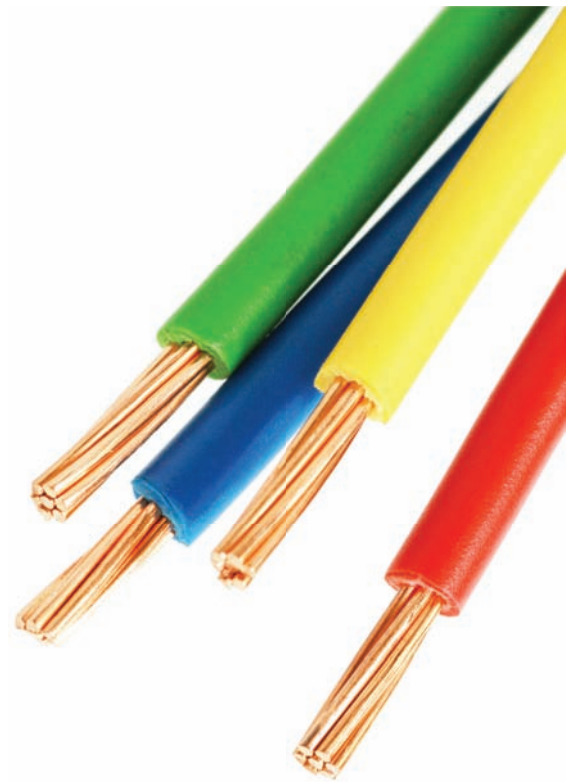
CHAPTER

23

Lipids



If you have ever worked with electrical wires, you know that a live bare wire will short circuit if it touches another conductor. To make sure that such a circuit does not do this, potentially causing a fire or an injury to an electrician, electrical wires are always insulated with a nonconducting material like plastic. Electrical signaling in our bodies occurs in much the same way through the connections between nerve cells. There, the insulation is provided by lipid-rich cells comprising the myelin sheath that wraps in layers encircling the long, thin nerve fibers called axons. In cross section, cells of the myelin sheath look much like the rings of a cut tree trunk, and by insulating the nerve cell axons the myelin sheath increases the overall speed of the electrical signals, or impulses, in the nervous system (where rates can reach as high as 100 meters per second). The myelin sheath is also critical for proper neurological functioning. For instance, too little sheathing of the nerves, a condition known as demyelination, can result from the autoimmune disorder multiple sclerosis; this condition usually leads to serious challenges in muscle movement, among other disorders. Too much of these lipids can cause problems as well, something encountered in Tay Sach's disease, an ailment fatal to children under the age of 3. As we shall see in this chapter, lipids play a number of varied biochemical roles, and they are often obtained from natural sources along with another special class of molecules called steroids that regulate a number of critical functions.

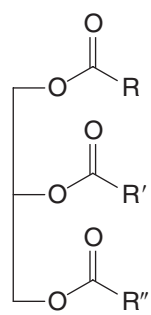
IN THIS CHAPTER WE WILL CONSIDER:

- the structures and properties of different lipids
- selected examples of important lipids and their functions
- how lipid-based molecules serve as precursors to a number of unique carbon frameworks, including steroids, waxes, and other signaling molecules

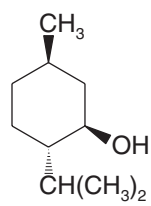
[WHY DO THESE TOPICS MATTER?] At the end of this chapter we will show how one particularly unique steroid can both account for a classical Greek myth as well as hold promise as a potential new cancer therapy.

23.1 INTRODUCTION

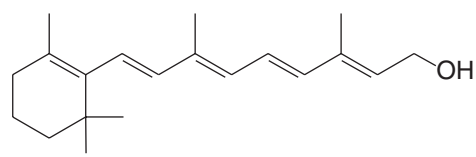
Lipids are compounds of biological origin that dissolve in nonpolar solvents, such as chloroform and diethyl ether. The name lipid comes from the Greek word *lipos*, for fat. Unlike carbohydrates and proteins, which are defined in terms of their structures, lipids are defined by the physical operation that we use to isolate them. Not surprisingly, then, lipids include a variety of structural types. Examples are the following:



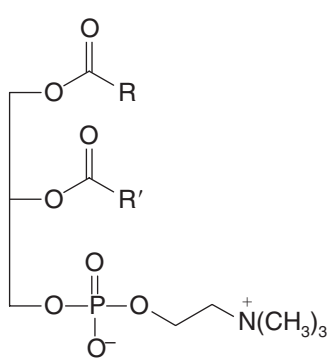
A fat or oil (a triacylglycerol)



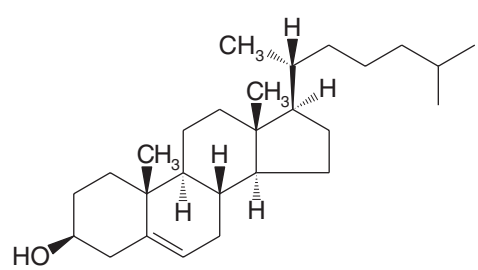
Menthol (a terpenoid)



Vitamin A (a terpenoid)



A lecithin (a phosphatide)



Cholesterol (a steroid)

23.2 FATTY ACIDS AND TRIACYLGLYCEROLS

Only a small portion of the total lipid fraction obtained by extraction with a nonpolar solvent consists of long-chain carboxylic acids. Most of the carboxylic acids of biological origin are found as *esters of glycerol*, that is, as **triacylglycerols** (Fig. 23.1).*

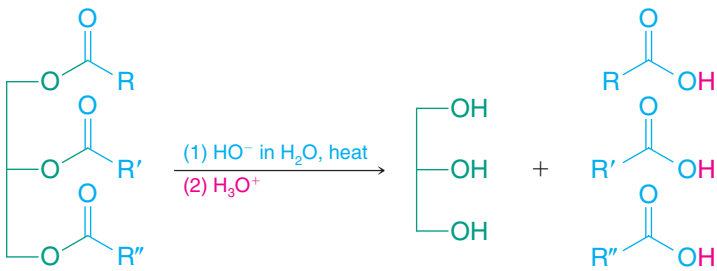
Triacylglycerols are the oils of plants and the fats of animal origin. They include such common substances as peanut oil, soybean oil, corn oil, sunflower oil, butter, lard, and tallow.

