantiomers as follows.



Cyclic forms of monosaccharides

Sugars are hydroxycarbonyl compounds that should be capable of intramolecular hemiacetal formation. Indeed, glucose and the other hexoses and pentoses exist as an equilibrium mixture with their cyclic hemiacetal isomers, in which the latter strongly predominate. In principle, any one of the five hydroxyl groups could add to the carbonyl group of the aldehyde. However, although five-membered ring formation is known, six-membered rings are usually the preferred products.

The six-membered ring structure of a monosaccharide is called a *pyranose*, a name derived from pyran, a six-membered cyclic ether. Sugars in the five-membered ring form are called *furanoses*, from furan.

Note that, on cyclisation, the carbonyl carbon turns into a new stereocenter. As a consequence, hemiacetal formation leads to two new compounds, two diastereomers with different configurations of carbon atom at position 1. The formed diasereomers are labelled as *α*- and *β-glucopyranose*. Because this type of diastereomer formation is unique to sugars, such isomers have been given a separate name: *anomers*. The new stereocenter is called the *anomeric carbon*. In the *Fischer projection* of the α form the anomeric OH points toward the right. In the Fischer projection of the β form the anomeric OH is on the left.

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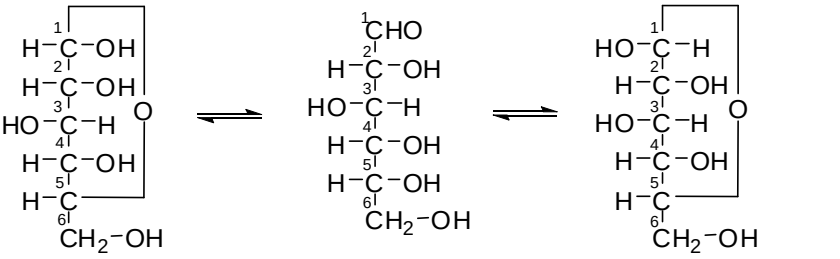


α-D-(+)-glucopyranose
α-D-(+)-glucose <1,5>

D-(+)-glucose

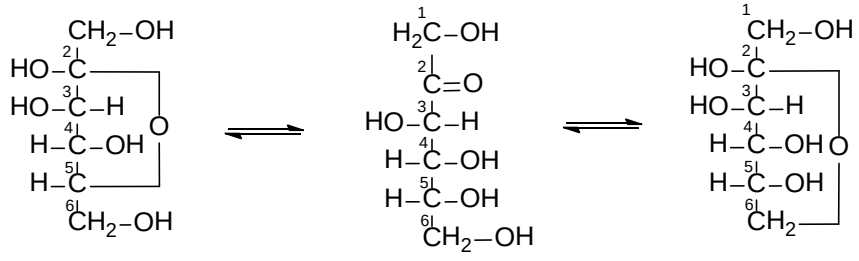
β-D-(+)-glucopyranose
β-D-(+)-glucose <1,5>

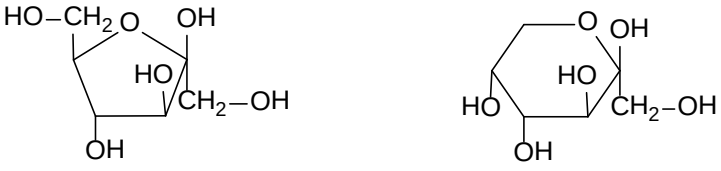
Haworth projections more accurately represent the real three-dimensional structure of the sugar molecule. The cyclic ether is written in line notation as a pentagon or a hexagon, the anomeric carbon placed on the right, and the ether oxygen put on top. The substituents located above or below the ring are attached to vertical lines. In relating the Haworth projection to a three-dimensional structure, the ring bond at the bottom (between C2 and C3) is understood to be in front of the plane of the paper, and the ring bonds containing the oxygen are understood to be in back.

α-D-(+)-glucopyranose
α-D-(+)-glucose <1,5>

β-D-(+)-glucopyranose
β-D-(+)-glucose <1,5>

In contrast with glucose which exists primarily as the pyranose, fructose forms both fructopyranose and fructofuranose structure. Crystalline fructose adopt furanose structure. In aqueous solution, however, besides the α ⇌ β anomerization (epimerization) the pyranose ⇌ furanose equilibrium is also exist.

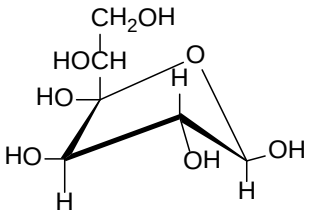




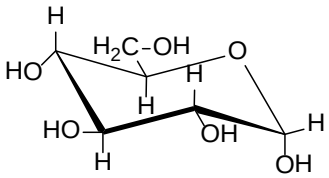
β-D(-)-fructopyranose
β-D(-)-fructose <2,5>

β-D(-)-fructofuranose
β-D(-)-fructose <2,6>

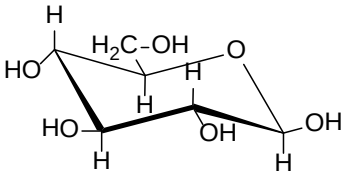
Haworth projections are used extensively in the literature, but here, to make use of our knowledge of conformation, the cyclic forms of sugars will be presented as envelope (for furanoses) or chair (for pyranoses) conformations. As in Haworth notation, the ether oxygen usually will be placed top right, and the anomeric carbon at the right vertex of the envelope or chair.



β-D-glucofuranose



α-D-glucopyranose



β-D-glucopyranose

Although there are exceptions, most aldohexoses adopt the chair conformation that places the bulky hydroxymethyl group at the C5 terminus in the equatorial position. For glucose, this preference means that, in the α form, four of the five substituents can be equatorial, and one is forced to lie axial; in the β form, all substituents can be equatorial. This situation is unique for glucose; the other seven D-aldohexoses contain one or more axial substituents.

VI.7.2 **Properties**

In general, monosaccharides and disaccharides are colourless crystalline compounds, sweet to taste and highly soluble in polar solvents (as water). On heating, the compounds undergo uncontrolled decomposition (*caramelisation*) accompanied by browning and formation of volatile flavour products.

Natural monosaccharides are optically active compounds. In the solid (crystalline) state they exist in cyclic form and distribution of the α and β anomers depends on the nature of the solvent used for crystallization. Optical activity of their freshly prepared aqueous solution is continuously changing to become constant. The observation, called *mutarotation*, results from spontaneous change of α to β forms and vice versa through the straight chain formula (α ⇌ open chain ⇌ β). Freshly prepared α-(+) D-glucopyranose solution has an angle of rotation +112.2, which gradually decreases to become constant at +52.7 Also, freshly prepared β-(+)-D-glucopyranose solution has an angle of rotation +19.3, which gradually increases to become constant at +52.7.
Mutarotation of D-glucose in aqueous solution can be described as follows.

β-D-(+)-glucose <1,5> ⇌ α-D-(-)-glucose <1,5>

$[\alpha]_D^{20} = +19.3$ ~ 64% ⇌ $[\alpha]_D^{20} = +112.2$ ~ 36%

$[\alpha]_D^{20} = +52.7$

The value indicates that it is β-D-(+) glucopyranose the dominant form in the equilibrium. This observation can be explained by comparison of conformation of the two diastereomers:

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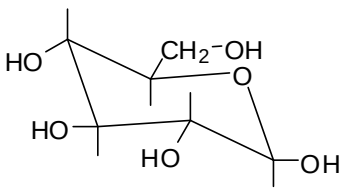
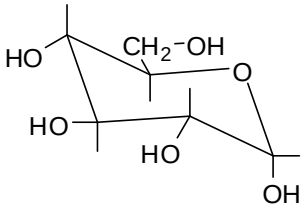


β-D-glucopyranose



α-D-glucopyranose

While each substituent of the β-D-glucopyranose epimer takes equatorial orientation, the *hemiacetalic hydroxyl group* takes axial position in the α-D-glucopyranose diastereomer.

Similar mutarotation can also be observed in the aqueous solution of D-fructose:

α-D-(-)-fructose <2,6> ⇌ β-D-(-)-fructose <2,6>

$[\alpha]_D^{20} = +223$ ~ 12% | $[\alpha]_D^{20} = -135$ ~ 88%

$[\alpha]_D^{20} = -92$

It is worth mentioning that contribution of the open chain forms – found in law concentrations (about 1 %) in the equilibrium mixtures – to the observed optical activity is negligible.

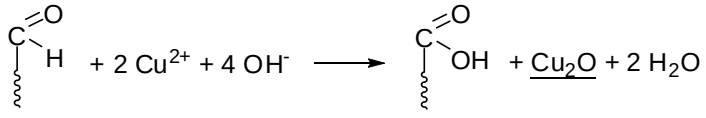
VI.7.3 **Reactions**

VI.7.3.1 Reactions of the carbonyl group

Oxidation to carboxylic acids

Fehling's and Tollens's tests detect reducing sugars

Because they are polyfunctional compounds, the open-chain monosaccharides undergo the reactions typical of each of their functional groups. For example, aldoses contain the oxidizable aldehyde group and therefore respond to the standard oxidation tests such as exposure to *Fehling's* or *Tollens's solutions*. The α-hydroxy substituent in ketoses is similarly oxidized.

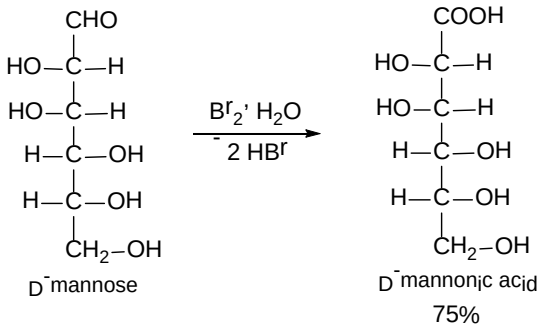


aldose blue aldonic acid red

In these reactions, the aldoses are transformed into *aldonic acids*. E.g. D-glucose is oxidized to *D-gluconic acid*. Sugars that respond positively to these tests are called *reducing sugars*. All natural monosaccharides are reducing sugars.

