Monosaccharides

1. MONOSACCHARIDES: STRUCTURE AND PROPERTIES

The following will assume that the reader is familiar with the structure and chemical properties of monosaccharides, and with the methods of study specific to this group, as well as with their biosynthesis, catabolism, and biological functions.

The principle and practice of characterization and measurement methods for monosaccharides and their derivatives, including chromatographic techniques (TLC, HPLC, GC), are detailed in classical biochemistry and analytical chemistry

textbooks, therefore they will not be covered here; moreover, several recent reviews are available (see bibliography).

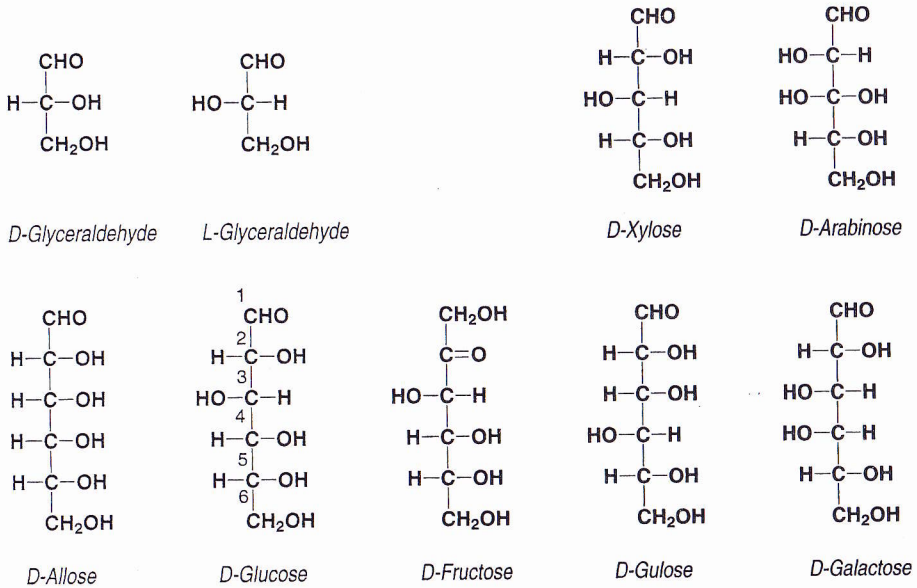
The introduction will merely be a reminder of elementary terminology and nomenclature specific to this group.

Naming

In general the naming of monosaccharides is based on the number of carbon atoms in the molecule: tetroses, pentoses, hexoses, heptoses..., and on the nature of their carbonyl function (for example D-ribose and D-xylose are aldoses, D-ribulose and D-xylulose are ketoses). The numbering of the carbon atoms begins with the aldehyde carbon, or, for ketoses, so as to give the ketone carbon the lower possible number.

D- and L-Series

Consider the simplest monosaccharide, glyceraldehyde (an aldotriose): it has one asymmetric carbon, so there are two enantiomers, (*R*) and (*S*). D-glyceraldehyde and L-glyceraldehyde are defined arbitrarily and by convention as having the secondary hydroxyl group on the right or on the left side of the molecule, respectively, in the Fischer projection (vertical representation, aldehyde carbon at the top).



D-Glyceraldehyde *L-Glyceraldehyde* *D-Xylose* *D-Arabinose*

D-Allose *D-Glucose* *D-Fructose* *D-Gulose* *D-Galactose*

Linear representation of monosaccharides: principal D-series monosaccharides

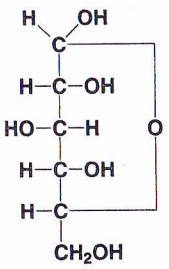
The four other hexoses are epimers at C-2 and are not shown: D-altrose (epimer of D-allose), D-mannose (epimer of D-glucose), D-idose (epimer of D-gulose) and D-tallose (epimer of D-galactose). The same applies to the two other pentoses, D-ribose and D-xylose.

Again by convention and by reference to glyceraldehyde, it is the orientation of the hydroxyl group most distant from the carbonyl group that determines if a monosaccharide belongs to the D or to the L series. Because this rule is arbitrary, the fact that a sugar belongs to either series does not predict its optical activity. The vast majority of natural monosaccharides belong to the D series (exceptions: L-rhamnose, L-arabinose, and L-fucose).

Cyclic Structure of Monosaccharides

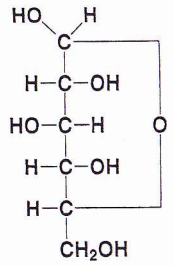
The particular chemical behavior of monosaccharides (see general biochemistry textbooks) has led to the postulate that they exist in a cyclic form involving the carbonyl group and one hydroxyl group. The principal consequences are as follows:

- depending on the nature of the bridge (1-4 or 1-5), the cycle is either a furan or a pyran (furanoses and pyranoses);
- generally, aldohexoses form pyranose rings and ketohexoses form furanose rings;
- cyclization leads to two isomeric hemiacetals, α and β, called anomers. The configuration of the anomeric carbon is α when the hemiacetal hydroxyl group is in the same orientation as the secondary hydroxyl group that determines the series, i.e., on the right side of the chain for the D series (in the Fischer projection). In the opposite case (on the left side for the D series) the configuration is β.



α-D-Glucopyranose

Cyclic form of monosaccharides: Fischer projection



β-D-Glucopyranose

Perspective Representation

This representation (Haworth projection) allows for better visualization of the cyclic form of monosaccharides. Keeping the cycle in the horizontal plane, those substituents that were on the right in the Fischer projection are projected down and those that were on the left are projected up. On cyclization, the hydroxymethyl group of pyran-type aldohexoses is brought above the plane in the D series, and below the plane in the L series.