*In the older literature triacylglycerols were referred to as triglycerides, or simply as glycerides. In IUPAC nomenclature, because they are esters of glycerol, they should be named as glyceryl trialkanoates, glyceryl trialkenoates, and so on.

- Triacylglycerols that are liquids at room temperature are generally called **oils**; those that are solids are called **fats**.

Triacylglycerols can be **simple triacylglycerols** in which all three acyl groups are the same. More commonly, however, the triacylglycerol is a **mixed triacylglycerol** in which the acyl groups are different.

- Hydrolysis of a fat or oil produces a mixture of **fatty acids**:



A fat or oil **Glycerol** **Fatty acids**

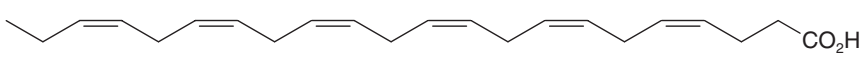
- Most natural fatty acids have **unbranched chains** and, because they are synthesized from two-carbon units, **they have an even number of carbon atoms**.

Table 23.1 lists some of the most common fatty acids, and Table 23.2 gives the fatty acid composition of a number of common fats and oils. Notice that in the **unsaturated fatty acids** in Table 23.1 **the double bonds are all cis**. Many naturally occurring fatty acids contain two or three double bonds. The fats or oils that these come from are called **polyunsaturated fats** or oils. The first double bond of an unsaturated fatty acid commonly occurs between C9 and C10; the remaining double bonds tend to begin with C12 and C15 (as in linoleic acid and linolenic acid). The double bonds, therefore, *are not conjugated*. Triple bonds rarely occur in fatty acids.

The carbon chains of **saturated fatty acids** can adopt many conformations but tend to be fully extended because this minimizes steric repulsions between neighboring methylene groups.

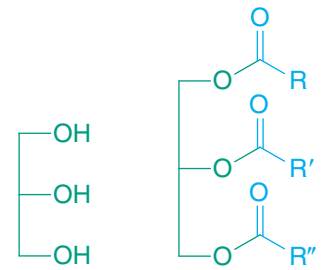
- Saturated fatty acids pack efficiently into crystals, and because dispersion force attractions are large, they have relatively high melting points. The melting points increase with increasing molecular weight.
- The cis configuration of the double bond of an unsaturated fatty acid puts a rigid bend in the carbon chain that interferes with crystal packing, causing reduced dispersion force attractions between molecules. Unsaturated fatty acids, consequently, have lower melting points.

Fatty acids known as omega-3 fatty acids are those where the third to last carbon in the chain is part of a carbon–carbon double bond. Long-chain omega-3 fatty acids incorporated in the diet are believed to have beneficial effects in terms of reducing the risk of fatal heart attack and easing certain autoimmune diseases, including rheumatoid arthritis and psoriasis. Oil from fish such as tuna and salmon is a good source of omega-3 fatty acids, including the C_{22} omega-3 fatty acid docosahexaenoic acid [DHA, whose full IUPAC name is (4*Z*, 7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-4,7,10,13,16,19-docosahexaenoic acid]. DHA is also found in breast milk, gray matter of the brain, and retinal tissue.



(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-4,7,10,13,16,19-Docosahexaenoic acid (DHA, an omega-3 fatty acid)

What we have just said about the fatty acids applies to the triacylglycerols as well. Triacylglycerols made up of largely saturated fatty acids have high melting points and are solids at room temperature. They are what we call *fats*. Triacylglycerols with a high proportion of unsaturated and polyunsaturated fatty acids have lower melting points and most are *oils*.

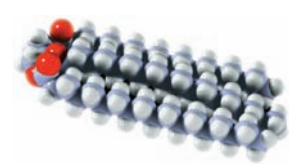


Glycerol **A triacylglycerol**
(*a*) (*b*)

FIGURE 23.1 (*a*) Glycerol. (*b*) A triacylglycerol. The groups R, R′, and R″ are usually long-chain alkyl groups. R, R′, and R″ may also contain one or more carbon–carbon double bonds. In a triacylglycerol R, R′, and R″ may all be different.

Helpful Hint

We saw how fatty acids are biosynthesized in two-carbon units in Special Topic E (*WileyPLUS*).