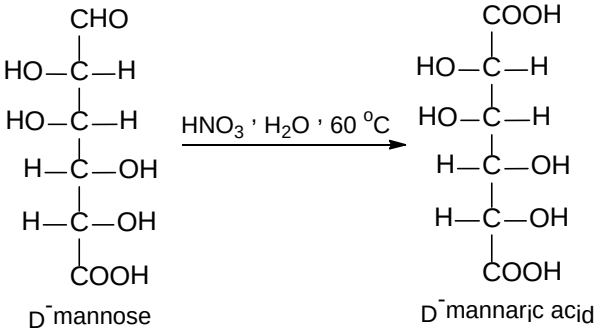
Oxidation of aldoses can give mono- or dicarboxylic acids

Aldonic acids are made on a preparative scale by oxidation of aldoses with bromine in buffered aqueous solution (pH = 5-6). For example, D-mannose yields D-mannonic acid in this way.



D-mannose D-mannonic acid 75%

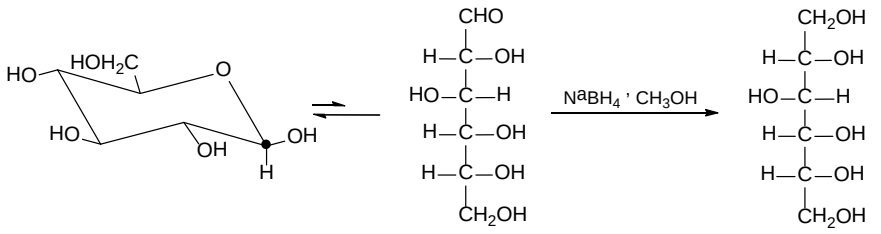
More vigorous oxidation of an aldose leads to attack at the primary alcohol function as well as at the aldehyde group. The resulting dicarboxylic acid is called an *aldaric acid*. This oxidation can be achieved with warm dilute aqueous nitric acid. For example, *D-mannose* is converted into *D-mannaric* acid under these conditions.



D-mannose D-mannaric acid

Reduction of monosaccharides to alditols

Aldoses and ketoses are reduced by the same types of reducing agents that convert aldehydes and ketones into alcohols. The resulting polyhydroxy compounds are called *alditols*. For example, D-glucose gives *D-glucitol* (older name *D-sorbitol*) when treated with sodium borohydride. The hydride reducing agent traps the small amount of the open-chain form of the sugar, in this way shifting the equilibrium from the unreactive cyclic hemiacetal to the product.



D-glucose D-glucitol (D-sorbitol)

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Many alditols occur in nature. *D-Glucitol* is found in red seaweed in concentrations as high as 14%, also in many berries (but not grapes), in cherries, in plums, in pears, and in apples.

Carbonyl condensations with amine derivates

The carbonyl function in aldoses and ketoses undergoes condensation reactions with amine derivates. For example, treatment of D-mannose with phenylhydrazine gives the corresponding hydrazone, D-mannose phenylhydrazone. Surprisingly, the reaction does not stop at this stage but can be induced to continue with additional phenylhydrazine (two extra equivalents). The final product is a double phenylhydrazone, also called an *osazone* (here, phenylosazone). In addition, one equivalent each of benzenamine (aniline), ammonia, and water is generated.

Sugars, like many other polyhydroxy compounds, are well known for their reluctance to crystallize from syrups. Their osazones, however, readily form yellow crystals with sharp melting points, thus simplifying the isolation and characterization of many sugars, particularly if they have been formed as mixtures or are impure.

VI.7.3.2 Reactions of the hydroxyl groups

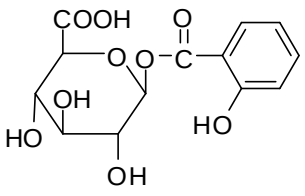
Ether formation: glycosides

Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called *glycosides*. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The diether product is stable to base and alkaline oxidants such as Tollen's reagent. Since acid-catalyzed aldolization is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.

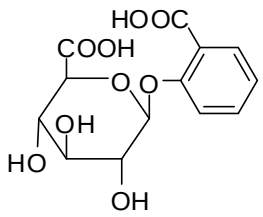
Ester formation

Carboxylic acids can also be linked to the hydroxyl groups of sugars; they react to form ester bonds. Phosphoric acid esters of sugars are important biomolecules among others in energy storage (ATP) and signal transduction of the cells. Formation of such derivatives are also of great importance in metabolic transformation of exogeneous substances in the humans and animals. Esters can be prepared from monosaccharides by standard techniques. Excess reagent will completely convert all hydroxyl groups, including the hemiacetal function.

The ester and ether derivatives of *D-glucuronic acid* and *salicylic acid* are shown below:



salicylic acid ester-glucuronide



salicylic acid ether-glucuronide

Oxidation by periodic acid

Glucose and other sugars are extensively cleaved by periodic acid, due to the abundance of vicinal diol moieties in their structure. This oxidative cleavage, known as the *Malaprade reaction* is particularly useful for the analysis of selective O-substituted derivatives of saccharides, since ether functions do not react. The stoichiometry of aldohexose cleavage is shown in the following equation:

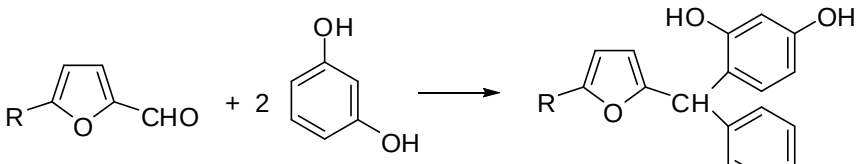
$$HOCH_2(CHOH)_4CHO + 5\ HIO_4 \longrightarrow H_2C{=}O + 5\ HCO_2H + 5\ HIO_3$$

Complex formation

Sugars containing an axial-equatorial-axial sequence of three hydroxyl groups in a six-membered ring, or a *cis-cis* sequence in a five-membered ring, form 1 : 1 complexes with metal cations in hydroxylic solvents. Lanthanum(III) ions form the strongest complexes in water, followed by calcium and strontium ions. Complexes with copper(II) ions have analytical importance.

Furfural formation

On heating with diluted hydrochloric acid pentoses yield *furfural* (R = H) while hexoses *(hydroxymethyl)furfural* (R = CH_2OH). Addition of resorcin to the acidic solution results in formation of a red colouration. Triphenylmethane-type derivatives are formed.

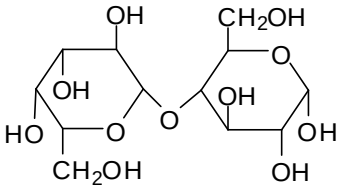


From pentoses: R = H
From hexoses: R = CH_2OH

Disaccharides

When the alcohol component of a glycoside is provided by a hydroxyl function on another monosaccharide, the compound is called a *disaccharide*. Two examples of disaccharides (lactose and saccharose) are shown in the following diagram. Notice that the glycoside bond may be *alpha*, as in saccharose, or *beta* as in lactose. Acid-catalyzed hydrolysis of disaccharides yields the respective monosaccharides.

Lactose:



(+)-[4-β-D-(+)-galactosyl <1,5>-α-D-(+)-glucose<1,5>]

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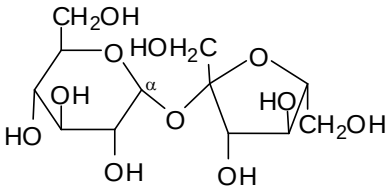
Saccharose:



(+)-[α-D-(+)-glucosyl<1,5>-β-D-(-)-fructoside<2,5>]

Saccharose (*sucrose*, table sugar), is one of the few natural chemicals consumed in unmodified form (water and NaCl are others). Sugar is isolated from sugar cane and sugar beets, in which it is particularly abundant (about 14-20% by weight), although it is present in many plants in smaller concentrations. The structure of sucrose can be deduced from its chemical behavior: acidic hydrolysis splits it into glucose and fructose. It is a *nonreducing* sugar. It does not undergo mutarotation. These findings suggest that the component monosaccharide units are linked by an acetal bridge connecting the two anomeric carbons; in this way, the two cyclic hemiacetal functions protect each other.

Sucrose has a *specific rotation* of +66.5. Treatment with aqueous acid decreases the rotation until it reaches a value of -20.0. The same effect is observed with the enzyme *invertase*. The phenomenon, known as the *inversion of sucrose*, is related to mutarotation of monosaccharides. It includes three separate reactions: hydrolysis of the disaccharide to the component monosaccharides α-*D-glucopyranose* and β-D-fructofuranose; mutarotation of α-D-glucopyranose to the equilibrium mixture with the β form; and mutarotation of β-D-fructofuranose to the slightly more stable β-D-fructopyranose. Because the absolute value for the specific rotation of fructose (-92) is more negative than the absolute value of glucose (+52.7), the resulting mixture, - sometimes called *invert sugar* - has a net negative rotation, inverted from that of the original (dextrorotatory) sucrose solution.

Sucrose contains an acetal linkage between the anomeric carbons of the component sugars. One could imagine other acetal linkages with other hydroxyl groups. Indeed, in *lactose*, which is a dimer of galactose and glucose, the hemiacetal oxygen of the galactose molecule (in the β anomeric form) is bound to C4 of the D-glucose unit.

VI.7.4 **Polysaccharides**

As the name implies, polysaccharides are large high-molecular weight molecules constructed by joining monosaccharide units together by glycosidic bonds. Their possible structural diversity is comparable to that of alkene polymers, particularly in variations of chain length and branching. Nature, however, has been remarkably conservative in its construction of such polymers. The three most abundant natural polysaccharides, *cellulose*, *starch*, and *glycoge*n, are derived from the same monomer-glucose.

Like *cellulose*, *starch* is a polyglucose, but its subunits are connected by α-acetal linkages. It functions as a food reserve in plants and (like cellulose) is readily cleaved by aqueous acid into glucose. Major sources of starch are corn, potatoes, wheat, and rice. Hot water swells granular starch and allows the separation of the two major components: amylose (~20%) and amylopectin (~80%).

Another polysaccharide similar to amylopectin but with greater branching (1 per 10 glucose units) and of much larger size (as much as 100 million Da molecular weight) is *glycogen*. This compound is of considerable biological importance because it is one

of the major energy-storage polysaccharides in humans and animals and because it provides an immediate source of glucose between meals and during (strenuous) physical activity. It is accumulated in the liver and in resting skeletal muscle in relatively large amounts. The manner in which cells make use of this energy storage is a fascinating story in biochemistry.