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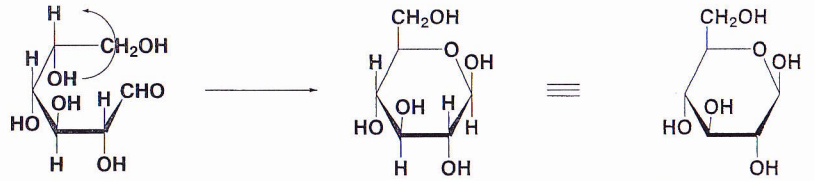
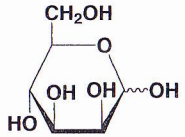
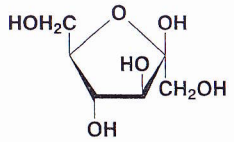


Cyclisation of D-glucose : β-D-glucopyranose

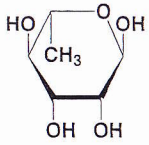
Haworth projection



D-Mannose



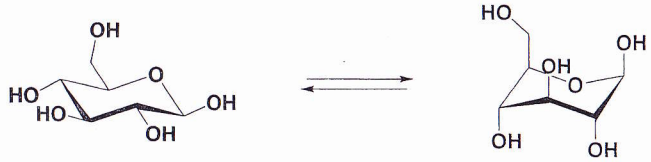
β-D-Fructofuranose



α-L-Rhamnose

Monosaccharide Conformation

Since the carbons in the cycle are sp^3, the latter may not be planar, and it adopts various conformations: chair, boat, half-chair... The preferred conformation is always the most stable: in the case—by far the most frequent—of aldohexopyranoses, it is the chair conformation that presents the minimal interactions, thus has lowest energy and is favored. Since the hydroxymethyl and secondary hydroxyl



$^4C_1$ $^1C_4$

β-D-Glucopyranose conformations

groups exert mutual repulsion forces, it is the *configuration* of the carbon atoms bearing these hydroxyl groups that determines the most stable conformation as that which places the largest number of substituents in the equatorial position. For example, in the case of D-glucopyranose, it is the β anomer that predominates in glucose solutions at equilibrium, and the favored *conformation* is $^4C_1$, the conformation in which all of the substituents are equatorial (in the case of the $^1C_4$ conformation all of the substituents are axial and the interactions are stronger*).

* Such a conformation may occur, however, when it is engaged in complex edifices; see certain ellagitannins (p. 373) and internal esters of algal polysaccharides.

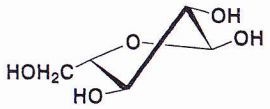
2. PRINCIPAL PLANT MONOSACCHARIDES

What characterizes plant monosaccharides is their great diversity: pentoses, deoxypentoses, hexoses, deoxyhexoses, dideoxyhexoses, uronic acids, polyalcohols, esters, ethers, and more. Several hundred compounds, some ubiquitous, some highly specific to a plant group, have been described. Some occur free, others are only known in glycosidic combinations; very often they are included in polymers. We shall cite, as examples, some sugars and derivatives which are among the most common in higher plants.

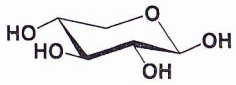
Tetroses. The four possible isomers of these monosaccharides form two pairs of enantiomers: D- and L-threose on the one hand, D- and L-erythrose on the other hand. They do not occur free. D-erythrose-4-phosphate plays a key role in the genesis of aromaticity (see phenolic compounds: shikimates, p. 233).

Pentoses. D-Ribose is universal (nucleic acids) and its phosphoric esters have a fundamental metabolic importance. The same applies to the corresponding ketose, D-ribulose.

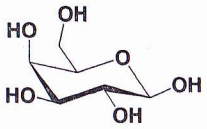
L-arabinose and D-xylose are common constituents of complex polysaccharides: hemicelluloses (xyloglucans, xylans, glucuronoxylans, arabinoxylans, glucurono-arabinoxylans), pectic polysaccharides, mucilages and plant secretion polymers (gums). They are encountered in various glycosides, particularly phenolic ones.



α-*L-Arabinofuranose*



β-*D-Xylopyranose*



β-*D-Galactose*

Hexoses. Most are virtually ubiquitous: such is the case for D-glucose and for D-mannose (2-epimer of D-glucose), and also for D-galactose (4-epimer of glucose). Although glucose is commonly free, as well as combined into polysaccharide structures (starch, cellulose, and other glucans), its 2- and 4-epimers are almost exclusively known as polymers (for example, mannans, gluco- and galactomannans of Fabaceae). D-galactose is rather common in glycosides.

The ketose corresponding to D-glucose and D-mannose is D-fructose. Abundant in the free state in fruits, it is just as common as a disaccharide (sucrose). It also occurs in oligosaccharides, for example galactose-containing derivatives of sucrose: raffinose, stachyose, and their higher homologs. This ketose can also form reserve polymers, the fructans (inulins, phleins).

Within oligomers and polymers, D-fructose is present in the form of β-D-fructo-furanose, whereas in the free state, the more stable β-D-fructopyranose form is favored. Other hexoses are much rarer in higher plants (e.g., D-allose, D-idose).

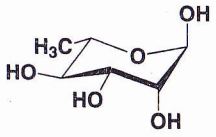
Deoxysugars. Except for 2-deoxyribose, which is ubiquitous as a DNA component, it is mostly in plants that sugars occur in which one or two alcohol functions have been eliminated by reduction; examples are 6-deoxyhexoses and 2,6-dideoxyhexoses.

