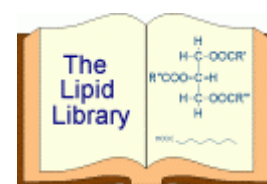


FATTY ACIDS: HYDROXY, EPOXY AND FURANOID

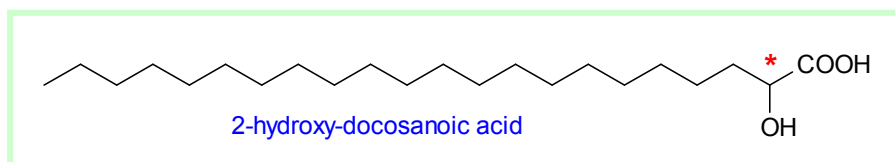


STRUCTURES, OCCURRENCE AND BIOCHEMISTRY

The prostaglandins and other eicosanoids are in essence hydroxy fatty acids, but these will be discussed elsewhere in this website. Similarly, hydroxy fatty acids may arise adventitiously from hydroperoxides, and these are not discussed here. Nor are the many oxygenated fatty acids that are produced by synthetic means for industrial applications. The following is not intended as a comprehensive list, but as a guide to the more important naturally occurring fatty acids in this category.

Hydroxy Fatty Acids in Animals

2-(*D*)-Hydroxy fatty acids are more conventional lipid components and are important constituents of animal sphingolipids (see the web pages on **Ceramides**, for example). The chain-lengths vary from about C₁₆ to C₂₆, and they are normally saturated, although monoenoic components are also known. Sphingomyelin containing 2-hydroxylated polyenoic very-long-chain fatty acids has been found in mammalian testes and spermatozoa. The hydroxyl group is believed to add to the hydrogen-bonding capacity of the sphingolipids, helping to stabilize membrane structures and strengthen the interactions with membrane proteins.



Such fatty acids, together with isomers containing *iso/anteiso*-methyl branches, have been found in the glycerophospholipids, especially phosphatidylethanolamine of sponges. They also occur in ester linkage in wool wax and Harderian gland secretions. 2,3-Dihydroxy-long-chain fatty acids are occasionally reported from the glycosphingolipids of marine invertebrates, and similar fatty acids have been found in the uropygial gland secretions of storks, together with 2- and 3-mono-hydroxy components.

2-Hydroxy-phytanic acid is formed during *alpha*-oxidation of phytanic acid (see the web page on **Branched chain** fatty acids) by liver mitochondria and peroxisomes, but it is detected in tissues only in patients with peroxisomal disorders.

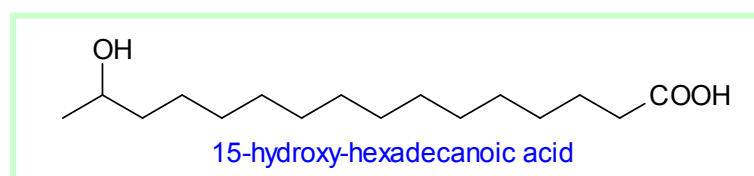
3-Hydroxy-fatty acids (C₆ to C₁₆) are formed during *beta*-oxidation of fatty acids in mammalian tissues, and increased concentrations of the free acids or acyl-carnitines in blood and urine are indicative of disorders of fatty acid oxidation. Similarly, 3-hydroxydicarboxylic acids, produced by *omega*-oxidation of 3-hydroxy fatty acids, are present in urine. 3-Hydroxy-pristanic acid has been found in the plasma of patients with defects of *beta*-oxidation. C₈ to C₁₂ 3-hydroxy acids are normal components of the wax secretions from the uropygial glands of certain bird species, however.

A family of enzymes, cytochromes P450s, in liver microsomes are involved in fatty acid oxidation with the 12-carbon lauric acid as the primary substrate, although other fatty acids can also be

utilized. The enzymes are unusual in that they hydroxylate with high specificity at the energetically unfavourable terminal (ω) or $\omega-1$ carbons, but the products do not appear to accumulate in significant amounts in tissues.