In the pharmaceutical practice polisaccharides are generally used as *excipients* (inactive substance formulated alongside the active pharmaceutical ingredient ("*API*") of a pharmaceutical product.)

Carbohydrates official in the Ph. Hg. VIII. (Selection)

Substance	Name	Use
Monosaccharides		
Fructose	Fructosum	excipient, sweetener
Glucose	Glucosum anhydricum	source of energy, sweetener
Glucose monohydrate	Glucosum monohydricum	source of energy, sweetener
Disaccharides		
Lactose monohydrate	Lactosum monohydricum	excipient
Saccharose	Saccharum	excipient
Polysacharides (selection)		
Agar	Agar	excipient
Cellulose acetate	Cellulosi acetas	excipient
Cellulose pulverised	Cellulosi pulvis	excipient
Microcrystalline cellulose	Cellulosum microcrystallinum	excipient
Dextran 40 for injection	Dextranum 40 ad iniectabile	antithrombotic
Dextrin	Dextrinum	excipient
Ethyl cellulose	Ethylcellulosum	excipient
Rice starch	Oryzae amylum	excipient
Wheat starch	Tritici amylum	excipient

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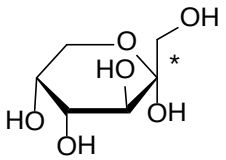
VI.7.5 **Pharmacopoeial qualifications**

FRUCTOSE

Fructosum



and epimer at C*

$C_6H_{12}O_6$ $M_r = 180.2$

DEFINITION

(-)-D-Arabino-hex-2-ulopyranose.

The substance described in this monograph is not necessarily suitable for parenteral use.

CHARACTERS

Appearance: white or almost white, crystalline powder.

It has a very sweet taste.

Solubility: very soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

A. Thin-layer chromatography.

Solvent mixture: water R, methanol R (2:3 *V/V*).

Test solution. Dissolve a 10 mg sample of the substance to be examined in the solvent mixture and dilute the solution to 20 ml with the solvent mixture.

Reference solution (a). Dissolve 10 mg of *fructose CRS* in the solvent mixture and dilute to 20 ml with the solvent mixture.

Reference solution (b). Dissolve 10 mg each of *fructose CRS, glucose CRS, lactose CRS* and *sucrose CRS* in the solvent mixture and dilute to 20 ml with the solvent mixture.

Plate: TLC silica gel G plate R.

Mobile phase: water R, methanol R, anhydrous acetic acid R, ethylene chloride R (10:15:25:50 *V/V/V/V*).

Measure the volumes accurately since a slight excess of water produces cloudiness.

Application: 2 µl; thoroughly dry the starting points.

Development A: over a path of 15 cm.

Drying A: in a current of warm air.

Development B: immediately, over a path of 15 cm, after renewing the mobile phase.

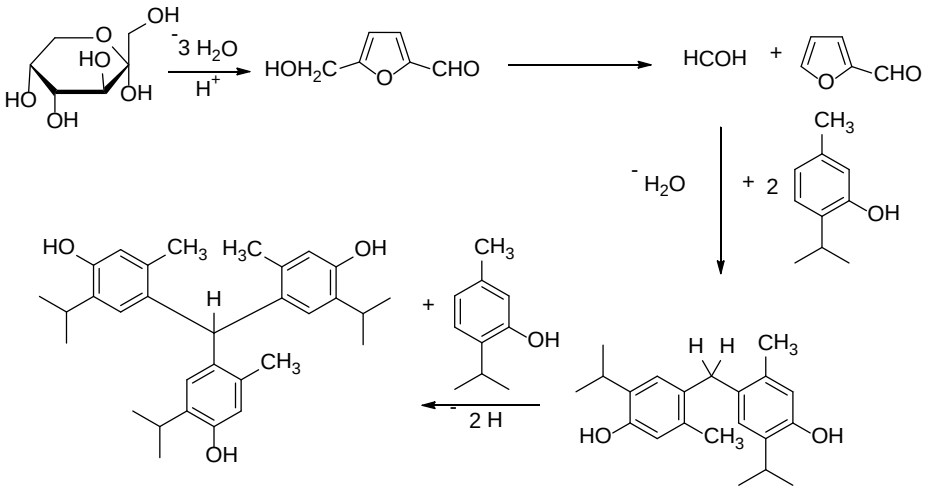
Drying B: in a current of warm air.

Detection: spray with a solution of 0.5 g of *thymol R* in a mixture of 5 ml of *sulphuric acid R* and 95 ml of *ethanol (96 per cent) R*. Heat at 130 ºC for 10 min.

System suitability: reference solution (b):

- the chromatogram shows 4 clearly separated spots.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).



B. Dissolve a 0.1 g sample in 10 ml of *water R*. Add 3 ml of *cupri-tartaric solution R* and heat the mixture. A red precipitate is formed.

Fehling reaction: it is a group reaction of α-hydroxycarbonyl compounds that have reducing properties. Every monosaccharide reacts, as well as 1,4-disaccharides. Based on new investigations the mechanism of the reaction is quite complex. Oxidation also involves breaking of the chain. Probably glucose decomposes in alkaline medium to 2 molecules of glyceraldehyde that is oxidized to glyceric acid, or perhaps with another chain breaking to formic acid and glycolic acid.

$$RCHO + 2\,Cu^{2+} + 4\,OH^- = RCOOH + \underline{Cu_2O} + 2\,H_2O$$

C. To 1 ml of *Solution S* (0.1 g in 1.0 ml of *distilled water R*) add 9 ml of *water R*. To 1 ml of the solution add 5 ml of *hydrochloric acid R* and heat the reaction mixture to 70 ºC. A brown colour develops.

Hexoses dehydrate to form 5-hydroxymethylfurfural (brown colour). It further decomposes to formaldehyde and furfural. See test D. Comparing monosaccharides, ketoses react much faster than aldoses.

D. Dissolve 1 g in *water R* and dilute the solution to 2 ml with the same solvent. To 0.5 ml of the solution add 0.2 g of *resorcinol R* and 9 ml of *dilute hydrochloric acid R* and heat the reaction mixture on a water-bath for 2 min. A red colour develops.

Selivanov reaction: Hexoses dehydrate to form 5-hydroxymethylfurfural. It further decomposes to formaldehyde that condensates with 3 molecules of resorcinol and a triarylmethane dye is formed. Other hexoses, like glucose, also react but much slower. If heating time and acid concentration are precisely observed the reaction is fairly specific to fructose.

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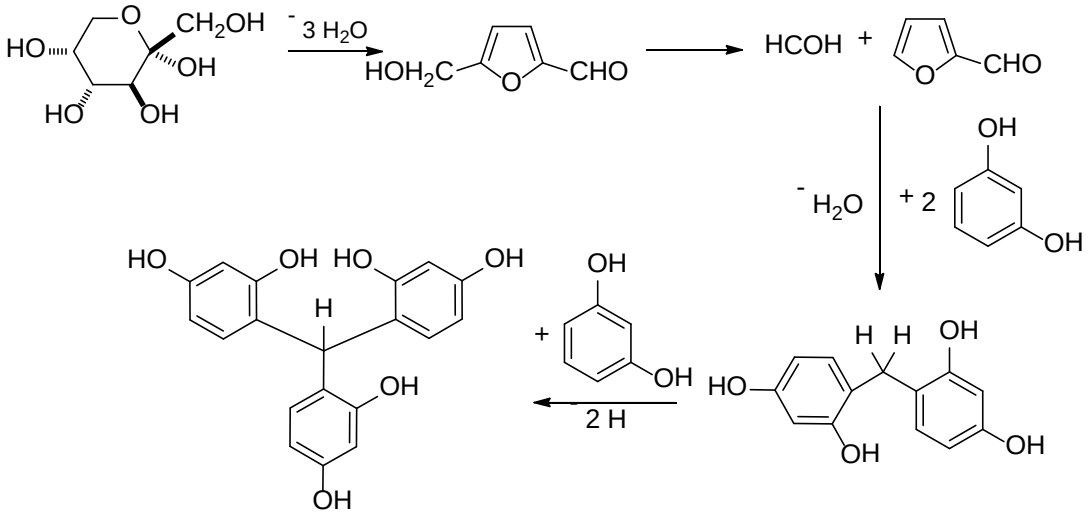
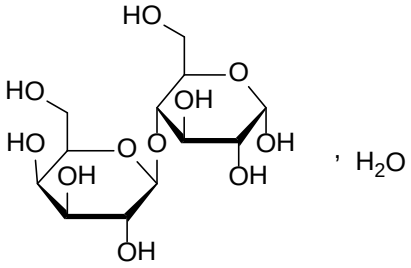


LACTOSE MONOHYDRATE

Lactosum monohydricum



$C_{12}H_{22}O_{11} \cdot H_2O$ $M_r = 360.3$

DEFINITION

O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate.

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely but slowly soluble in water, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

B. Thin-layer chromatography.

Solvent mixture: water R, methanol R (2:3 *V/V*).

Test solution. Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute the solution to 20 ml with the solvent mixture.

Reference solution (a). Dissolve 10 mg of *lactose CRS* in the solvent mixture and dilute it to 20 ml with the solvent mixture.

Reference solution (b). Dissolve 10 mg each of *fructose CRS, glucose CRS, lactose CRS* and *sucrose CRS* in the solvent mixture and dilute the solution to 20 ml with the solvent mixture.

Plate: TLC silica gel G plate R.

Mobile phase: water R, methanol R, glacial acetic acid R, ethylene chloride R (10:15:25:50 *V/V/V/V*).
Measure the volumes accurately since a slight excess of water produces cloudiness.
Application: 2 µl; thoroughly dry the starting points.
Development A: over a path of 15 cm.
Drying A: in a current of warm air.
Development B: immediately, over a path of 15 cm, after renewing the mobile phase.
Drying B: in a current of warm air.
Detection: spray with a solution of 0.5 g of *thymol R* in a mixture of 5 ml of *sulphuric acid R* and 95 ml of *ethanol (96 per cent) R*. Heat at 130 ºC for 10 min.
System suitability: reference solution (b):

- the chromatogram shows 4 clearly separated spots.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.25 g in 5 ml of *water R*. Add 5 ml of *ammonia R* and heat the mixture in water-bath at 80 ºC for 10 min. A red colour develops.