A saturated triacylglycerol

TABLE 23.1 COMMON FATTY ACIDS

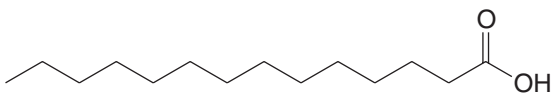
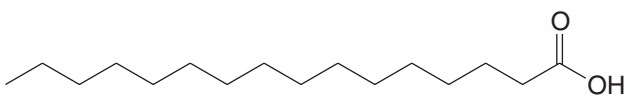
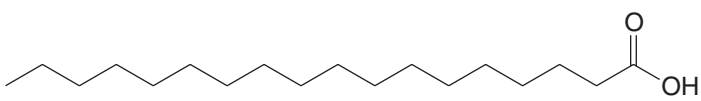
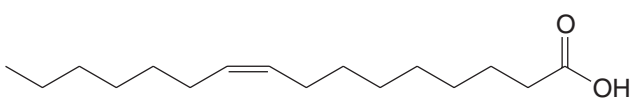
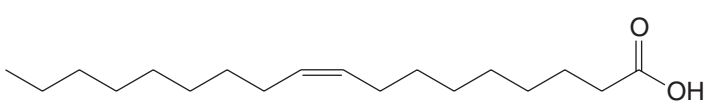
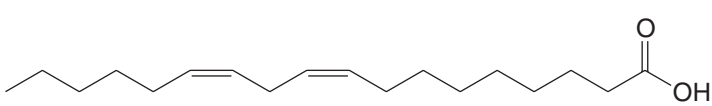
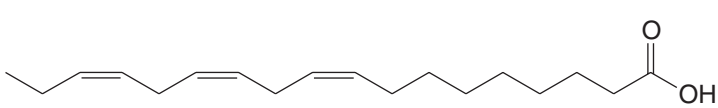
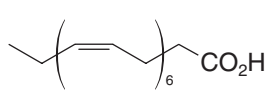
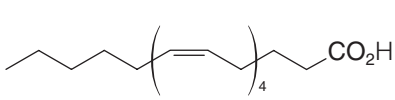
	mp (°C)
Saturated Carboxylic Acids	
 **Myristic acid (tetradecanoic acid)**	54
 **Palmitic acid (hexadecanoic acid)**	63
 **Stearic acid (octadecanoic acid)**	70
Unsaturated Carboxylic Acids	
 **Palmitoleic acid (*cis*-9-hexadecenoic acid)**	32
 **Oleic acid (*cis*-9-octadecenoic acid)**	4
 **Linoleic acid (*cis*,*cis*-9,12-octadecadienoic acid)**	−5
 **Linolenic acid (*cis*,*cis*,*cis*-9,12,15-octadecatrienoic acid)**	−11
 **DHA, an omega-3 fatty acid [(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-4,7,10,13,16,19-docosahexaenoic acid]**	−44
 **Arachidonic acid, an omega-6 fatty acid [(5*Z*,8*Z*,11*Z*,14*Z*)-5,8,11,14-eicosatetraenoic acid]**	−49

TABLE 23.2 FATTY ACID COMPOSITION OBTAINED BY HYDROLYSIS OF COMMON FATS AND OILS

	Average Composition of Fatty Acids (mol %)											
	Saturated								Unsaturated			
Fat or Oil	C_4 Butyric Acid	C_6 Caproic Acid	C_8 Caprylic Acid	C_{10} Capric Acid	C_{12} Lauric Acid	C_{14} Myristic Acid	C_{16} Palmitic Acid	C_{18} Stearic Acid	C_{16} Palmitoleic Acid	C_{18} Oleic Acid	C_{18} Linoleic Acid	C_{18} Linolenic Acid
Animal Fats												
Butter	3–4	1–2	0–1	2–3	2–5	8–15	25–29	9–12	4–6	18–33	2–4	
Lard						1–2	25–30	12–18	4–6	48–60	6–12	0–1
Beef tallow						2–5	24–34	15–30		35–45	1–3	0–1
Vegetable Oils												
Olive						0–1	5–15	1–4		67–84	8–12	
Peanut							7–12	2–6		30–60	20–38	
Corn						1–2	7–11	3–4	1–2	25–35	50–60	
Cottonseed						1–2	18–25	1–2	1–3	17–38	45–55	
Soybean						1–2	6–10	2–4		20–30	50–58	5–10
Linseed							4–7	2–4		14–30	14–25	45–60
Coconut		0–1	5–7	7–9	40–50	15–20	9–12	2–4	0–1	6–9	0–1	
Marine Oils												
Cod liver						5–7	8–10	0–1	18–22	27–33	27–32	

Reprinted with permission of John Wiley & Sons, Inc., from Holum, J. R., *Organic and Biological Chemistry*, p. 220. Copyright 1978.

Figure 23.2 shows how the introduction of a single cis double bond affects the shape of a triacylglycerol and how catalytic hydrogenation can be used to convert an unsaturated triacylglycerol into a saturated one.

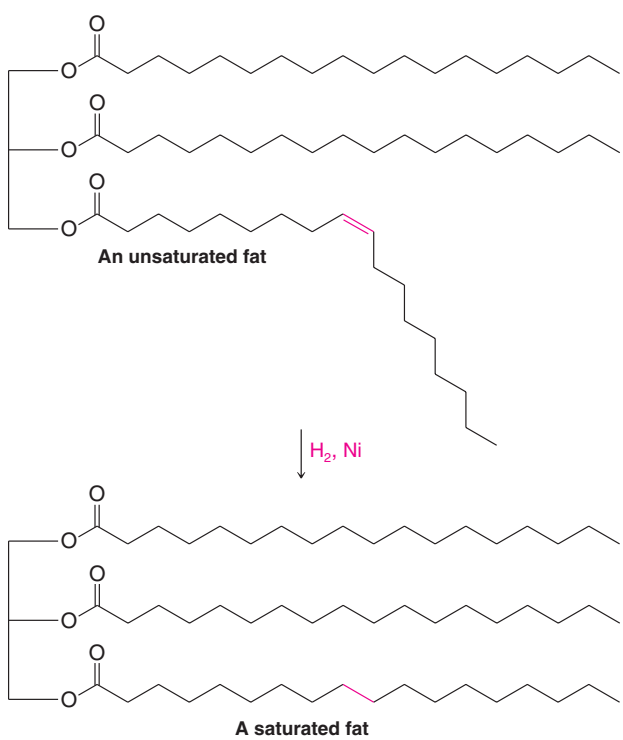


FIGURE 23.2 Two typical triacylglycerols, one unsaturated and one saturated. The cis double bond of the unsaturated triacylglycerol interferes with efficient crystal packing and causes an unsaturated fat to have a lower melting point. Hydrogenation of the double bond causes an unsaturated triacylglycerol to become saturated.