• 6-Deoxyhexoses. Also called (improperly) 6-methylpentoses, in some cases they are very widespread, as is L-rhamnose (= 6-deoxy-L-mannose), a constituent of heterogeneous polysaccharides and of countless glycosides. In other cases, they have a narrower distribution. Thus L-fucose, which is 6-deoxy-L-galactose, is characteristic of the polymers from Phaeophyceae algae, and of certain gums (tragacanth gum). D-Quinovose (= 6-deoxy-D-glucose) is the sugar moiety of the triterpenoid aglycone-containing glycosides present in *Cinchona* spp.

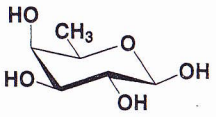
Some 6-deoxyhexoses occur as methyl ethers and are specific to cardiotonic glycosides, such as L-thevetose (= 6-deoxy-3-*O*-methyl-L-glucose) and D-digitalose (=6-deoxy-3-*O*-methyl-D-galactose).

• 2,6-Dideoxyhexoses. These sugars, as those above, are often methylated and specific to cardiac glycosides, including D-digitoxose (= 2,6-dideoxy-D-allose), L-oleandrose (= 2,6-dideoxy-3-*O*-methyl-L-mannose), and D-cymarose (= 2,6-dideoxy-3-*O*-methyl-D-allose).

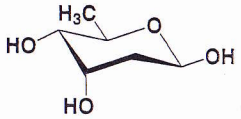
Uronic Acids. Uronic acids are the products of hexose oxidation by specific dehydrogenases in which the primary alcohol function is oxidized to a carboxylic acid. D-Glucuronic acid and D-galacturonic acid are normal constituents of parietal polysaccharides (particularly pectin), of mucilages (e.g., marshmallow), and of most polysaccharide-containing secretions (e.g., *Sterculia* gum). Other acids are less frequent, but are also constituents of polymers, such as D-mannuronic acid and L-guluronic acid, from which alginic acid arises in the genus *Fucus*.



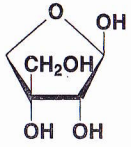
α-*L-Rhamnose*



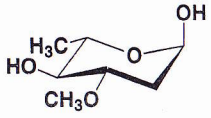
β-*D-Fucose*



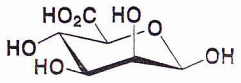
β-*D-Digitoxose*



β-*D-Apiose*

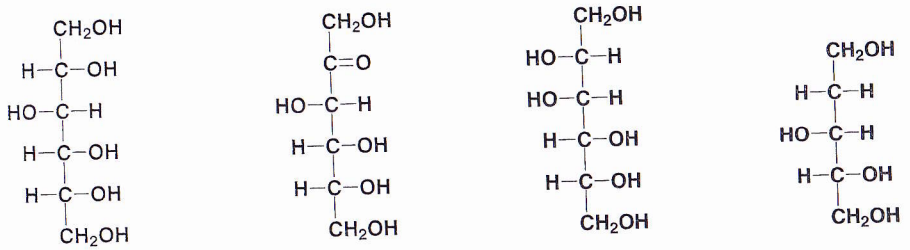


α-*L-Oleandrose*



β-*D-Mannuronic acid*

Polyalcohols. Polyalcohols result from the reduction of the carbonyl function of monosaccharides. Although D-glucitol, D-mannitol, and *meso*-galactitol are fairly widespread, others are distributed sporadically, for example *meso*-erythritol in the primrose roots and D-glycero-D-galacto-heptitol in the avocado tree. They sometimes accumulate in certain fruits (D-sorbitol), in secretions, or in some algal (D-mannitol). [Note: these "alditols" should not be confused with cyclic polyalcohols.]



Amino Sugars. Amino sugars are fundamental constituents of bacterial polysaccharides. They are polymerized in arthropods and crustaceans (chitin), are constituent parts of animal glycoproteins, and they are present in some fungi but rare in higher plants (for example, 2-acetamido-2-deoxy-D-glucose of glycoproteins and glycolipids).

Branched Sugars. Branched sugars are frequent in fungi and exceptional in higher plants. They do not occur in the free state, but as esters (D-hamamelose = 2-C-[hydroxymethyl]-D-ribose, see tannins) or as glycosides (D-apiose = 3-C-[hydroxymethyl]-glyceroaldotetrose, see apioside, frangulin, onjisaponins, among others).