The skin from pigs and humans contains O-acyl ceramides in which a long-chain fatty acid component (up to C₃₀) has a terminal hydroxyl group, which may be in the free form or esterified with another fatty acid (see the web page on **Ceramides**). Fatty acids with hydroxyl groups in either the 2- or terminal position are components of di- and triesters from meibomian glands of some animal species. Cow's milk contains small amounts of a range of saturated and monoenoic hydroxy- and keto-fatty acids with the hydroxyl group in positions 5 to 16, but their biosynthetic origin is obscure.

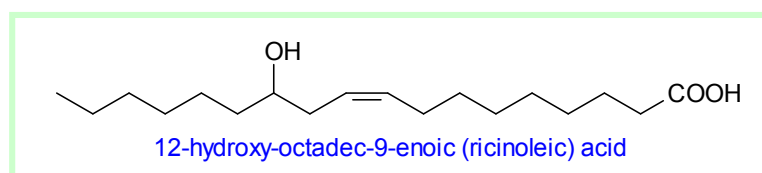
15-Hydroxy-hexadecanoic and 17-hydroxy-octadecanoic acids are important constituents of beeswax (together with small amounts of other homologues and ($\omega-2$)-hydroxy-isomers). Royal jelly, a secretion produced by worker bees, contains a number of mono- and dihydroxy fatty acids (C₈ to C₁₄). Many other insect waxes and secretions contain hydroxy fatty acids, and perhaps the best known of these is the insect *Tachardia (Laccifer) lacca*, which produces the polymeric material shellac. This contains substantial amounts of 9,10,16-trihydroxy-hexadecanoic (aleuritic) and 6-hydroxy-tetradecanoic acids, amongst others.



Hydroxy Fatty Acids in Higher Plants

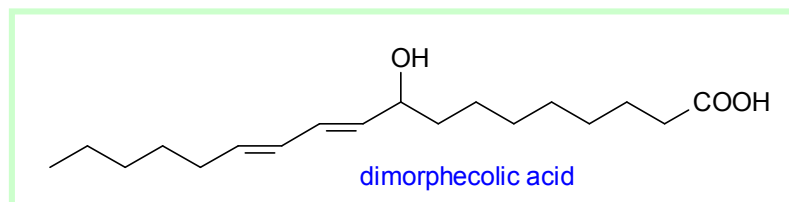
As in animal tissues, 2-(D)-hydroxy fatty acids occur in appreciable amounts in the sphingolipids of plants. Other 2-hydroxy acids may be encountered in seed oils. For example, 2-hydroxy-octadeca-9,12,15-trienoate is a minor component of the seed oil of *Thymus vulgaris*, 2-hydroxy-oleic and linoleic acids are found in *Salvia nilotica*, and 2-hydroxy-sterculic acid is occasionally encountered in seed oils of the Malvales.

The seed oils of higher plants contain a number of hydroxy acids, some of which are important agricultural commodities. The best known of these is ricinoleic acid (D-(-)-12-hydroxy-octadec-cis-9-enoic acid), which comprises up to 90% of castor oil (from *Ricinus communis*). It is also a major component of the lipids of the fungus ergot (*Claviceps purpurea*), where it is found esterified to glycerol in triacylglycerols, which may be linked to further ricinoleate molecules via ester bonds; such lipids are termed 'estolides'.



The homologous 14-hydroxy-eicos-cis-11-enoic (lesquerolic) acid is a component of seed oils from the genus *Lesquerella*, while the isomeric 9-hydroxy-octadeca-cis-12-enoic (isoricinoleic) acid is found in the genus *Strophanthus*. Other non-conjugated dienoic fatty acids, which appear to be related biosynthetically to these monoenes have been reported in seed oils, and include 12-hydroxy-octadeca-cis-9,cis-15-dienoic (densipolic) and 14-hydroxy-eicosa-cis-11,cis-17-dienoic (auricollic) acids.