23.2A Hydrogenation of Triacylglycerols

Solid commercial cooking fats are manufactured by partial hydrogenation of vegetable oils. The result is the familiar "partially hydrogenated fat" present in so many prepared foods. Complete hydrogenation of the oil is avoided because a completely saturated triacylglycerol is very hard and brittle. Typically, the vegetable oil is hydrogenated until a semisolid of appealing consistency is obtained. One commercial advantage of partial hydrogenation is to give the fat a longer shelf life. Polyunsaturated oils tend to react by autoxidation (Section 10.12D), causing them to become rancid. One problem with partial hydrogenation, however, is that the catalyst isomerizes some of the unreacted double bonds from the natural cis arrangement to the unnatural trans arrangement, and there is accumulating evidence that trans fats are associated with an increased risk of cardiovascular disease.

23.2B Biological Functions of Triacylglycerols

The primary function of triacylglycerols in animals is as an energy reserve. When triacylglycerols are converted to carbon dioxide and water by biochemical reactions (i.e., when triacylglycerols are *metabolized*), they yield more than twice as many kilocalories per gram as do carbohydrates or proteins. This is largely because of the high proportion of carbon–hydrogen bonds per molecule.

In animals, specialized cells called **adipocytes** (fat cells) synthesize and store triacylglycerols. The tissue containing these cells, adipose tissue, is most abundant in the abdominal cavity and in the subcutaneous layer. Men have a fat content of about 21%, women about 26%. This fat content is sufficient to enable us to survive starvation for 2–3 months. By contrast, glycogen, our carbohydrate reserve, can provide only one day's energy need.

All of the saturated triacylglycerols of the body, and some of the unsaturated ones, can be synthesized from carbohydrates and proteins. Certain polyunsaturated fatty acids, however, are essential in the diets of higher animals.

The amount of fat in the diet, especially the proportion of saturated fat, has been a health concern for many years. There is compelling evidence that too much saturated fat in the diet is a factor in the development of heart disease and cancer.

THE CHEMISTRY OF... Olestra and Other Fat Substitutes

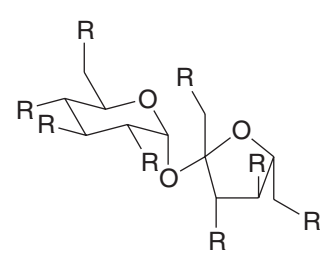
Olestra is a zero-calorie commercial fat substitute with the look and feel of natural fats. It is a synthetic compound whose structure involves a novel combination of natural components. The core of olestra is derived from sucrose, ordinary table sugar. Six to eight of the hydroxyl groups on the sucrose framework have long-chain carboxylic acids (fatty acids) appended to them by ester linkages. These fatty acids are from C_8 to C_{22} in length. In the industrial synthesis of olestra, these fatty acids derive from cottonseed or soybean oil.

Roberto Brosan/Time Life Pictures/Getty Images

A food product made with olestra.

(Illustration in center reprinted with permission from Doyle, E. Olestra? The Jury's Still Out. *Journal of Chemical Education*, Vol. 74, No. 4, 1997, pp. 370–372; © 1997, Division of Chemical Education, Inc. Copyright 1997 American Chemical Society.)

Olestra.



Olestra

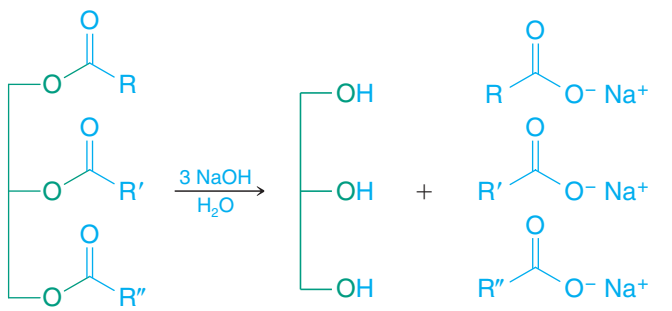
Six to eight of the R groups are fatty acid esters, the remainder being hydroxyl groups.

The presence of fatty acid esters in olestra bestows on it the taste and culinary properties of an ordinary fat. Yet, olestra is not digestible like a typical fat. This is because the steric bulk of olestra renders it unacceptable to the enzymes that catalyze hydrolysis of ordinary fats. Olestra passes through the digestive tract unchanged and thereby adds no calories to the diet. As it does so, however, olestra associates with and carries away some of the lipid-soluble vitamins, namely, vitamins A, D, E, and K. Foods prepared with olestra are supplemented with these vitamins to compensate for any loss that may result from their extraction by olestra. Studies conducted since olestra's approval have demonstrated that people report no more bothersome digestive effects when eating Olean (the trademark name for olestra) snacks than they do when eating full-fat chips.

Many other fat substitutes have received consideration. Among these are polyglycerol esters, which presumably by their steric bulk would also be undigestible, like the polyester olestra. Another approach to low-calorie fats, already in commercial use, involves replacement of some long-chain carboxylic acids on the glycerol backbone with medium- or short-chain carboxylic acids (C_2 to C_4). These compounds provide fewer calories because each CH_2 group that is absent from the glycerol ester (as compared to long-chain fatty acids) reduces the amount of energy (calories) liberated when that compound is metabolized. The calorie content of a given glycerol ester can essentially be tailored to provide a desired calorie output, simply by adjusting the ratio of long-chain to medium- and short-chain carboxylic acids. Still other low-calorie fat substitutes are carbohydrate- and protein-based compounds. These materials act by generating a similar gustatory response to that of fat, but for various reasons produce fewer calories.