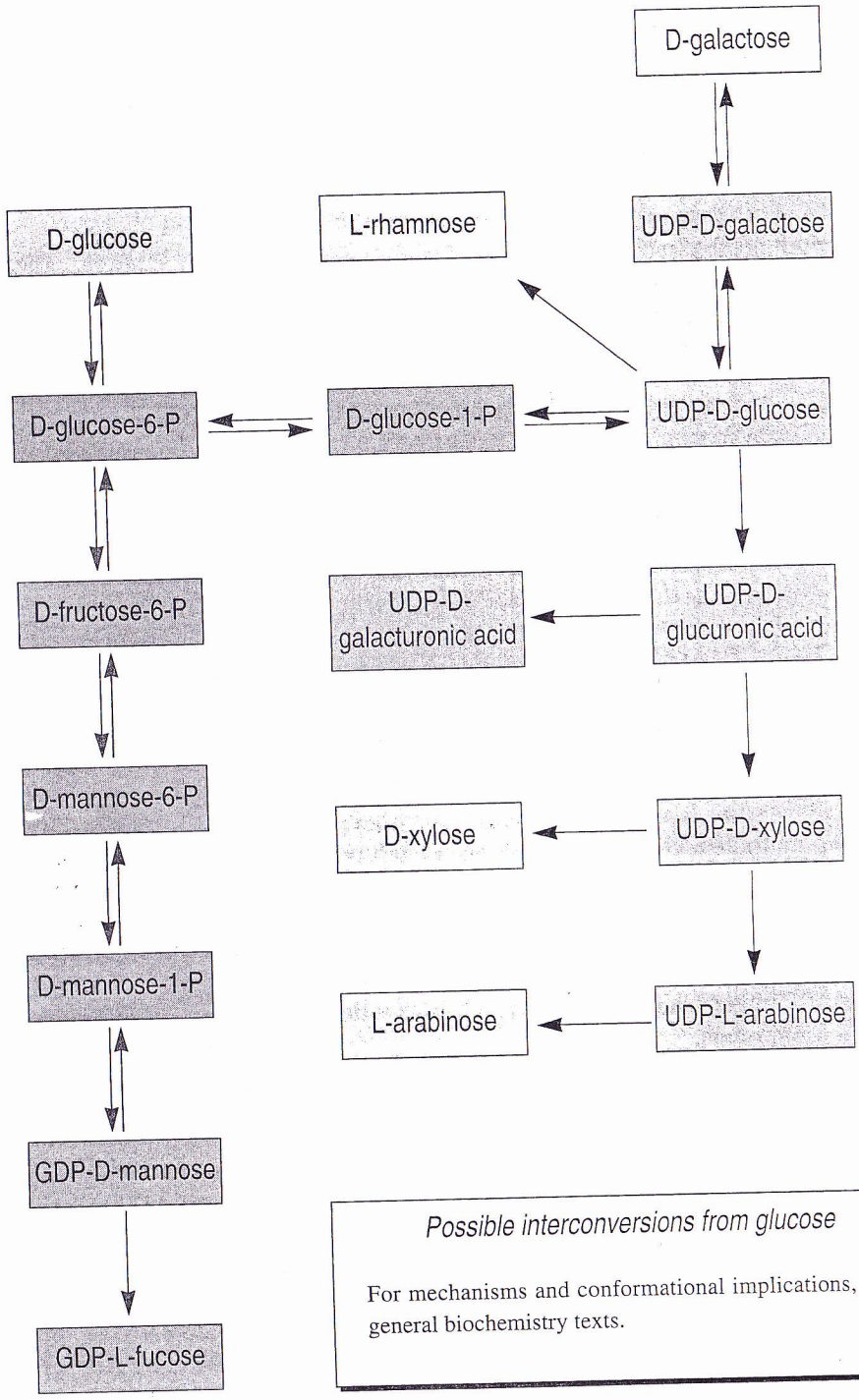
The structural diversity of monosaccharides is easy to understand when considering the numerous possibilities for interconversion and isomerization within a series. The following table summarizes the main interconversions that D-glucose can undergo. Interconversions within a series involve the monosaccharide as a nucleotide diphosphate, whereas epimerization at C-2 proceeds through phosphoric esters.

3. PRINCIPAL MONOSACCHARIDES USED IN PHARMACY

A. D-Glucose

Although it is present in substantial quantities in many plant species, glucose is not extracted for commercial use. It is prepared by enzymatic hydrolysis of starch through the combined action of α-amylase and amyloglucosidase (see below).

The 3rd edition of the European Pharmacopoeia devotes monographs to three different forms of glucose: anhydrous glucose, glucose monohydrate, and liquid glucose (1999 add.). The 10th edition of the French Pharmacopoeia describes



Possible interconversions from glucose

For mechanisms and conformational implications, see general biochemistry texts.

anhydrous and monohydrated glucose for drug pre-mixes. These glucoses must pass rigorous tests: solubility, neutrality, test for absence of starch and dextrins, and limit tests for sulfites, chlorides, sulfates, barium, arsenic, cadmium, and lead. The difference between the two French official glucose powders is that the second one is the monohydrate (water between 7 and 9.5%). Official liquid glucose has a DE>20 —the DE is the *dextrose equivalent* or percentage of reducing sugars relative to the dry matter, expressed as glucose (dextrose).

Glucose is prepared for parenteral administration in aqueous solution. The indications for injectable solutions (at 5 and 10%) are the following: prevention of intra- and extracellular dehydration; common rehydration (when the water loss exceeds loss of sodium chloride and other electrolytes); prophylaxis and treatment of ketosis in malnutrition. These solutions are a means of caloric intake, as well as vehicles for therapeutic administration in the immediate pre- through postoperative periods. The hypertonic injectable solutions (at 15, 20, 30, and 50%) are intended for parenteral feeding (caloric intake) and for the treatment of hypoglycemia. Their administration (by slow perfusion) is carried out with biological monitoring (glycosuria, acetonuria, blood potassium level) with insulin and potassium supplementation as needed; they are contraindicated in cases of water retention.

B. Other Starch Industry Products

Industrial products from starch include maltodextrins, glucose syrups, fructose syrups, and liquid glucose.

• Maltodextrins have a low *dextrose equivalent* (DE<20). White dextrin is, according to the latest edition of the French Pharmacopoeia, a "mixture of polysaccharides resulting from the partial hydrolysis of starch". It is a white powder which, upon suspension in water, gives a thick liquid. The assay includes, in addition to the common tests (ashes, loss on drying, and more), a quantitation of the reducing sugars (limit 7.5%). Maltodextrins are used in infant food products, in adhesives for surgical bandages, and as a pharmaceutical aid for granulation, or as a carrier in atomization.

• Glucose syrups are characterized by their DE and by the *degree of polymerization* (DP) of the saccharides that constitute them. Syrups with low DE (20-30) still contain 40 to 50% saccharides of DP>7. The syrups richest in glucose have a DE of 95% and are composed of over 90% glucose (DP 1). They are mostly used in food technology.