Wöhlk reaction: The exact mechanism of the reaction is not known. Probably aldehydes are formed by ring opening or chain breaking and they give coloured products by aldol dimerization. Glucose and fructose give yellow products and sucrose does not react.

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VI.8 Heterocycles

VI.8.1 Introduction

The group of the heterocyclic compounds involves cyclic molecules with ring skeleton containing one or more carbon atoms, or one or more heteroatoms (atoms other than carbon and hydrogen). These molecules have a special significance, because of their important role in biological systems. Apart from the derivatives which consist of a small number of atoms, the majority of compounds can be characterised by the high stability of the ring skeleton.

VI.8.2 Nomenclature

The general principles of the nomenclature were established by the international association of the chemists (IUPAC). Many heterocycles, especially amines, were identified early on, and received trivial names which are still preferred.

The *Hantzsch-Widman system* provides a systematic method of naming heterocyclic compounds. It makes use of the same hetero atom prefix followed by a suffix designating ring size and saturation. As outlined in the following table, each suffix consists of a ring size root and an ending intended to designate the degree of unsaturation in the ring. In this respect, it is important to recognize that the saturated suffix applies only to *completely saturated ring systems*, and the unsaturated suffix applies to rings incorporating *the maximum number of non-cumulated double bonds*. Systems having a lesser degree of unsaturation require an appropriate prefix, such as "*dihydro*"or "*tetrahydro*".

Member number of the ring	Prefix	Ring size	Heteroatom: O		Heteroatom: S		Heteroatom: N	
			unsatu-rated	saturated	unsatu-rated	saturated	unsatu-rated	saturated
3	tri	-ir-	oxirene	oxirane	thiirene	thiirane	azirine	aziridine
4	tetra	-et-	oxete	oxetane	thiete	thiethane	azete	azetidine
5		-ol-	oxole	oxolane	thiole	thiolane	azole	azolidine
6		-in-/-an-	oxine	oxane	thiine	thiane	azine	perhydroazine
7	hepta	-ep-	oxepine	oxepane	thiepine	thiepane	azepine	perhydroazepine
8	octa	-oc-	oxocine	oxocane	thiocine	thiocane	azocine	perhydroazocine
9	nona	-on-	oxonine	oxonane	thionine	thionane	azonine	perhydroazonine
10	deca	-ec-	oxecine	oxecane	thiecine	thiecane	azecine	perhydroazecine

While numbering of the heterocyclic ring with one heteroatom, the hetero atom is assigned position 1 and the substituents are then counted around the ring in a manner so as to give them the lowest possible numbers. While writing the name of the compound, the substituents are placed in an alphabetical order.

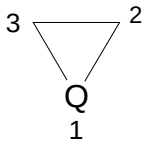
If there is more than one hetroatom of the same type the ring is numbered in such a way that the heteroatoms are assigned the lowest possible set of number of locants. Numbering starts at the saturated one, e.g. imidazole.

If there is more than one type of the heteroatoms, the ring is numbered starting at the heteroatom of the higher priority (O>S>N) and it continues in the direction to give the other heteroatoms the lower numbers as possible. The ring is numbered from the atom of preference in such a way so as to give the smallest possible number to the other hetero atoms in the ring. As a result the position of the substituent plays no part in determining how the ring is numbered in such compound.

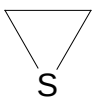
VI.8.3 **Classification of heterocyclic compounds**

Heterocyclic compounds are generally classified according to the ring size, the degree of unsaturation as well as the number and the nature of heteroatom(s). Based on the degree of unsaturation *heteroaromatic* (unsaturated), *heteroalicyclic* (saturated), and *heteroolefinic* (partially saturated) heterocyclic rings can be distinguished.

VI.8.3.1 3-membered heterocyclic rings

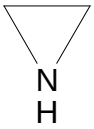


Saturated 3-membered heterocyclic rings



thiirane
ethylene sulfide

oxirane
ethylene oxide

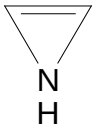


aziridine
ethyleneimine

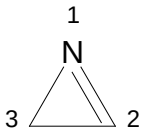
Unsaturated 3-membered heterocyclic group

thiirene

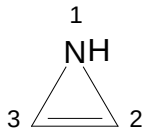
oxirene



azirine



1-azirine



2-azirine

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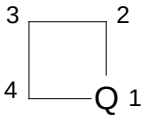
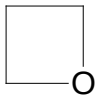
VI.8.3.2 4-membered heterocyclic rings

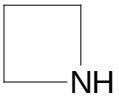


Saturated 4-membered heterocyclic rings

thiethane

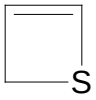


oxethane
trimethylene oxide



azetidine
trimethyleneimine

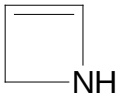
Unsaturated 4-membered heterocyclic rings



thiete

oxete

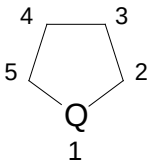
1-azetine



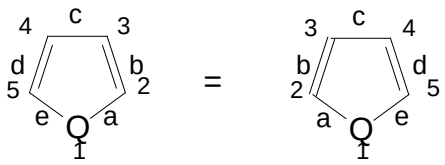
2-azetine

azete

VI.8.3.3 5-membered heterocyclic rings



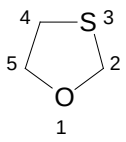
Indication of the position of bonds in the 5–membered heterocyclic compounds:



indication of the position of bonds
in the 5-membered heterocyclic rings

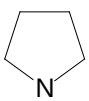
Saturated 5-membered heterocyclic rings

oxolane
tetrahydrofuran
tetramethylene oxide



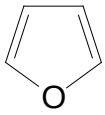
1,3-oxathiolane

thiolane
tetrahydrothiophene
tetramethylene sulfide

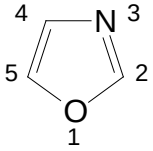


azolidine
pyrrolidine

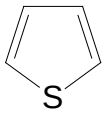
Unsaturated 5-membered heterocyclic rings



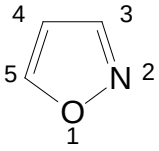
oxole
furan



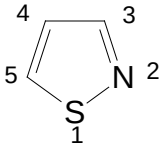
1,3-oxazole
oxazole



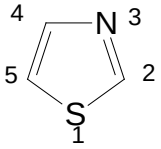
thiole
thiophene



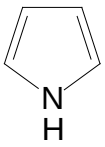
1,2-oxazole
isoxazole



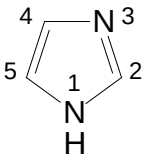
1,2-thiazole
isothiazole



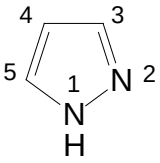
1,3-thiazole
thiazole



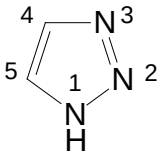
azole
pyrrole



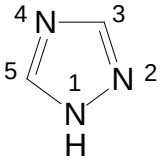
1,3-diazole
imidazole



1,2-diazole
pyrazole

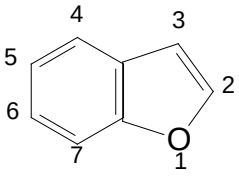


1,2,3-triazole

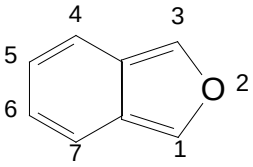


1,2,4-triazole

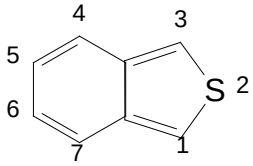
Polycyclic derivatives of 5-membered heterocyclic rings



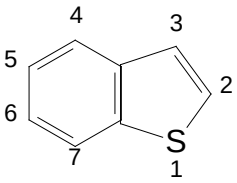
benzo[2,3]furan
benzo[*b*]furan
coumarone



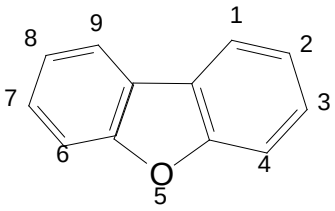
benzo[3,4]furan
benzo[*c*]furan
isocoumarone; isobenzofuran



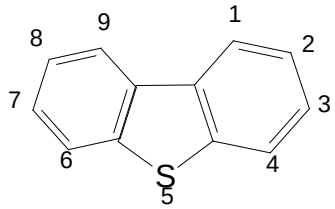
benzo[3,4]thiophene
benzo[*c*]thiophene
isothionaphthene



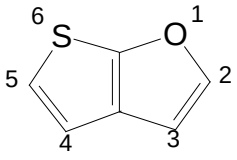
benzo[2,3]thiophene
benzo[*b*]thiophene
thionaphthene



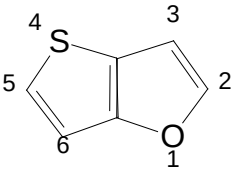
dibenzofuran
diphenylene oxide



dibenzothiophene
diphenylene sulfide

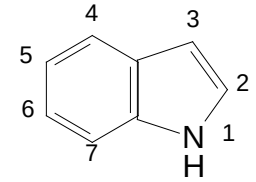


thieno[*2.3-b*]furan

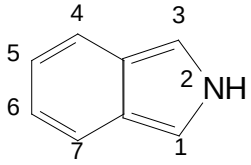


thieno[*3,2-b*]furan

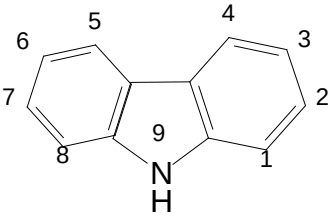
The project is supported by the European Union and
co-financed by the European Social Fund



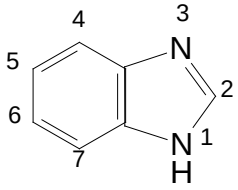
benzo[2,3]pyrrole
benzo[*b*]pyrrole
indole



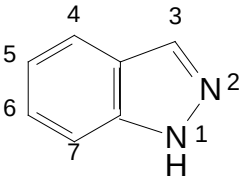
benzo[3,4]pyrrole
benzo[*c*]pyrrole
isoindole