23.2C Saponification of Triacylglycerols

- **Saponification** is the alkaline hydrolysis of triacylglycerols, leading to glycerol and a mixture of salts of long-chain carboxylic acids:



These salts of long-chain carboxylic acids are **soaps**, and this saponification reaction is the way most soaps are manufactured. Fats and oils are boiled in aqueous sodium hydroxide until hydrolysis is complete. Adding sodium chloride to the mixture then causes the soap to precipitate. (After the soap has been separated, glycerol can be isolated from the aqueous phase by distillation.) Crude soaps are usually purified by several reprecipitations. Perfumes can be added if a toilet soap is the desired product. Sand, sodium carbonate, and other fillers can be added to make a scouring soap, and air can be blown into the molten soap if the manufacturer wants to market a soap that floats.

The sodium salts of long-chain carboxylic acids (soaps) are almost completely miscible with water. However, they do not dissolve as we might expect, that is, as individual ions. Except in very dilute solutions, soaps exists as **micelles** (Fig. 23.3). Soap micelles

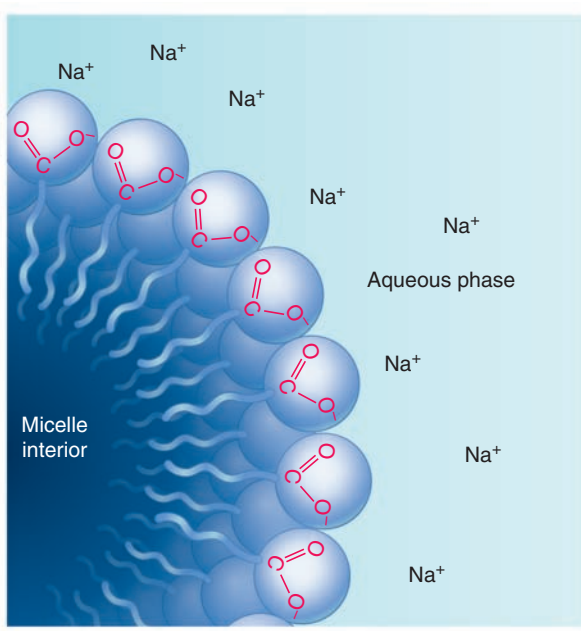


FIGURE 23.3 A portion of a soap micelle showing its interface with the polar dispersing medium.
(Reprinted with permission of John Wiley & Sons, Inc., from Karp, G., *Cell and Molecular Biology: Concepts and Experiments*, Fourth Edition, Copyright 1999.)

are usually spherical clusters of carboxylate anions that are dispersed throughout the aqueous phase. The carboxylate anions are packed together with their negatively charged (and thus, *polar*) carboxylate groups at the surface and with their nonpolar hydrocarbon chains on the interior. The sodium ions are scattered throughout the aqueous phase as individual solvated ions.

Micelle formation accounts for the fact that soaps dissolve in water. The nonpolar (and thus **hydrophobic**) alkyl chains of the soap remain in a nonpolar environment—in the interior of the micelle. The polar (and therefore **hydrophilic**) carboxylate groups are exposed to a polar environment—that of the aqueous phase. Because the surfaces of the micelles are negatively charged, individual micelles repel each other and remain dispersed throughout the aqueous phase.

Soaps serve their function as "dirt removers" in a similar way. Most dirt particles (e.g., on the skin) become surrounded by a layer of an oil or fat. Water molecules alone are unable to disperse these greasy globules because they are unable to penetrate the oily layer and separate the individual particles from each other or from the surface to which they are stuck. Soap solutions, however, *are* able to separate the individual particles because their hydrocarbon chains can "dissolve" in the oily layer (Fig. 23.4). As this happens, each individual particle develops an outer layer of carboxylate anions and presents the aqueous phase with a much more compatible exterior—a polar surface. The individual globules now repel each other and thus become dispersed throughout the aqueous phase. Shortly thereafter, they make their way down the drain.

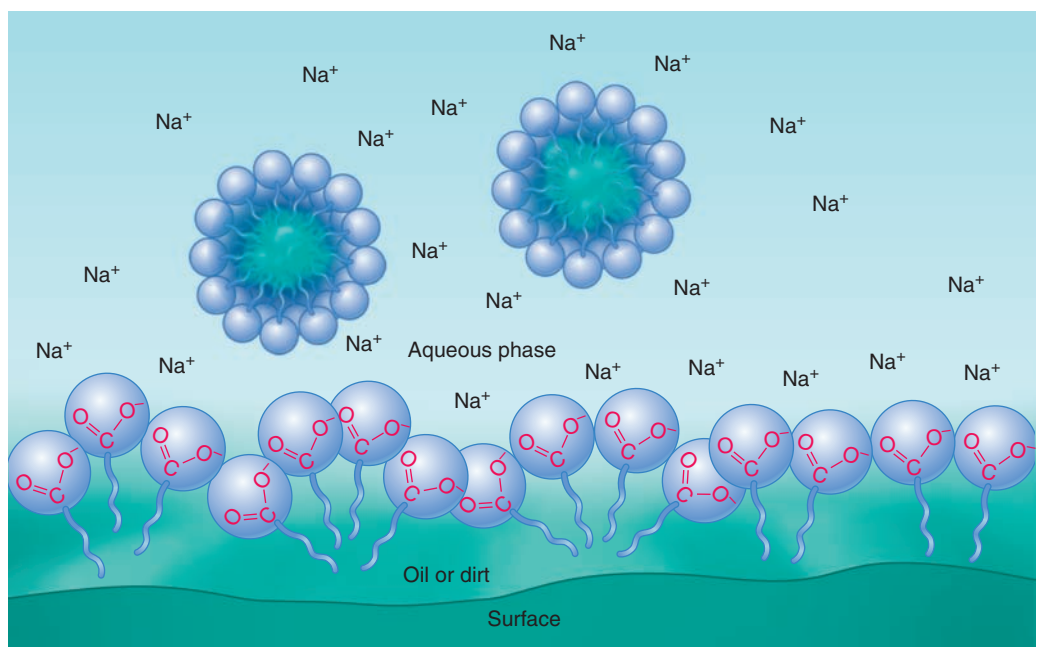


FIGURE 23.4 Dispersal of a hydrophobic material (e.g., oil, grease, or fat) by a soap.
(Adapted with permission of John Wiley & Sons, Inc., from Karp, G., *Cell and Molecular Biology: Concepts and Experiments*, Fourth Edition, Copyright 1999.)