• Glucose syrups enriched in fructose (HFCSs, *high fructose corn syrups*) are also called "isoglucoses". They contain 40 to 90% fructose and are prepared by enzymatic conversion of glucose syrups followed, for the HFCS 80-90, by glucose separation by chromatography on resins. HFCSs, mainly HFCS-42 and HFCS-55, may be used as sweeteners in liquid preparations. They are widely used in food technology (e.g., in carbonated beverages, dairy products, and bakery products; annual world production, 8.2 million metric tons in 1995).

C. D-Fructose

Present in practically all fruits, as well as in honey, D-fructose can be obtained industrially by hydrolyzing inulin (a polymer characteristic of certain Asteraceae: Jerusalem artichoke and chicory, among others), by separation from invert sugar*, or from HFCSs. D-Fructose appears as levulose in the latest edition of the French Pharmacopoeia. It must pass tests similar to those for glucose.

It can be used for parenteral feeding. It is also an interesting sugar in the diet of certain diabetics and for exercise nutrition: its intestinal resorption is slow and does not trigger insulin secretion; its metabolism is hepatic. It is also a sweetener in the food context: its sweetening power is 1.7 times that of sucrose.

4. MONOSACCHARIDE DERIVATIVES USED IN PHARMACY

A. D-Sorbitol (= D-glucitol, Eur. Ph., 3rd Ed.: sorbitol, 70% sorbitol [crystallizable and noncrystallizable]).

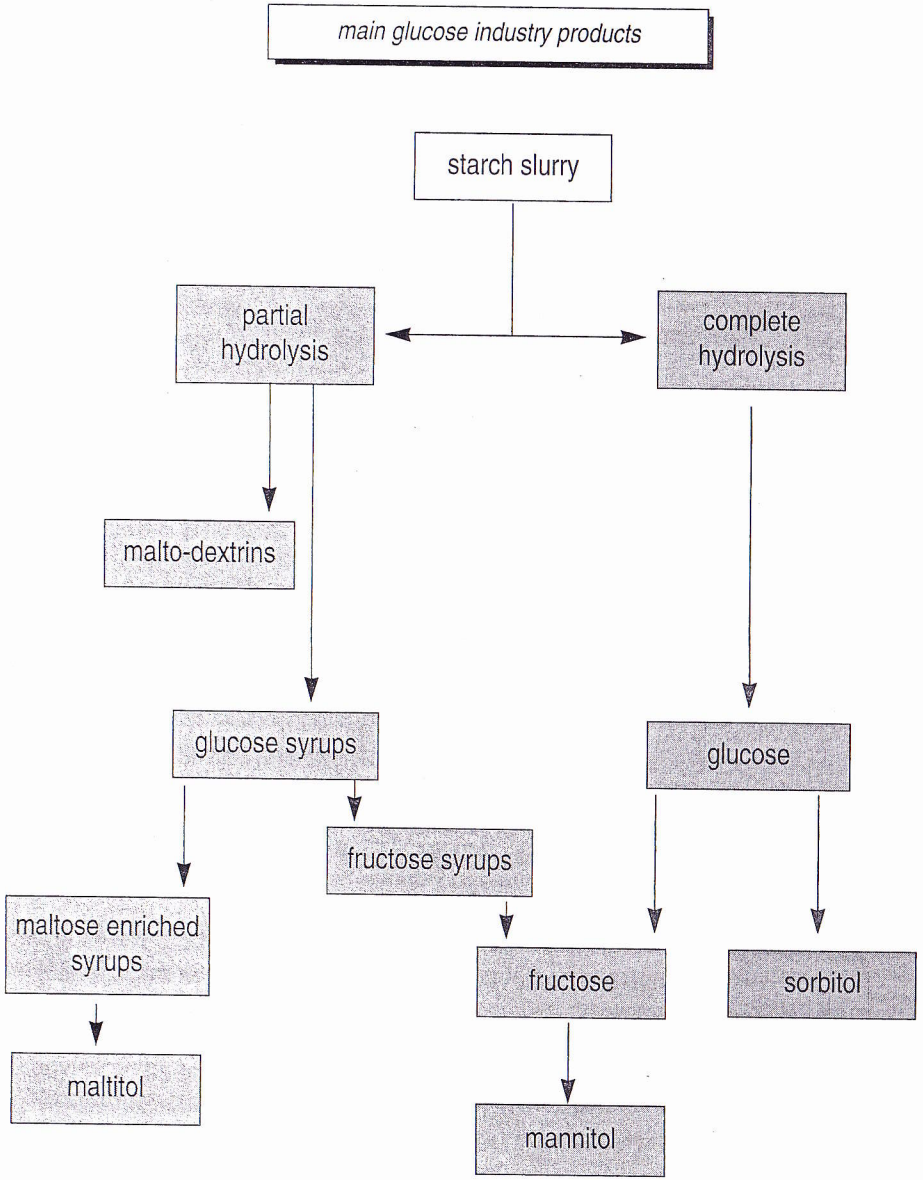
This polyalcohol occurs naturally in the fruit of various Rosaceae, particularly that of the mountain ash, *Sorbus aucuparia* L., as well as in the thallus of certain seaweeds. Industrially, it is obtained by catalytic hydrogenation under pressure or by electrolytic reduction of D-glucose.

Identified by the melting point of its acetylated derivative and by TLC, sorbitol must pass many tests: specific optical rotation, neutrality of its solution, limit tests (chloride, sulfate, nickel, lead), water (for anhydrous sorbitol <1.5%), relative density, refractive index (for 70% sorbitol), quantitation of reducing sugars, periodate oxidation, and, if it is intended for use in the preparation of parenteral formulations without further procedures to remove bacterial endotoxins, these must be evaluated.