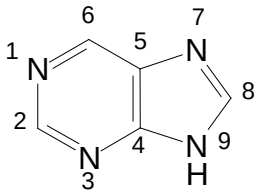
dibenzopyrrole
carbazole



benzoimidazole
benzimidazole

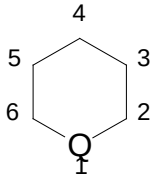


benzopyrazole
benzpyrazole

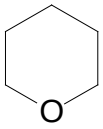


pyrimido[*4,5-d*]imidazole
purine

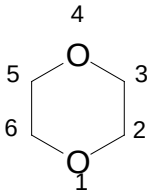
VI.8.3.4 6-membered heterocyclic rings



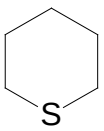
Saturated 6-membered heterocyclic rings



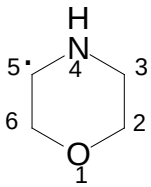
oxane
tetrahydropyran
pentamethylene oxide



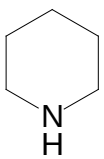
1,4-dioxane
dioxane



thiane
tetrahydrothiopyran
pentamethylene sulfide

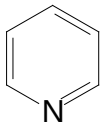


perhydro[1,4]oxazine
morpholine

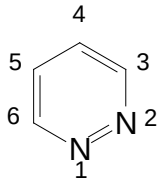


hexahydropyridine
piperidine

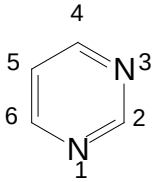
Unsaturated 6-membered heterocyclic rings



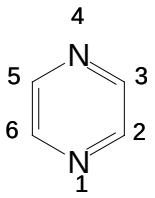
azine
pyridine



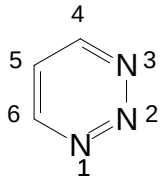
1,2-diazine
pyridazine



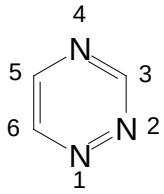
1,3-diazin
pyrimidine



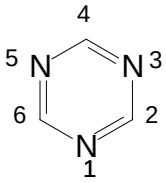
1,4-diazin
pyrazine



1,2,3-triazine
ν-triazine

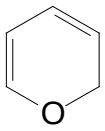


1,2,4-triazine
as-triazine

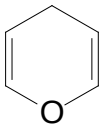


1,2,5-triazine
s-triazine

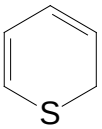
Partially saturated 6-membered heterocyclic rings



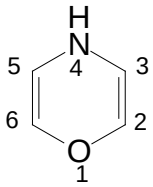
2-oxine
α-pyran
2*H*-pyran



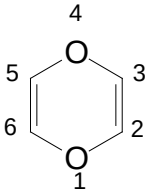
4-oxine
γ-pyran
4*H*-pyran



2-thiine
α-thiopyran
2*H*-thiopyran

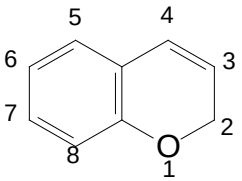


4*H*[1,4]oxazine

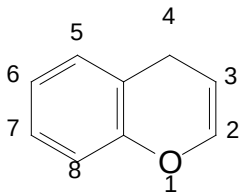


1,4-dioxine

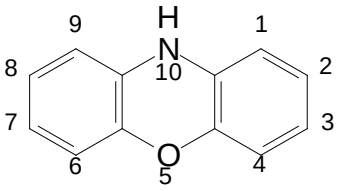
Polycyclic derivatives of 6-membered heterocyclic rings



benzo[5,6]*2H*-pyran
benzo[*e*]*2H*-pyran
α-chromone

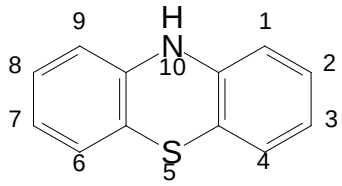


benzo[2,3]*4H*-pyrane
benzo[*e*]*4H*-pyrane
β-chromone

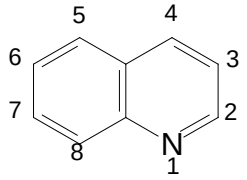


dibenzo[1,4]oxazine
phenoxazine

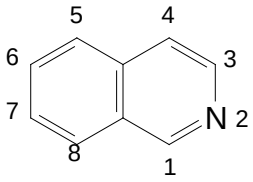
The project is supported by the European Union and
co-financed by the European Social Fund



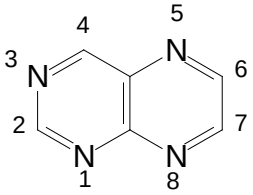
dibenzo[1,4]thiazine
phenothiazine



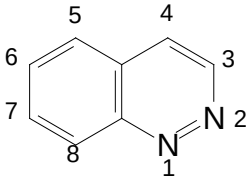
1-azanaphthalene
benzo[2,3]pyridine
benzo[*b*]pyridine
quinoline



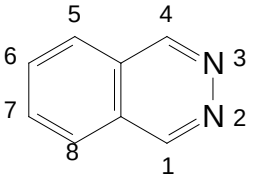
2-azanaphthalene
benzo[3,4]pyridine
benzo[*c*]pyridine
isoquinoline



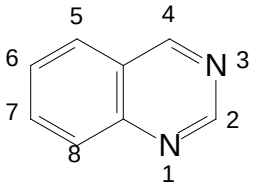
primido[*4,5-b*]pyrazine
pteridine



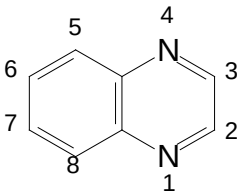
1,2-diazanaphthalene
benzo[3,4]pyridazine
benzo[*c*]diazine[1,2]
cinnoline



2,3-diazanaphthalene
benzo[4,5]pyridazine
benzo[*d*]diazine[1,2]
phthalazine

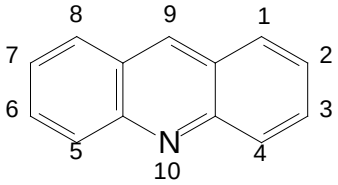


1,3-diazanaphthalene
benzopyrimidine*
benzodiazine[1,3]
quinazoline

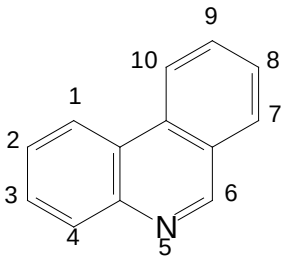


1,4-diazanaphthalene
benzopyrazine*
benzodiazine[1,4]
quinoxaline

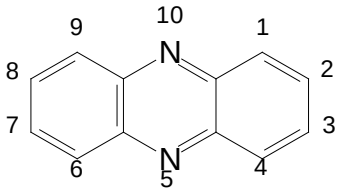
* the indiciation of the position of the anellation is unnecessary, because only one benzologe can be derived form the heterocyclic parent compound



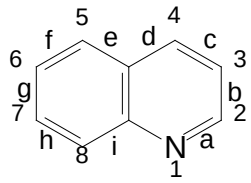
9-azaanthracene
dibenzo[2,3-5,6]pyridine
dibenzo[*b,e*]pyridine
acridine



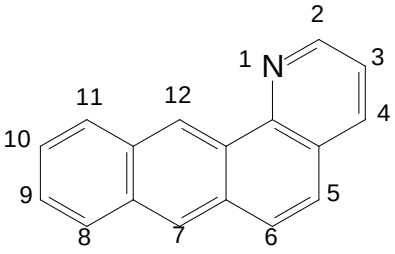
9-azaphenantrene
dibenzo[2,3-4,5]pyridine
dibenzo[*b,d*]pyridine
phenantridine



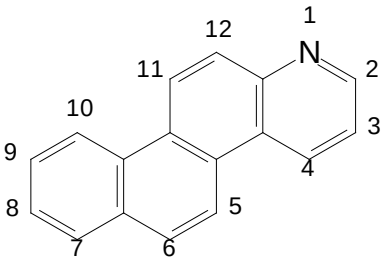
9,10-diazaantracene
dibenzopyrazine
phenazine



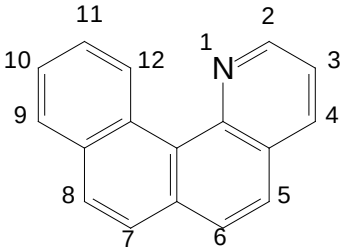
indication of the position of the bondings in the quinoline



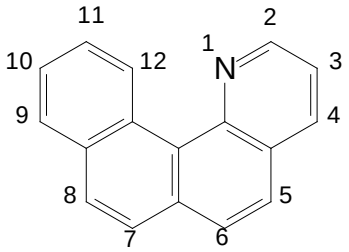
naphtho[2',3'-7,8]quinoline
naphtho[*2,3-h*]quinoline



naphtho[2',1'-5,6]quinoline
naphtho[*2,1-f*]quinoline

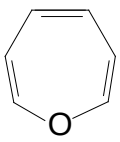


naphtho[2',1'-7,8]quinoline
naphtho[*2,1-h*]quinoline

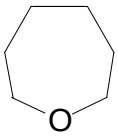


naphtho[2',1'-7,8]quinoline
naphtho[*2,1-h*]quinoline

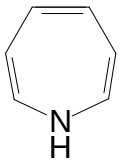
VI.8.3.5 7-membered heterocyclic rings



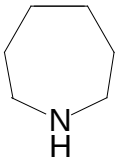
oxepine



oxepane
hexamethylene oxide



azepine



hexahydroazepine

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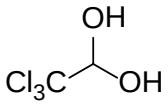
VII Pharmacopoeial qualifications of active pharmaceutical ingredients (Selection)

✙ CHLORAL HYDRATE

Chlorali hydras



$C_2H_3Cl_3O_2$ $M_r = 165.4$

DEFINITION

2,2,2-Trichloroethane-1,1-diol.
Content: 98.5 per cent to 101.0 per cent.

CHARACTERS

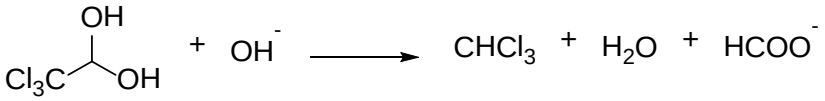
Appearance: colourless, transparent crystals.
Solubility: very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

Solution S. Dissolve 2.0 g in *carbon dioxide-free water R* and dilute the solution to 20 ml with the same solvent.