Synthetic detergents (Fig. 23.5) function in the same way as soaps; they have long nonpolar alkane chains with polar groups at the end. The polar groups of most synthetic detergents are sodium sulfonates or sodium sulfates. (At one time, extensive use was made of synthetic detergents with highly branched alkyl groups. These detergents proved to be nonbiodegradable, and their use was discontinued.)

Synthetic detergents offer an advantage over soaps; they function well in "hard" water, that is, water containing Ca^{2+}, Fe^{2+}, Fe^{3+}, and Mg^{2+} ions. Calcium, iron, and

magnesium salts of alkanesulfonates and alkyl hydrogen sulfates are largely water soluble, and thus synthetic detergents remain in solution. Soaps, by contrast, form precipitates—the ring around the bathtub—when they are used in hard water.

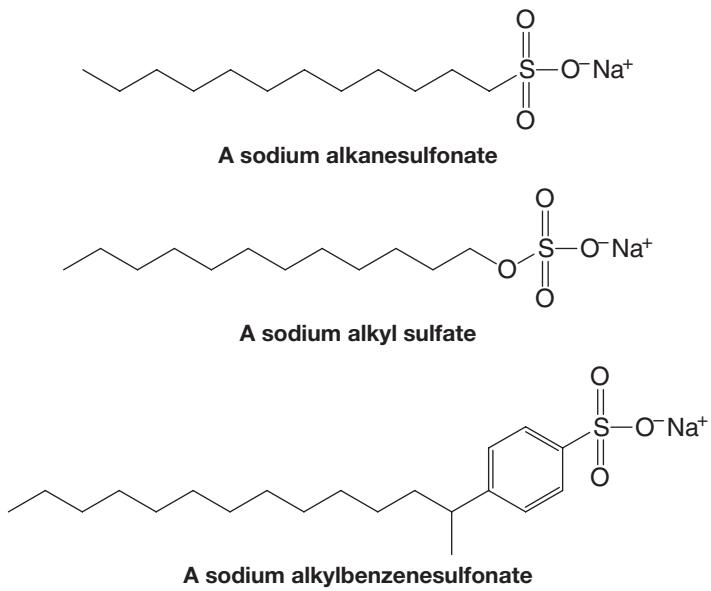
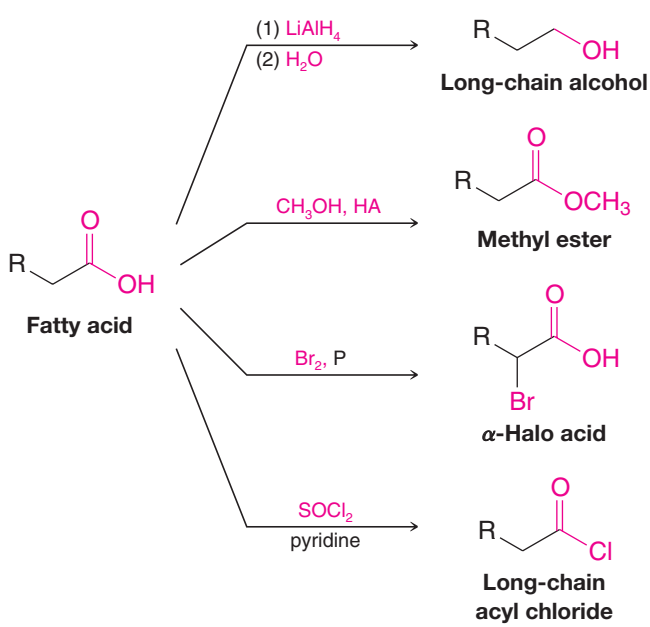


FIGURE 23.5 Typical synthetic detergents.

23.2D Reactions of the Carboxyl Group of Fatty Acids

Fatty acids, as we might expect, undergo reactions typical of carboxylic acids (see Chapter 17). They react with $LiAlH_4$ to form alcohols, with alcohols and mineral acid to form esters, with bromine and phosphorus to form α-halo acids, and with thionyl chloride to form acyl chlorides:

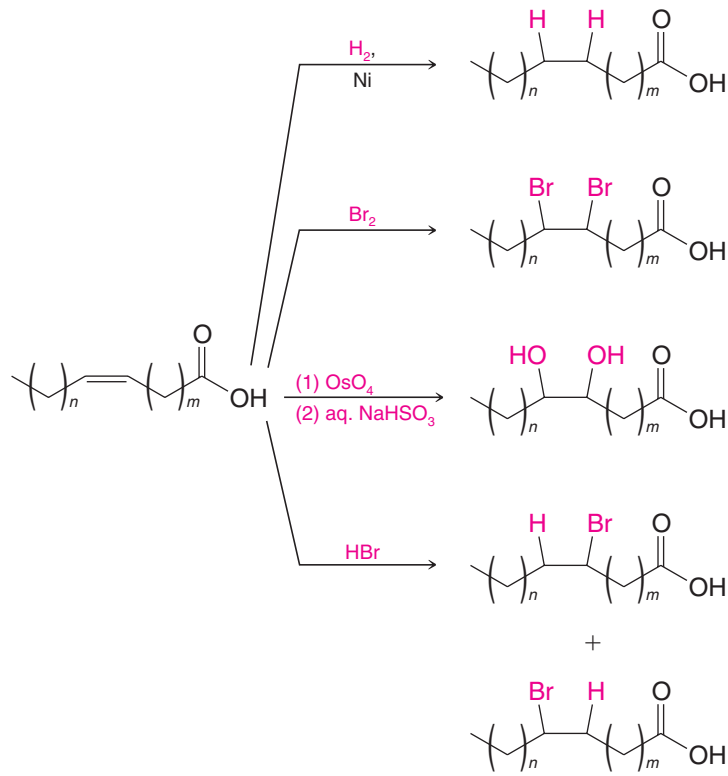


Helpful Hint

The reactions presented in Sections 23.2D and 23.2E in the context of fatty acids are the same as those we studied in earlier chapters regarding carboxylic acids and alkenes.