In therapeutics, sorbitol is used for its cholecystokinetic properties. It is indicated in the symptomatic treatment of constipation and used in the symptomatic treatment of dyspepsia. Contraindications include organic inflammatory colopathy, occlusion, and undiagnosed abdominal pain. It must not be combined with sodium polystyrene sulfonate (a resin that binds intestinal potassium and is used to treat hyperkalemia). For infusion, solutions at 5 and 10% are used exactly like glucose solutions for prevention of dehydration, common rehydration (when the water loss exceeds the

* Mixture of sucrose, glucose, and fructose obtained by various processes from sucrose (acidic hydrolysis, enzymatic hydrolysis, or inversion by strongly acidic cationic resins), of which 50% of the dry weight is composed of glucose and fructose.

loss of sodium chloride and other electrolytes), prophylaxis and treatment of ketosis in malnutrition, caloric intake, and as a vehicle for therapeutic administration in the immediate pre- and postoperative periods. Precautions are the same as for glucose.



As a sweetener, sorbitol is used as a substitute for sucrose for diabetics (it is converted to D-fructose, which is subsequently metabolized to glycogen). It is commonly used in pharmaceutical technology, e.g., to regulate the moisture content of powders, to stabilize texture in pastes, as a plasticizer for gelatin, and to retard the crystallization of sugars.

Since sorbitol ferments very slowly, it does not alter the pH of the dental pulp; therefore, it is not very cariogenic. Because it is very soluble, very hygroscopic, not susceptible to participation in Maillard's reactions, and not prone to microbial degradation, it is largely used as a manufacturing aid in food technology. Its European identification code (Eur. id. code) is E420. It is particularly interesting for its depressing effect on the activity of water, its "plasticizing" effect on texture, and for its "cool" sweet flavor due to a negative heat of solution.

B. D-Mannitol

Origin. D-Mannitol (Fr. Ph., 10th Ed.) occurs naturally in the manna of manna ash, and in substantial quantities in the thallus of brown algae (laminaria). It is prepared industrially by the epimerization of D-glucose in alkaline medium, followed by catalytic or electrolytic reduction. It can also be obtained by hydrogenation of D-fructose and fractional crystallization of the two resulting alditols. It is identified by its melting point and by TLC, and it must pass many tests: absence of D-sorbitol (TLC) and of reducing sugars, limit test for metals (Ni, Pb) and for anions (e.g., chlorides and sulfates). It is quantitated by periodate oxidation.

Properties. D-Mannitol is not readily metabolized and is an osmotic diuretic by parenteral administration. It undergoes rapid glomerular filtration and practically no tubular reabsorption.

Uses. Mannitol is a cholecystokinetic agent and a laxative. It is proposed for oral administration in the symptomatic treatment of dyspepsia (gastric dilation, impairment of digestion, nausea) and in the adjunctive therapy of constipation. Contraindication: biliary tract obstruction. It can also be used for colon preparation before endoscopy, although it increases the risk of colon gases formation, and therefore of explosion in the case of a procedure using electrical current (for example electrocoagulation): nitrogen insufflation or preventive antibiotic therapy may be considered. Because of this risk, products such as PEG 4000 are preferred. Hypertonic solutions are used by IV infusion in the following indications: oligurias and anurias of various etiologies and of recent onset (solution at 10%); reduction of intracranial pressure for the treatment of certain cerebral edemas, elevated intraocular pressure (solution at 20%). Contraindications are pre-existing plasmatic hyperosmolarity and dehydration that is predominantly intracellular.

Barely hygroscopic and hardly cariogenic, it is an excipient in the formulation of various solid forms. It can be used in human nutrition (Eur. id. code E421) and as a sweetener for diabetics.

- MANNA ASH,
  Fraxinus ornus L., Oleaceae

This ash is a small tree with penta- to nonafoliolate leaves and whitish flowers, and it is a Mediterranean species. Following incision of the bark during the warm and dry season an exudate appears: manna. This manna * consists of irregular, yellowish, and odorless fragments called flake manna, or tears, or sorts.

D-Mannitol, the main constituent, occurs alongside D-glucose, D-fructose, and oligosaccharides. The dried exudate of manna ash is classified as a bulk laxative **, therefore the phytopharmaceuticals that contain it may claim the following indication: symptomatic treatment of constipation. Like for all other laxatives in this group, detailed information must be provided to health professionals and to the public [French Expl. Note, 1998, Annex IV.B., p. 77 sqq., see also p. 107).

C. *Meso*-Xylitol

Origin and properties. *meso*-Xylitol is obtained by catalytic oxidation of D-xylose, which comes from the hydrolysis of xylans (corncobs, birch wood, extracted sugar cane stems [bagasse], wood shavings, straw). It can be used by the oral, as well as by the intravenous route, as a substituent for sucrose, and is metabolized by the pentose cycle after dehydrogenation to D-xylulose.

Uses. Xylitol (Eur. Ph., 3rd Ed., 1999 Add.) , like D-sorbitol or D-glucose, may replace sucrose in syrup formulation. These formulations generally require a thickener. This polyalcohol is a sweetener, and as such, its use is allowed in France (Eur. id. code E967). The same applies to other polyalcohols (D-mannitol, D-sorbitol, maltitol [E965], isomalt [E953] lactitol [E966]) and to polydextrose (*Arrêté* (= French decree) of July 4, 1987, *Journal Officiel de la République Française*, 24-07-1987, pp. 8 261-8 262). In France the presence of these sweeteners in foodstuffs must be mentioned on the label (*édulcoré à...* or sweetened by...). Note also that the label must mention the following:

- that the product must not be given to children under three years of age;
- that excessive daily consumption may cause minor gastrointestinal problems (administration of massive quantities may lead to flatulence and diarrhea).