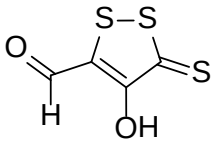
A. To 10 ml of *Solution S* add 2 ml of *dilute sodium hydroxide solution R*. The mixture becomes cloudy and, when heated, gives off an odour of chloroform.

Chloral hydrate is decomposed in alkaline solution and chloroform can be recognized of its odour.



B. To 1 ml of *Solution S* add 2 ml of *sodium sulphide solution R*. A yellow colour develops which quickly becomes reddish-brown. On standing for a short time, a red precipitate may be formed.

Ogston reaction*: the probable structure of the product (4-hydroxy-3-thioxo-3H-1,2-dithiol-5-carbaldehyde) is:*

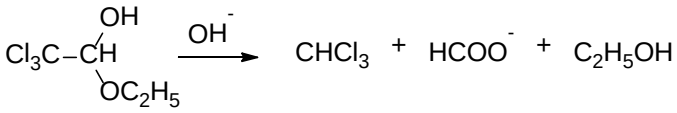


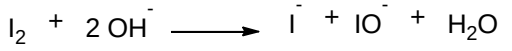
TESTS

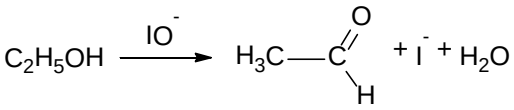
pH. The pH of *Solution S* is 3.5 to 5.5.

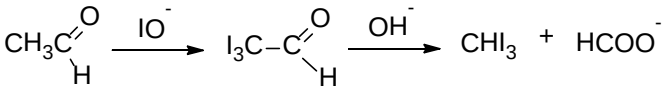
Chloral alcoholate. Warm 1.0 g with 10 ml of *dilute sodium hydroxide solution R*, filter the supernatant solution and add *0.05 M iodine* dropwise until a yellow colour is obtained. Allow the reaction mixture to stand for 1 h. No precipitate is formed.

Chloral alcoholate is an intermediate product of the production of chloral hydrate, which can be present as a contamination in the sample. Chloral alcoholate is decomposed in alkaline solution, the formed ethanol can be recognized due to the iodoform reaction.









ASSAY

Dissolve 4.000 g in 10 ml of *water R* and add 40.0 ml of *1 M sodium hydroxide*. Allow the solution to stand for exactly 2 min and titrate it with *0.5 M sulphuric acid*, using 0.1 ml of *phenolphthalein solution R* as indicator. Titrate the neutralized solution with *0.1 M silver nitrate*, using 0.2 ml of *potassium chromate solution R* as indicator. Calculate the number of milliliters of *1 M sodium hydroxide* used by deducting from the volume of *1 M sodium hydroxide*, added at the beginning of the titration, the volume of *0.5 M sulphuric acid* used in the first titration and two-fifteenths of the volume of *0.1 M silver nitrate* used in the second titration.

a) Acidimetry. A known amount of sodium hydroxide is added, chloroform and formiate ions are produced. The excess alkali is back-titrated with sulfuric acid using phenolphthalein as indicator.
b) The hydroysis of chloroform, however, also consumes NaOH. The reaction leaves chloride ions in the solution.

Any Cl^- content of the titrated solution is back-titrated with silver nitrate, using potassium chromate solution as indicator based on the Mohr method.

This titration is used to correct the result of the acidimetric titration. The amount of NaOH consumed by the hydrolysis of chloroform can be calculated and it should be used to correct the acidimetric NaOH consumption: 1 ml 0.1 M $AgNO_3$ solution is equivalent to 4/3 ml 0.1 M or 4/30 ml 1 M NaOH solution.

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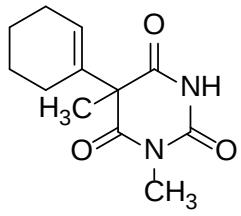
✙HEXOBARBITAL

Hexobarbitalum



$C_{12}H_{16}N_2O_3$ $M_r = 236.27$

DEFINITION

Hexobarbital contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (5*RS*)-5-(cyclohex-1-enyl)-1,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione, calculated with reference to the dried substance.

CHARACTERS

A white or almost white crystalline powder, very slightly soluble in water, sparingly soluble in alcohol. It forms water-soluble compounds with alkali hydroxides and carbonates and with ammonia.

IDENTIFICATION

C. Examine it by thin-layer chromatography, using *silica gel* GF_{254} *R* as the coating substance.

Test solution. Dissolve 0.1 g of the substance to be examined in *chloroform R* and dilute the solution to 100 ml with the same solvent.

Reference solution. Dissolve 0.1 g of *hexobarbital CRS* in *chloroform R* and dilute the solution to 100 ml with the same solvent.

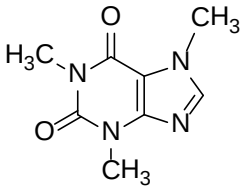
Apply 10 µl volumes of each solution separately to the plate.

Develop over a path of 18 cm using the lower layer of a mixture of 5 volumes of *concentrated ammonia R*, 15 volumes of *alcohol R* and 80 volumes of *chloroform R*. Examine immediately in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. To about 10 mg add 1.0 ml of a 10 g/l solution of *vanillin R* in *alcohol R* and 2 ml of a cooled mixture of 1 volume of *water R* and 2 volumes of *sulphuric acid R*. Shake the mixture and allow it to stand for 5 min. A greenish-yellow colour develops. Heat it on a water-bath for 10 min. The colour becomes dark red.

CAFFEINE

Coffeinum



$C_8H_{10}N_4O_2$ $M_r = 194.2$

DEFINITION

Caffeine contains not less than 98.5 per cent and not more than the equivalent of 101.5 per cent of 1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione, calculated with reference to the dried substance.

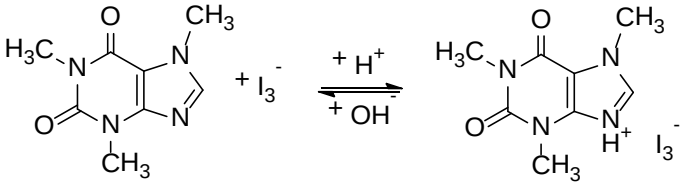
CHARACTERS

White or almost white, crystalline powder or silky crystals, sublimes readily, sparingly soluble in water, freely soluble in boiling water, slightly soluble in ethanol. It dissolves in concentrated solutions of alkali benzoates or salicylates.

IDENTIFICATION

C. To 2 ml of saturated solution add 0.05 ml of *iodinated potassium iodide solution R*. The solution remains clear. Add 0.1 ml of *dilute hydrochloric acid R*. A brown precipitate is formed. Neutralise it with *dilute sodium hydroxide solution R*. The precipitate dissolves.

Caffeine, similar to other xanthine derivatives, is protonated in strongly acidic solutions and forms a precipitate with triiodide ions. Upon the addition of an alkali, the caffeine cation is deprotonated and the precipitate is dissolved. Many other alkaloid cations react in the same way.



D. In a glass-stoppered tube, dissolve about 10 mg in 0.25 ml of a mixture of 0.5 ml of *acetylacetone R* and 5 ml of *dilute sodium hydroxide solution R*. Heat the solution in a water-bath at 80 ºC for 7 min. Cool it and add 0.5 ml of *dimethylaminobenzaldehyde solution R2*. Heat the solution again in a water-bath at 80 ºC for 7 min. Allow it to cool and add 10 ml of *water R*. An intense blue colour develops.

In alkaline medium the pyrimidine ring of caffeine is cleaved by hydrolysis and caffeidine is formed. It reacts with acetylacetone, and then, after an intramolecular condensation it condensates with 2 molecules of dimethylaminobenzaldehyde to form a blue dye. The reaction is specific to caffeine, as theobromine hydrolyses slower in alkaline medium, and as the product of the hydrolysis of theophylline (theophyllidine), reacts with its imidazole ring.

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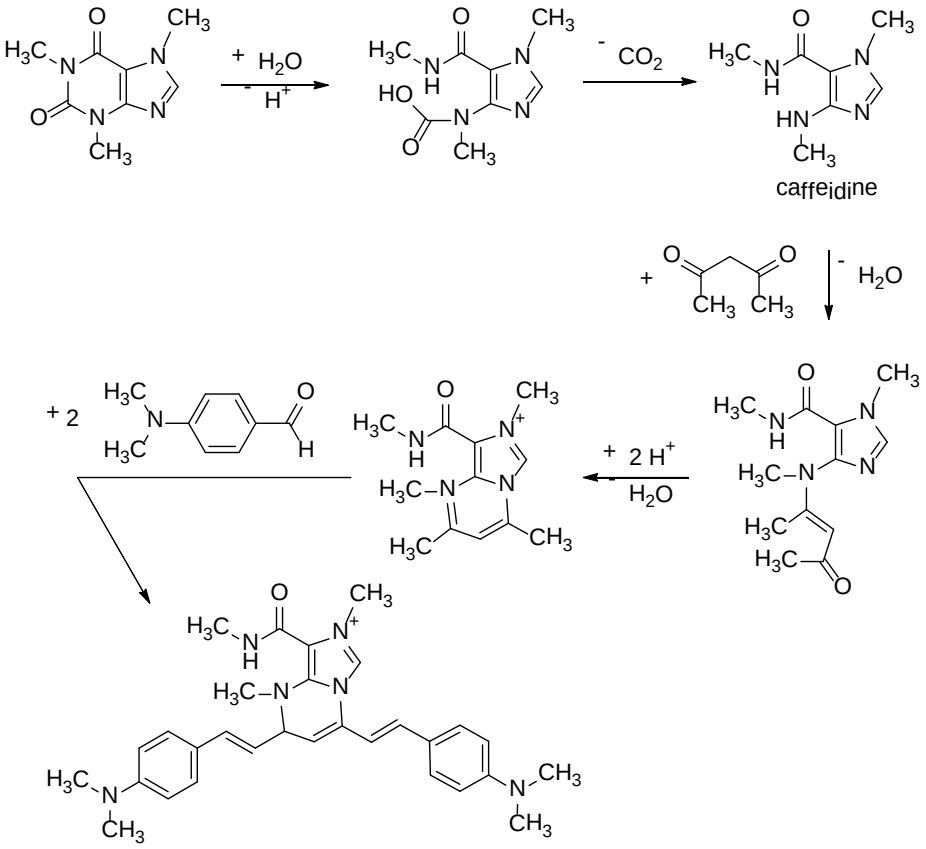
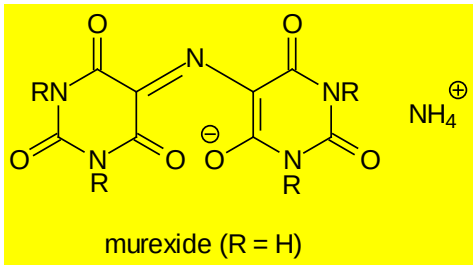


F. Xanthines. To a few milligrams add 0.1 ml of *strong hydrogen peroxide solution R* and 0.3 ml of *dilute hydrochloric acid R*. Heat it to dryness on a water-bath until a yellowish-red residue is obtained. Add 0.1 ml of *dilute ammonia R2*. The colour of the residue changes to violet-red.