23.2E Reactions of the Alkenyl Chain of Unsaturated Fatty Acids

The double bonds of the carbon chains of fatty acids undergo characteristic alkene addition reactions (see Chapters 7 and 8):



PRACTICE PROBLEM 23.1 **(a)** How many stereoisomers are possible for 9,10-dibromohexadecanoic acid?

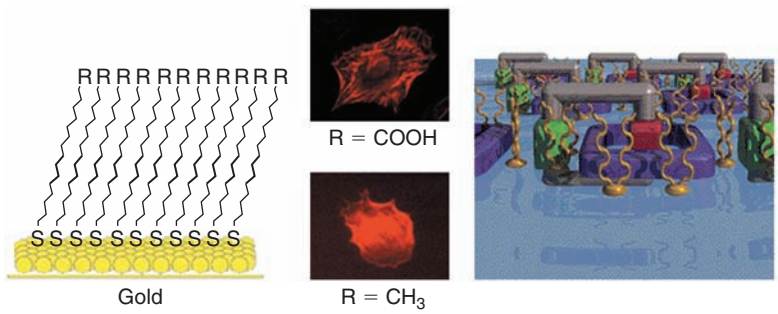
(b) The addition of bromine to palmitoleic acid yields primarily one set of enantiomers, (±)-*threo*-9,10-dibromohexadecanoic acid. The addition of bromine is an anti addition to the double bond (i.e., it apparently takes place through a bromonium ion intermediate). Taking into account the cis stereochemistry of the double bond of palmitoleic acid and the stereochemistry of the bromine addition, write three-dimensional structures for the (±)-*threo*-9,10-dibromohexadecanoic acids.

THE CHEMISTRY OF... Self-Assembled Monolayers—Lipids in Materials Science and Bioengineering

The graphic shown below (*a*) depicts a self-assembled monolayer of alkanethiol molecules on a gold surface. The alkanethiol molecules spontaneously form a layer that is one molecule thick (a monolayer) because they are tethered to the gold surface at one end by a covalent bond to the metal and because van der Waals intermolecular forces between the long alkane chains cause them to align next to each other in an approximately perpendicular orientation to the gold surface. Many researchers are exploiting self-assembled monolayers (SAMs) for the preparation of surfaces that have specific uses in medicine, computing, and telecommunications. One example in biomedical engineering that may lead to advances in surgery involves testing cells for their response to SAMs with varying head groups. By varying the structure of the exposed head group of the monolayer, it may be possible to create materials that have either affinity for or resistance against cell binding (*b*). Such properties could be useful in organ transplants for inhibiting rejection by cells of the immune system or in prosthesis surgeries where the binding of tissue to the artificial device is desired.

Monolayers called Langmuir–Blodgett (LB) films also involve self-assembly of molecules on a surface. In this case, however, the molecules do not become covalently attached to the surface. These LB films are inherently less stable than covalently bonded monolayers, but they have characteristics that are useful for certain applications in nanotechnology. For example, an LB film made from phospholipid (Section 23.6) and catenane molecules was used in making the array of molecular switches we discussed in

"The Chemistry of ... Nanoscale Motors and Molecular Switches" (Chapter 4). This LB monolayer (*c*) was formed at a water–air interface where the polar phosphate head groups of the phospholipid buried themselves in water and the hydrophobic carbon tails projected out into the air. Interspersed among them were the catenane molecules. In later steps, this monolayer was lifted from the water–air surface and transferred onto a solid gold surface.



(*a*) A self-assembled monolayer of alkanethiol molecules on a gold surface (R = CH_3 or COOH). (*b*) Spreading of a Swiss 3T3 fibroblast cell plated on a COOH-terminated self-assembled monolayer (top) indicates effective signaling on the surface. The fibroblast cell on a CH_3-terminated monolayer (bottom) curls away from surface. The cells were stained with a rhodamine-tagged toxin that binds to filamentous actin and then were imaged under fluorescent light. (*c*) A Langmuir–Blodgett (LB) film formed from phospholipid molecules (golden color) and catenane molecules (purple and gray with green and red groups) at an air–water interface.

(Part (*c*) is reprint with permission from Pease, A. R.; Jeppensen, J. O.; Stoddart, J. F.; Luo, Y.; Colier, C. P.; Heath, J. R., *Accounts of Chemical Research*, **2001**, *34*, 433–444.)

23.3 TERPENES AND TERPENOIDS

People have isolated organic compounds from plants since antiquity. By gently heating or by steam distilling certain plant materials, one can obtain mixtures of odoriferous compounds known as **essential oils**. These compounds have had a variety of uses, particularly in early medicine and in the making of perfumes.

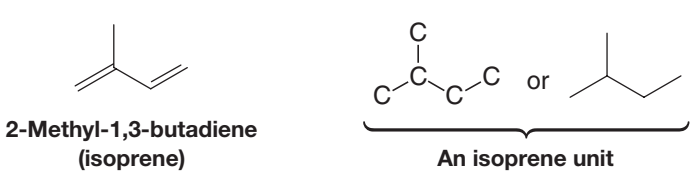
As the science of organic chemistry developed, chemists separated the various components of these mixtures and determined their molecular formulas and, later, their structural formulas. Even today these natural products offer challenging problems for chemists interested in structure determination and synthesis. Research in this area has also given us important information about the ways the plants themselves synthesize these compounds.