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* The term manna is applied to various sweet exudations. The manna of the Hebrews is probably a small, very light lichen, which can be carried by the wind over very long distances (*Lecanora esculenta* DC.).

** Other drugs also fall within this scope: the plum tree fruit (*Prunus domestica* L. Rosaceae), the apple tree fruit (*Malus* spp.), the fig tree fruit (p. 224), the fruits of oats (*Avena sativa* L.) and of rye, buckthorn fruit pulp (p. 439), wheat bran (pp. 63, 79), tamarind fruit pulp (p. 24), as well as various seaweeds (p. 51 *sqq.*) and mucilage-containing plants (p. 106-111, 117 *sq.*).

Chemical and bacteriological experiments as well as several controlled clinical trials have clearly established that xylitol is not cariogenic. On the contrary, regular consumption would decrease the frequency of dental caries; it is more efficacious than sorbitol and the other hexitols. *meso*-Xylitol is widely used in confectionery: in addition to being non-cariogenic, it has a fresh flavor. In 1996, 40% of the six billion chewing gum packs sold in France were sugar-free (sorbitol, maltitol, mannitol, xylitol).

D. Derivatives of Polyalcohols

• ***1,5-Anhydro-D-sorbitol*** (polygalitol, aceritol). 1,5-Anhydro-D-sorbitol is now prepared by heating D-sorbitol in sulfuric acid. It is a starting material for the manufacture of sorbitan esters: sorbitan laurate, oleate, palmitate, stearate, and trioleate (Eur. Ph., 3rd Ed.) as well as their polyoxyethylenated derivatives (Spans, Tweens, Polysorbates). These amphophilic molecules are highly prized emulsifiers in pharmaceutical technology.

• ***Other derivatives of polyalcohols***. Several synthetic derivatives that are polyalcohol nitroesters are coronary vasodilators used in the prophylactic treatment of angina pectoris (see therapeutic chemistry textbooks). More generally, alditol nitroesters are unstable and are used in the explosive industry: meso-galactitol hexanitrate (nitrodulcitol), D-mannitol hexanitrate, and of course trinitroglycerol.

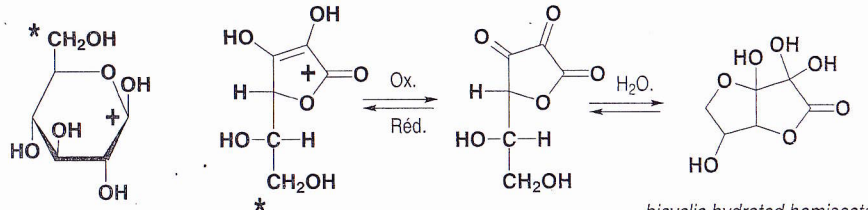
5. SUGAR DERIVATIVES: ASCORBIC ACID AND OTHER ACIDS

Vitamin C is L-(+)-*threo*-ascorbic acid. Biosynthetically, it arises—in plants—directly from D-glucose with conservation of the carbon chain sequence. The acidity of the molecule and its reducing character are linked to the fact that its enediol structure is easily oxidized to a bicyclic structure, dehydroascorbic acid. It is metabolized to oxalic acid, threonic acid, and tartaric acid; the latter can be formed *via* threonic acid or, in some families, directly (Vitaceae). In certain species the resulting acids accumulate (for example, L-(+)-tartaric acid in grape juice).

Properties. Vitamin C can play a role in various oxidoreduction reactions. It is required for the hydroxylation of proline, and therefore for the formation and for the maintenance of the integrity of collagen in animals, and also for that of extensins, which are proteins involved in the formation of vegetable cell walls.

Vitamin C is not synthesized by primates, therefore humans must obtain it from their diet (recommended intake: 80 mg/day in France). Although epidemiological studies clearly show a relationship between the consumption of fruits and vegetables rich in ascorbic acid and a protective effect against cancer (especially of the stomach, esophagus, and colon), it appears that intervention studies have never shown the protective effect against digestive tract cancers without ambiguity. Based

on animal experimentation, it is accepted that ascorbic acid is a scavenger of harmful free radicals and that it inhibits the formation of nitrosamines.



D-Glucose — *Ascorbic acid* — *Dehydroascorbic acid* — *bicyclic hydrated hemiacetal of Dehydroascorbic acid*

* and + : *labels showing biosynthetic origin*

Uses. Vitamin C is indicated at vitamin-like doses (*i.e.*, 10-50 mg/day): 1. for the treatment of scurvy; 2. for the prophylaxis of vitamin C deficiencies resulting from poorly balanced or insufficient nutrition. At high doses (i.e., 0.5 g/day), it is used for the treatment of coryza-, flu-, and convalescence-related asthenia. Despite the fact that very high doses seem well tolerated (intestinal distress in isolated cases), the *Conseil supérieur d'hygiène publique de France* has proposed a maximum safe dose of 15 mg/kg/day (about 1 g/day for an adult). Ascorbic acid (Eur. id. code E300), its salts (Na, E301, K, E302) and its fatty acid esters (E304) are authorized as food additives (acidifiers, preservatives, antioxidants); the maximum dose is 300 mg/L.

Sources. Ascorbic acid is present in large quantities in various fruits: sea buckthorn (*Hippophae rhamnoides* L., Elaeagnaceae), kiwi (*Actinidia "sinensis"*, [= *A. deliciosa* (A. Chev.) Liang & A.R. Ferg., *A. arguta* (Siebold & Zucc.) Miq.] Actinidiaceae), paprika (*Capsicum annuum* L., Solanaceae), jabotica (*Myrciaria cauliflora* [C. Martius] O. Berg. and other species, Myrtaceae), acerola (*Malpighia glabra* (*punicifolia*) L., Malpighiaceae), to name only the richest. It is particularly abundant in rose hips.