Conjugated dienoic fatty acids with a hydroxyl group are also known from a number of seed oils, and some may have commercial importance. Almost all are C₁₈ in chain-length. These include 9-hydroxy-octadeca-*trans*-10,*trans*-12-dienoic (dimorphecolic) acid from the seed oil of *Dimorphothea sinuata*, while the geometrical isomer with a *cis*-double bond in position 12 is present in the seed oil of *Calendula officinalis* amongst others. 13-Hydroxy-octadeca-*cis*-9,*trans*-11-dienoic (coriolic) acid has been reported from *Coriaria nepalensis* seed oil. Further conjugated hydroxy-fatty acids have acetylenic bonds, including ximenynolic (8-hydroxy,9a,11t) and isanolic (8-hydroxy,9a,11a,17e) acids.



Dihydroxy acids, such as 9,10-dihydroxy-octadecanoic acid and higher homologues, can be minor components of several seed oils, including castor oil, but they occur in significant concentrations in the seed oil of *Cardamine impatiens*. Trihydroxy acids (+)-*threo*-9,10,18-trihydroxyoctadecanoic (phloionolic) acid and (+)-*threo*-9,10-,18-trihydroxy-*cis*-12-octadecenoic acid occur in the seed oil of *Chamaepeuce afra*.

Cutin: The aerial surfaces of higher plants are covered with a continuous extracellular layer, termed the cuticle that contains cutin as the major structural component. Suberin is a related but distinct material that forms near the plasma membrane of plant cells in specific regions, and it comprises both aliphatic and aromatic polymers. The function of these layers is to act as barriers to control the movement of gases, water and solutes, and to impart resistance to pathogens or herbivores. Both cutin and suberin contain polyesters with linear and branched chains that consist mainly of mono-, di- and trihydroxy fatty acids (together with dibasic acids); in cutin, these have chain lengths of 16 and 18 carbons, while suberin is much more complex as the range of chain-lengths can go up to C₂₈. The cutin-suberin layers are distinct from and support the waxy layer that covers the external surface (see our web page on [waxes](#)).

The fatty acids of cutins include ω-monohydroxy acids, 9(or 10),16-dihydroxy-hexadecanoic acid (and analogous C₁₈ acids), 9,10,18-trihydroxy-octadecanoic acid, and occasionally related fatty acids with epoxy or keto groups in central positions, e.g. 9,10-epoxy,18-hydroxy-octadecanoate. Suberins contain similar fatty acids but with a wider range of chain-lengths and varying degrees of oxygenation. For example, oleic acid is believed to be the biosynthetic precursor of 18-hydroxy-oleic, 9,10,18-trihydroxy-octadecanoic, 1,18-octadec-9-enedioic and 9,10-dihydroxy-1,18-octadecanedioic acids, together with 9,10-epoxy analogues. The best-known and characterized source of suberin is cork, derived from the bark of the cork oak (*Quercus suber*). A hydroxyl group at or close to terminal carbon atom is introduced into an existing fatty acid by means of cytochrome P450-dependent fatty acid hydroxylases.

The plant **oxylipins**, which include hydroxy, epoxy and keto fatty acids, are discussed elsewhere on this website.

Hydroxy Fatty Acids in Microorganisms

2-Hydroxy fatty acids are found in a wide range of microorganisms. For example in yeasts and fungi, they are major constituents of sphingolipids (amide linked), as in plants and animals. In some species of fungi, there is an additional *trans* double bond in position 3. 2,3-Dihydroxy fatty acids have also been reported from yeasts. Ester- and/or amide-bound 2-hydroxy fatty acids, with

both straight and branched chains, are common constituents of bacterial lipids. As such they are often found in environmental samples, such as soils, biofilms or sediments. Fatty acids of this kind are usually saturated, in some instances with *iso*- or *anteiso*-methyl branches, but monoenes are occasionally found.