Murexide and its methyl derivatives are formed.



TESTS

Related substances. Examine by thin-layer chromatography using *silica gel GF_{254} R* as the coating substance.

Test solution. Dissolve 0.2 g of the substance to be examined in a mixture of 4 volumes of *methanol R* and 6 volumes of *methylene chloride R* and dilute the solution to 10 ml with the same solvent.

Reference solution. Dilute 0.5 ml of the test solution to 100 ml with a mixture 4 volumes *methanol R* and 6 volumes of *methylene chloride R.*

Apply 10 µl of each solution to the plate. Develop over a path of 15 cm using a mixture of 10 volumes of *concentrated ammonia R*, 30 volumes of *acetone R*, 30 volumes of *methylene chloride R* and 40 volumes of *butanol R.* Allow the plate to dry in air and examine it in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with the reference solution (0.5 per cent).

Sulphates. maximum 500 ppm.

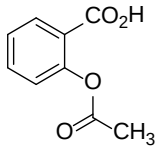
Dissolve 0.15 g with heating in 15 ml of *carbon dioxide-free water R* prepared from *distilled water R.*

Add 3 ml of a 250 g/l solution of *barium chloride R* to 4.5 ml of *sulphate standard solution (10 ppm SO_4) R1*. Shake the mixture and allow it to stand for 1 min. To 2.5 ml of this solution, add 15 ml of the solution to be examined and 0.5 ml of *acetic acid R*. Prepare the standard in the same manner using a mixture of 7.5 ml of *sulphate standard solution (10 ppm SO_4) R* and 7.5 ml of *distilled water R* instead of the solution to be examined.

After 5 min, any opalescence in the test solution is not more intense than that in the standard.

ACETYLSALICYLIC ACID

Acidum acetylsalicylicum



$C_9H_8O_4$ $M_r = 180.2$

DEFINITION

2-(Acetyloxy)benzoic acid.

Content: 99.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless crystals.

Solubility: slightly soluble in water, freely soluble in ethanol (96 per cent).

Mp: about 143 ºC (instantaneous method).

IDENTIFICATION

C. In a test-tube mix 0.1 g with 0.5 g of *calcium hydroxide R*. Heat the mixture and expose to the fumes produced a piece of filter paper impregnated with 0.05 ml of

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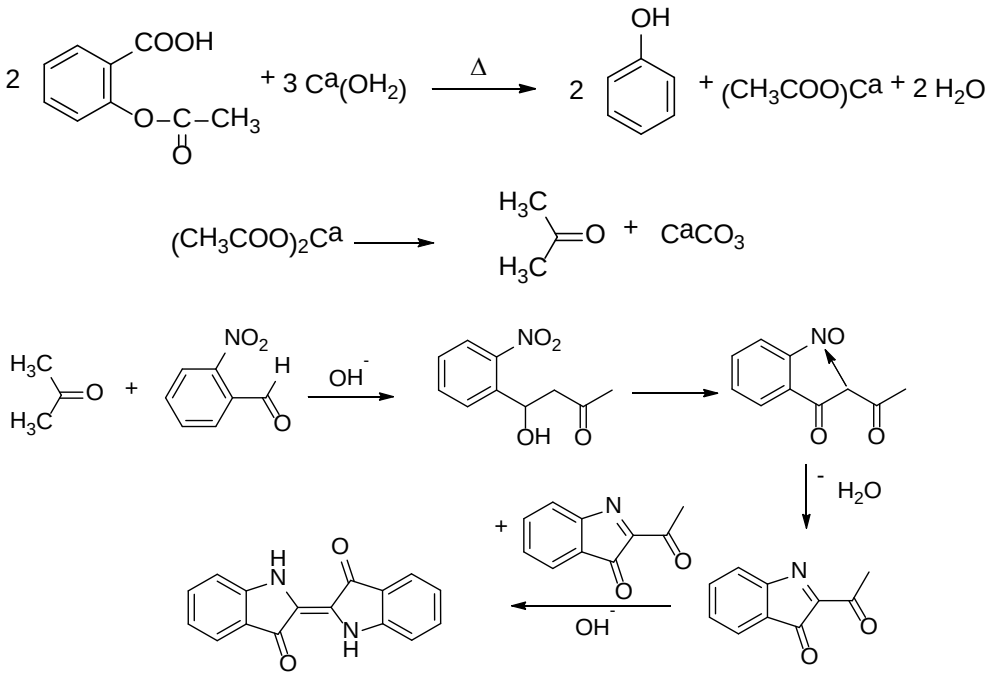
nitrobenzaldehyde solution R. A greenish-blue or greenish-yellow colour develops on the paper. Moisten the paper with *dilute hydrochloric acid R*. The colour becomes blue.

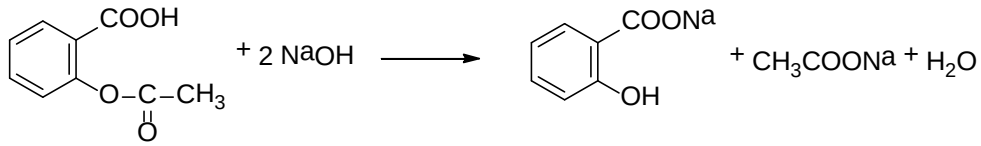
Calcium acetate is formed by heating that decomposes into calcium carbonate and acetone. Blue indigo is formed from the reaction of acetone and nitrobenzaldehyde.



ASSAY

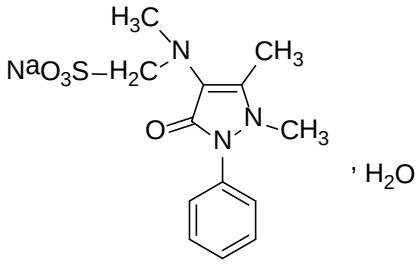
In a flask with a ground-glass stopper, dissolve 1.000 g in 10 ml of *ethanol (96 per cent) R*. Add 50.0 ml of *0.5 M sodium hydroxide*. Close the flask and allow it to stand for 1 h. Using 0.2 ml of *phenolphthalein solution R* as indicator, titrate it with *0.5 M hydrochloric acid*. Carry out a blank titration.

Hydrolysis of acetylsalicylic acid takes place in the alkaline solution. The excess of the known amount of NaOH is back-titrated with HCl.



+METAMIZOLE SODIUM

Metamizolum natricum



$C_{13}H_{16}N_3NaO_4S \cdot H_2O$ $M_r = 351.4$

DEFINITION

Sodium [1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-N-methylamino] methanesulphonate monohydrate.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

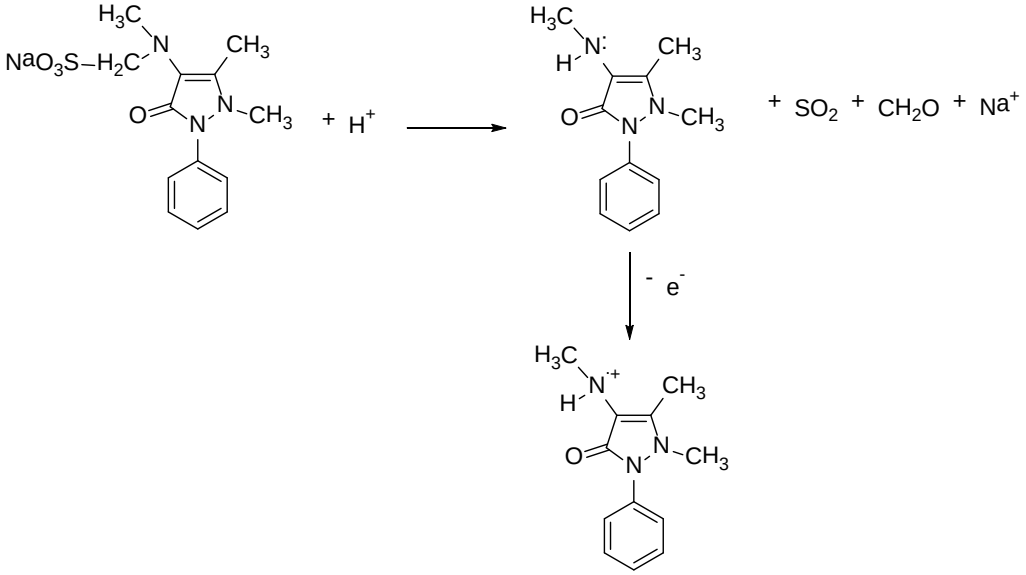
Appearance: white or almost white, crystalline powder.

Solubility: very soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

B. Dissolve 50 mg in 1 ml of *strong hydrogen peroxide solution R*. A blue colour is produced which fades rapidly and turns to intense red in a few minutes.

During hydrolysis the methanesulphonic acid moiety is cleaved and the noraminophenazone residue is oxidized, in the first step a blue cation radical is formed.



The cation radical takes part in additional oxidation processes (red colour).