• DOG ROSE, *Rosa canina* L., Rosaceae

The dog rose is a very bushy shrub with erect stems, armed with very strong thorns, composite pinnate bluish leaves, stipules fused to the petiole, and pale pink flowers. The drug— rose hips—consists of the ripe and dried receptacle cup, as well as the akenes within. It is listed in the latest edition of the French Pharmacopoeia, and must contain not less than 0.2% ascorbic acid as titrated with dicholorophenol-indophenol. Ascorbic acid can be detected by TLC (alcoholic extract, revealed by the same reagent). Rose hips are elongated red pseudofruits containing very hard polyhedral akenes. The internal epidermis of the receptacle cups bear long hairs (1-3 mm) with very thick walls.

Rose hips owe their color to carotenoids. They contain tannins, pectin, sugars, and like many other fruits of the family Rosaceae, D-sorbitol. Vitamin C (up to 1.7%) occurs alongside malic acid and citric acid.

In France, phytopharmaceutical drugs based on rose hips may claim the following indications by the oral route [French Expl. Note, 1988]: "traditionally used 1. in functional asthenias, and 2. to facilitate weight gain".

The German Commission E monograph includes a long list of the uses of the drug (treatment and prevention of influenza-type infections, infectious diseases, and vitamin C deficiencies, to facilitate digestion, for arthritis, as a diuretic, as an astringent, and so on). The monograph states that none of these uses is justified and, citing the rapid decrease in the vitamin C content of the drug, does not recommend the therapeutic use of rose hips. On the other hand, there is no reason not to use them to enhance the flavor of herbal tea mixtures or in the food industry.

- **RED SORREL,**
  Hibiscus sabdariffa L., Malvaceae

The calyx and calyculus of this subtropical Malvaceae are boiled to prepare a refreshing beverage. The drug, which comes from Sudan, Egypt, and southeast Asia, and is called *karkadé* in some European countries, contains heterogeneous acidic polysaccharides and numerous phenolic compounds: 3-glycoside of gossypetine, anthocyanins (glycosides of delphinidin and cyanidin). It is characterized by a high level of organic acids (15-30%): citric, malic, tartaric acids, and the lactone of hydroxycitric acid. The drug assay (Fr. Ph., 10th Ed.) includes TLC of anthocyanidins on a hydrochloric acid decoction; to be official in France it must contain not less than 13.5% acids (calculated as citric acid) and 40% water-extractible materials.

Various properties have been attributed to this drug, which seems to be spasmolytic and, by virtue of the presence of anthocyanins, may protect against angina pectoris. Like rose hips, the calyxes and calicles of red sorrel are traditionally used, in France, by the oral route, in functional asthenias and to facilitate weight gain [French Expl. Note, 1998]. The German Commission E monograph states that the therapeutic use of red sorrel flowers cannot be recommended, since their efficacy for the indications that are claimed has not been demonstrated.

- **TAMARIND,**
  Tamarindus indica L., Cæsalpiniaceae

This African tree is cultivated in various tropical regions of the globe (India, Antilles). The fruit is an indehiscent pod with fleshy mesocarp which holds from 4 to 12 irregular seeds. The pulp is reddish-brown, has a mild sweet taste, and is rich in pectins and monosaccharides (20-40%). It also contains 10-15% organic acids such as tartaric acid, malic acid, and citric acid, in the free state and as salts (the main component is potassium hydrogen tartrate). The odor is linked to the presence of monoterpenoid and aromatic compounds (cinnamates), and to that of pyrazine. Locally prized as a condiment, this drug is a bulk laxative [French Expl. Note, 1998] which may claim the following indication: symptomatic treatment of constipation (see comment p. 107).

The seed contains 15-20% proteins, 3-7% lipids, and 65-70% non-fibrous polysaccharides. The commercial "gum" is obtained by crushing the endosperm after elimination of the teguments by treating with heat and pounding. The reserve polymer in this seed is a complex molecule with a backbone of β-(1->4)-linked D-glucoses, substituted in the 6-positions by xylosyl, arabinosyl, and galactoxylosyl groups. Tamarind "gum" is used by various non-food industries for its ability to form viscous solutions with pseudoplastic behavior. The cosmetic industry uses polysaccharide fractions from the seed to "stimulate the repair of damaged skin."

Sorbic acid = 2,4-(*E*,*E*)-hexadienoic acid. Sorbic acid occurs naturally in the fruit of mountain ash as a lactone called parasorbic acid; it is produced synthetically. The acid itself (Eur. id. code E200) and its salts (sodium, potassium, calcium, E201-203) are authorized preservatives that inhibit mold growth.

6. CYCLITOLS

Cyclohexanehexol or inositol plays a fundamental biological role, thus it has been the topic of much research. Six of nine possible isomers occur naturally Phosphoric esters of myo-inositol, particularly phytic acid, constitute the mos abundant form of phosphates throughout nature.

The sodium salt of phytic acid (*international nonproprietary name* = INN: fytic acid) causes intestinal calcium to precipitate as insoluble and non-absorbable phytate Its indications are as follows: hypercalciurias, infected lithiasis involving calcium and calcium metabolism tests. The treatment of hypercalciurias requires a diet low ir calcium and the regular monitoring of calciuria. The calcium salt of phytic acid is used in combination with various compounds (e.g., vitamins, kola) in pharmaceutica preparations used in the symptomatic treatment of functional asthenia.

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