3(or β)-Hydroxy long-chain fatty acids are important constituents of lipopolysaccharides and lipid A, from gram-negative bacteria especially, and they are essential to the endotoxin activity. Indeed, endotoxin levels in samples are often determined by analysis of the content of 3-hydroxy acids. The fatty acids can be linked by both ester and amide bonds to glucosamine or other amino-sugars in these lipids. Again, they are often found in environmental samples, such as dust, aerosols, soils and sewage. Most fatty acids of this type tend to be fully saturated, sometimes with *iso*- or *anteiso*-methyl branches. However, as the ubiquitous *beta*-oxidation system is involved in their synthesis, monoenes and even cyclopropyl fatty acids of this type have been reported. 3-Hydroxy acids are the main fatty acid constituents of rhamnolipids produced by pseudomonads. Mycolic acids, discussed elsewhere in the pages, also contain a hydroxyl group in position 3, and can have keto and methoxyl groups elsewhere in the chain.

The short-chain hydroxy acid, β -hydroxybutyrate, occurs in the form of a polyester in intracellular inclusions in many bacterial species, where it functions as a reserve of carbon and of energy. Currently, these are of considerable interest to industry as a source of biodegradable polymers, substituting for petroleum-derived plastics

10-Hydroxy-stearic acid is a major component of the protozoon *Cryptosporidium parvum*. It can also be produced by a number of bacterial species, including lactic acid bacteria, from oleic acid added to the growth medium. Also, 10-hydroxyoctadecanoate and 10-hydroxyhexadecanoate, together with the corresponding oxo fatty acids, are major components of adipocere, the waxy material produced by microbial decay in corpses. A number of microbial reactions of this type that produce saturated and unsaturated hydroxy and keto acids are being studied, as the products may have some industrial value. Unusual fatty acids with hydroxyl groups in central positions, together with methyl groups and double bonds, have been found in species of fungi, lichens and slime moulds. For example, 7-hydroxy-8,14-dimethyl-9-hexadecenoic acid, and structurally related fatty acids, were found in fungal species belonging to the Ascomycetes and Basidiomycetes. 9,10,13- and 9,12,13-Trihydroxyoctadecenoic acids found in beer are derived from microbial fermentation of linoleic acid.

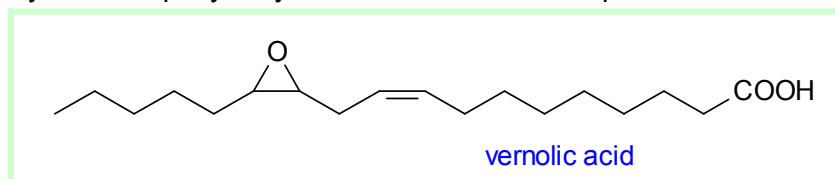
Some bacterial species are capable of hydroxylating fatty acids close to the terminal part of the molecule. For example, preparations from *Bacillus megaterium* are able to convert palmitic acid to 14-hydroxypalmitate mainly, although 15- and 13-hydroxypalmitate are also produced. 27-Hydroxy-octacosanoic acid is a characteristic component of the lipopolysaccharide Lipid A from all soil bacteria of the family Rhizobiaceae. Yeasts produce extra-cellular glycosides containing ω -1 hydroxy fatty acids (C_{16} and C_{18}). Certain filamentous fungi of the genus, *Ustilago*, contain ustilagic acids, i.e. 15,16-dihydroxy- and 2,15,16-trihydroxyhexadecanoic acids linked to β -cellobiose. As discussed above, the fungus ergot produces ricinoleic acid.

Epoxy and Furanoid Fatty Acids

The first natural epoxy fatty acid to be found was (+)-vernolic acid, or *cis*-12,13-epoxy-octadec-*cis*-9-enoic acid, from the seed oil of *Vernonia anthelmintica*. In this instance, the stereochemistry of the epoxy group was shown to be 12*S*,13*R*, but the optical antipode, (-)-vernolic acid, has been isolated from certain seed oils of the Malvaceae.

Subsequently, the isomeric *cis*-9,10-epoxy-octadec-*cis*-12-enoic ('coronanic') acid, *cis*-15,16-epoxy-octadeca-*cis*-9,12-dienoic acid, and *cis*-9,10-epoxy-octadecanoic were found in seed oils.