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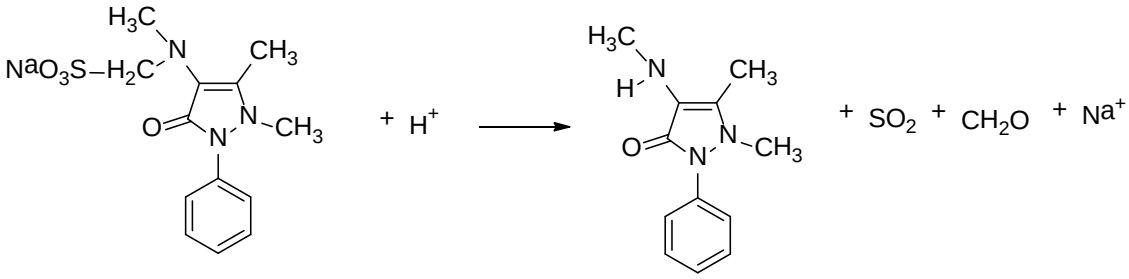
C. Place 0.10 g in a test-tube, add some glass beads and dissolve the substance in 1.5 ml of *water R*. Add 1.5 ml of *dilute hydrochloric acid R* and place a filter paper wetted with a solution of 20 mg of *potassium iodate R* in 2 ml of *starch solution R* at the open end of the test-tube. Heat the tube gently, the evolving vapour of sulphur dioxide colours the filter paper blue. After heating gently for 1 min take a glass rod with a drop of a 10 g/l solution of *chromotropic acid, sodium salt R* in *sulphuric acid R* and place in the opening of the tube. Within 10 min, a blue-violet colour develops in the drop of the reagent.



During hydrolysis sulphur dioxide is formed that reduces iodate to iodine, which forms a blue coloured complex with starch.

$$5\ SO_2 + 2\ IO_3^- + 4\ H_2O = 5\ SO_4^{2-} + I_2 + 8\ H^+$$

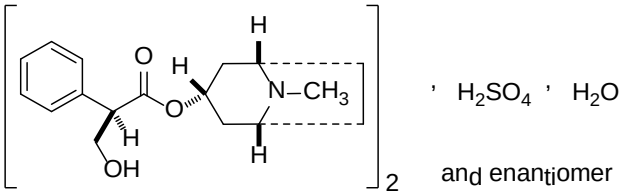
Formaldehyde produced during hydrolysis can be identified by its reaction with chromotropic acid. (See the monograph of Ethanol.) Sulphuric acid acts as a hygroscopic and oxidizing agent.

D. Sodium. Dissolve 0.1 g in 2 ml of *water R*. Add 2 ml of a 150 g/l solution of *potassium carbonate R* and heat the mixture to boiling. No precipitate is formed. Add 4 ml of *potassium pyroantimonate solution R* and heat it to boiling. Allow it to cool in iced water and if necessary rub the inside of the test-tube with a glass rod. A dense white precipitate is formed.

See Identification reactions: Sodium.

++ ATROPINE SULPHATE

Atropini sulfas



$C_{34}H_{48}N_2O_{10}S \cdot H_2O$ $M_r = 695$

DEFINITION

Atropine sulphate contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of bis[(1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-3-hydroxy-2-phenylpropanoate] sulphate, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, crystalline powder or colourless crystals, very soluble in water, freely soluble in alcohol.

It melts at about 190 ºC with decomposition, determined on the substance dried at 135 ºC for 15 min.

IDENTIFICATION

D. To about 1 mg add 0.2 ml of *fuming nitric acid R* and evaporate to dryness in a water-bath. Dissolve the residue in 2 ml of *acetone R* and add 0.1 ml of a 30 g/l solution of *potassium hydroxide R* in *methanol R*. A violet colour develops.

Vitali reaction: *In concentrated nitric acid the benzene ring is nitrated in para position and the alcoholic hydroxyl group forms an ester. This ester is unstable in aqueous solutions and with the elimination of a nitric acid molecule transforms into 4'-nitroapoatropine (it can also be formed directly from atropine). Its nitrate is yellow. In alkaline solutions, after a Michael addition of water and subsequent loss of a proton, a violet anion with many mesomeric structures is formed. The added acetone (modification of the Vitali reaction by Morin) increases the sensitivity of the reaction, but also renders it less specific. 4'-nitroatropine formes a coloured Meisenheimer complex with the anion of acetone. Other compounds with an activated methylene group and a nitratable benzene ring can also react. Esters with a tropane skeleton but containing mandelic acid do not react, because nitric acid oxidizes secondary alcoholic groups to ketones, thus the anion with mesomeric structures cannot be formed.*

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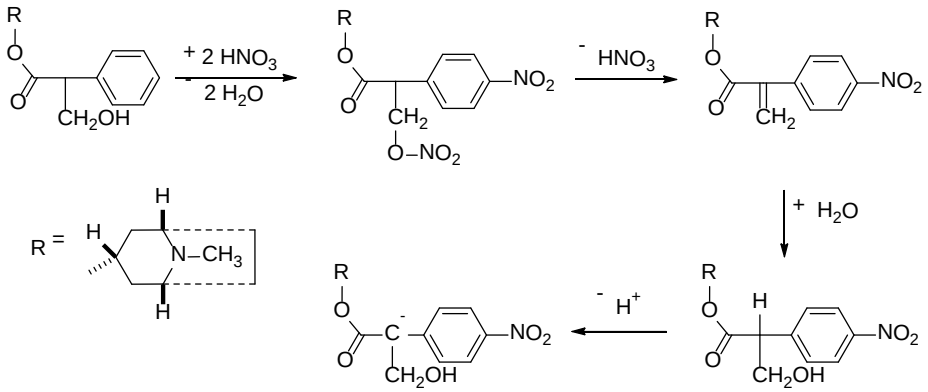


E. Sulphates. Dissolve about 45 mg in 5 ml of *water R.* Add 1 ml of *dilute hydrochloric acid R* and 1 ml of *barium chloride solution R1*. A white precipitate is formed.

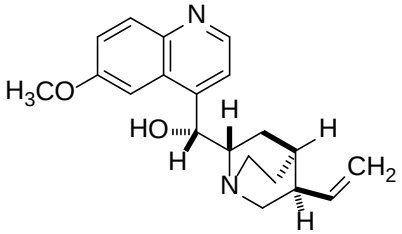
See Identification reactions of iones: Sulphates.

F. Alkaloids. Dissolve a few milligrams in 5 ml of *water R,* add *dilute it with hydrochloric acid R* until an acid reaction occurs, then 1 ml of *potassium iodobismuthate solution R*. An orange or orange-red precipitate is formed immediately.

See Identification reactions of functional groups: Alkaloids.

QUININE HYDROCHLORIDE

Chinini hydrochloridum



, HCl , 2 H_2O

$C_{20}H_{25}ClN_2O_2 \cdot 2\ H_2O$ $M_r = 396.9$

DEFINITION

Content: 99.0 per cent to 101.0 per cent of alkaloid monohydrochlorides, expressed as (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl](6-methoxyquinolin-4-yl)methanol hydrochloride (dried substance).

CHARACTERS

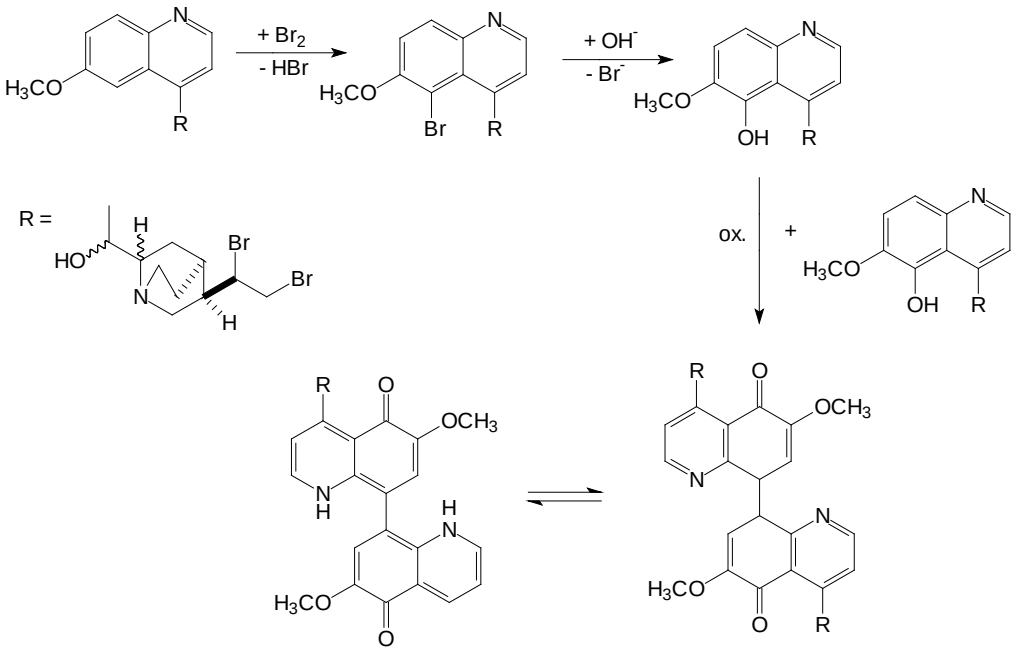
Appearance: white or almost white or colourless, fine, silky neddles, often in clusters.

Solubility: soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

B. Dissolve about 10 mg in *water R* and dilute the solution to 10 ml with the same solvent. To 5 ml of this solution add 0.2 ml of *bromine water R* and 1 ml of *dilute ammonia R2.* A green colour develops.

Thalleioquin reaction*: precondition of a positive reaction is the presence of an oxygen-containing functional group on the quinoline ring at C6. The observed green colour belongs to a mixture containing a red and a blue radical of yet unknown structure.*



C. Dissolve a 0.1 g in 3 ml of *dilute sulphuric acid R* and dilute the solution to 100 ml with *water R*. When examined in ultraviolet light at 366 nm, an intense blue fluorescence appears which disappears almost completely on the addition of 1 ml of *hydrochloric acid R*.

Fluorescence can be observed in the presence of oxygen-containing acids, another precondition of a positive reaction is in the presence of an oxygen-containing functional group on the quinoline ring at C6. Halide ions quench the fluorescence.

D. Chlorides. Dissolve 0.1 g in 2 ml *water R*. Acidify the solution with *dilute nitric acid R* and add 0.4 ml of *silver nitrate solution R1*. Shake and allow it to stand. A curled, white precipitate is formed, which dissolves easily in 1.5 ml of *ammonia R*.

See Identification reactions: Chloride ions.

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