They are usually minor components, but vernolic acid can amount to 60% of the total fatty acids in the seed oil of *Vernonia galamensis*. On prolonged storage, small amounts of epoxy (or hydroxy) acids of defined stereochemistry are generated by enzymic processes in many different seed oils. As described briefly above, epoxy fatty acids can also occur in plant cutins.

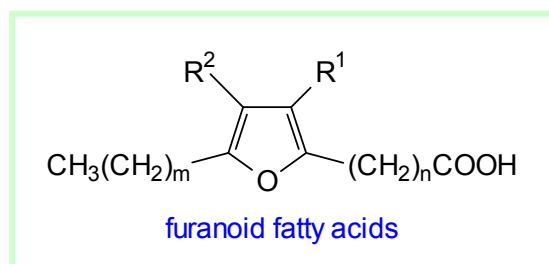


Vernolic and coronaric acids have an obvious biosynthetic relationship to linoleic acid. This is also the source of low levels of these acids in bacteria and in animal tissues, where they are termed 'leukotoxins' (the term includes a range of diverse compounds), because they produce their primary toxic effects against leukocytes. At high dosages, they have toxic cardiovascular effects, which can even result in death. However, the diols formed on ring opening rather than leukotoxins *per se* may be responsible for these effects.

Saturated epoxy fatty acids, such as 9,10-epoxy-octadecanoic and 9,10-epoxy,18-hydroxy-octadecanoate acids, are found in plant cutins (see above).

Furanoid fatty acids with the general structural formula illustrated are minor but widespread components of plant lipids. However, interest in these compounds was stimulated by the discovery that they were present at low levels in fish, especially in their reproductive tissues. Subsequently, they were found other animal products, and in human plasma and erythrocytes.

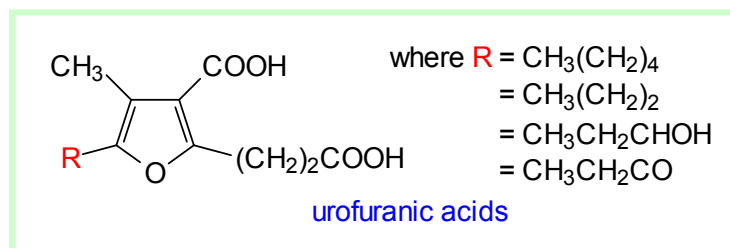
The first natural acid of this type (with $R^1 = R^2 = H$, $m = 6$ and $n = 7$) was found in the seed oil of *Exocarpus cupressiformis*, although there has been a suggestion that it may have been an artefact of the isolation method. It is much more usual to encounter furanoid fatty acids with a methyl substituent in positions 3 (R^1) of the ring, or with two methyl substituents in the ring ($R^1 = R^2 = CH_3$), the latter being more common. The natural fatty acids found to date can have 16 to 22 carbon atoms, and they occur in series with either a terminal propyl group ($m = 2$) or a terminal pentyl group ($m = 4$). At least fourteen different furanoid fatty acids have now been detected in fish lipids, but the most common is 12,15-epoxy-13,14-dimethyleicosa-12,14-dienoic acid, together with its homologues, and smaller relative proportions of monomethyl acids, such as 12,15-epoxy-13-methyleicosa-12,14-dienoic acid. In fish, furanoid fatty acids occur in triacylglycerols and cholesterol esters, whereas in human and bovine plasma they are present mainly in phospholipids.



Similar fatty acids have been found in a variety of plant sources. For example, in the latex of the rubber tree *Hevea brasiliensis*, 10,13-epoxy-11,12-dimethyloctadeca-10,12-dienoic acid has been identified as the main component of the lipid fraction, and this and other furanoid fatty acids have been detected as minor components in numerous other plants (seeds, leaves and fruit), yeasts, algae and marine bacteria. Indeed, it is suggested that plants, algae and bacteria via the food chain are the main source of furanoid fatty acids in animals and fish, especially for the pentyl-substituted fatty acids. Linoleic acid is the biosynthetic precursor of the more abundant furanoid fatty acids with the methyl substituents derived from adenosylmethionine. The origin of the propyl-substituted compounds is less certain, but they may be derived from metabolism of 9,12-hexadecadienoic acid in algae such as *Phaeodactylum tricornutum*. Furanoid fatty acids can arise spontaneously from autoxidation of fatty acids with conjugated double bonds.

A number of short-chain dibasic furanoid fatty acids have been isolated from human blood and plasma, and have been termed urofuranic acids. They are believed to be metabolites of the longer-

chain furanoid fatty acids. When kidney function is impaired, 3-carboxy-4-methyl-5-propyl-2-furanopropanoic acid in particular can accumulate, and may be a significant uremic toxin.

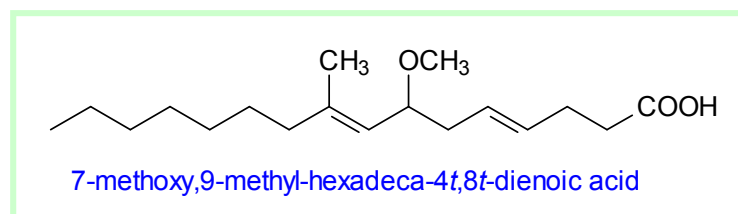


A tetrahydropyran ring-containing fatty acid, i.e. 2,3-dihydroxy-9,13-oxy-7-*trans*-octadecenoic acid, has been found linked to taurine in the protozoon *Tetrahymena thermophila*. Recently, furanoid fatty acids were detected in bacterial species for the first time (from *Dehalococcoides* sp.). 9-(5-Pentyl-2-furyl)-nonanoate, 9-(5-butyl-2-furyl)-nonanoate, and 8-(5-pentyl-2-furyl)-octanoate were present in the phospholipids.

Furanoid fatty acids are scavengers of hydroxyl and hydroperoxyl radicals, and there is a suggestion that they may play a part in the cardio-protective effects of dietary fish oils.

Methoxy Fatty Acids

The mycolic acids, described in our web page on branched-chain fatty acids, are unusual in many ways not least in that they contain methoxyl substituents. Otherwise, methoxy fatty acids are not common in nature. However, a number of 2-methoxy substituted fatty acids, all with the *R*-configuration at the chiral centre, have been isolated from sponges, especially those of Caribbean origin. They include saturated, monoenoic and very-long chain dienoic acids. In addition, some mid-chain methoxylated fatty acids have been isolated from marine algae, where they exist as *N*-substituted amides termed 'malyngamides'. One of these unusual fatty acids, which also contain double bonds of the *trans* configuration, is illustrated below. Other methoxy fatty acids are occasionally reported from algae, fungi and bacteria. Methoxy fatty acids are currently of great pharmaceutical interest as they display antibacterial, antifungal, anticancer and antiviral activities.



Unfortunately, methoxyl groups can also be introduced to fatty acyl chains artefactually during analysis, if cyclopropane or brominated fatty acids are methylated by inappropriate methods.

Recommended Reading

There are no general reviews on this topic currently available, but the following are useful guides to naturally occurring oxygenated fatty acids.

- o Badami, R.C. and Patil, K.B. Structure and occurrence of unusual fatty acids in minor seed oils. *Prog. Lipid Res.*, 19, 119-153 (1981).
- o Carballeira, N.M. New advances in the chemistry of methoxylated lipids. *Prog. Lipid Res.*, 41, 437-456 (2002).

- o Gunstone, F.D., Harwood, J.L. and Dijkstra, A.J. (Editors), *The Lipid Handbook (3rd Edition)*. (CRC Press, Boca Raton) (2007).
- o Pollard, M., Beisson, F., Li, Y. and Ohlrogge, J.B. [Building lipid barriers: biosynthesis of cutin and suberin](#). *Trends Plant Sci.*, **13**, 236-246 (2008).
- o Smith, C.R. [Occurrence of unusual fatty acids in plants](#). *Prog. Chem. Fats other Lipids*, **11**, 137-177 (1971).
- o Spiteller, G. [Furan fatty acids: Occurrence, synthesis, and reactions. Are furan fatty acids responsible for the cardio protective effects of a fish diet?](#) *Lipids*, **40**, 755-771 (2005).

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