- Hydrocarbons known generally as **terpenes** and oxygen-containing compounds called **terpenoids** are the most important constituents of essential oils.
- Most terpenes have skeletons of 10, 15, 20, or 30 carbon atoms and are classified in the following way:

Number of Carbon Atoms	Class
10	Monoterpenes
15	Sesquiterpenes
20	Diterpenes
30	Triterpenes

- One can view terpenes as being built up from two or more C_5 units known as **isoprene units**. Isoprene is 2-methyl-1,3-butadiene.

Isoprene and the isoprene unit can be represented in various ways:

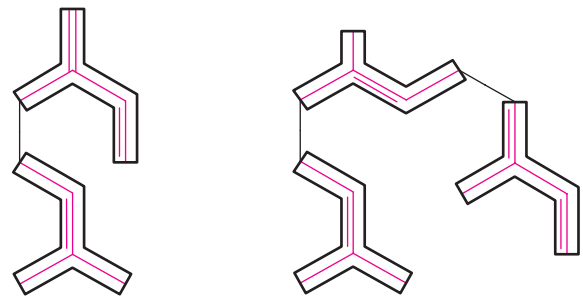


2-Methyl-1,3-butadiene (isoprene) — **An isoprene unit**

Helpful Hint

Terpene biosynthesis is described in Special Topic E (*WileyPLUS*).

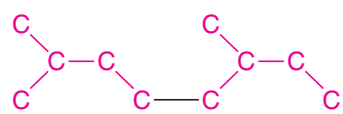
We now know that plants do not synthesize terpenes from isoprene (see Special Topic E, *WileyPLUS*). However, recognition of the isoprene unit as a component of the structure of terpenes has been a great aid in elucidating their structures. We can see how if we examine the following structures:



The isoprene units in myrcene and α-farnesene are outlined.

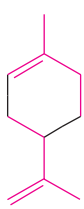
Myrcene (isolated from bay oil) **α-Farnesene (from natural coating of apples)**

By the outlines in the formulas above, we can see that the monoterpene (myrcene) has two isoprene units; the sesquiterpene (α-farnesene) has three. In both compounds the isoprene units are linked head to tail:

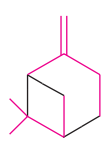


(head) (tail) (head) (tail)

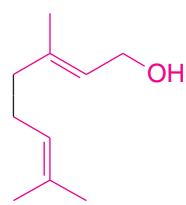
Many terpenes also have isoprene units linked in rings, and others (terpenoids) contain oxygen:



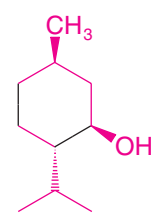
Limonene (from oil of lemon or orange)



β-Pinene (from oil of turpentine)



Geraniol (from roses and other flowers)



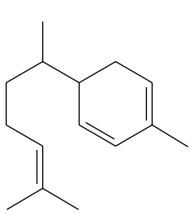
Menthol (from peppermint)

SOLVED PROBLEM 23.1

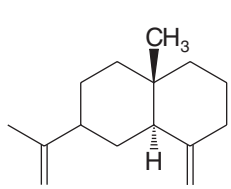
Hydrogenation of the sesquiterpene caryophyllene ($C_{15}H_{24}$) produces a compound with the molecular formula $C_{15}H_{28}$. What information does this provide about the structure of caryophyllene?

STRATEGY AND ANSWER: The molecular formula $C_{15}H_{24}$ gives an index of hydrogen deficiency (IHD) of 4 for caryophyllene. Its reaction with two molar equivalents of hydrogen suggests that caryophyllene has two double bonds or one triple bond, accounting for two of the four units of hydrogen deficiency. The remaining two units of hydrogen deficiency are due to rings. (The structure of caryophyllene is given in Practice Problem 23.2.)

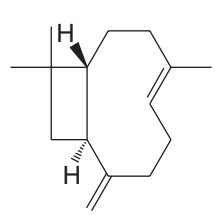
PRACTICE PROBLEM 23.2 **(a)** Show the isoprene units in each of the following terpenes. **(b)** Classify each as a monoterpene, sesquiterpene, diterpene, and so on.



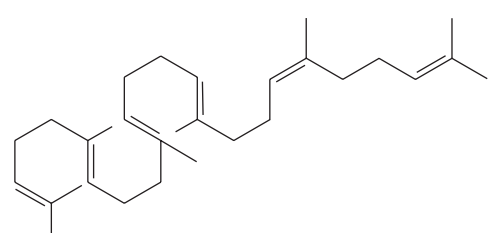
Zingiberene (from oil of ginger)



β-Selinene (from oil of celery)



Caryophyllene (from oil of cloves)

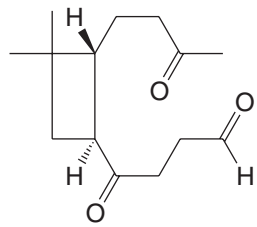


Squalene (from shark liver oil)

SOLVED PROBLEM 23.2

What products would you expect to obtain if caryophyllene were subjected to ozonolysis followed by workup with dimethyl sulfide?

ANSWER:



and HCHO (formaldehyde)

PRACTICE PROBLEM 23.3

What products would you expect to obtain if each of the following terpenes were subjected to ozonolysis and subsequent treatment with dimethyl sulfide?

(a) Myrcene **(b)** Limonene **(c)** α-Farnesene **(d)** Geraniol **(e)** Squalene

PRACTICE PROBLEM 23.4

Give structural formulas for the products that you would expect from the following reactions:

(a) β-Pinene $\xrightarrow{KMnO_4,\ heat}$

(b) Zingiberene $\xrightarrow{H_2,\ Pt}$

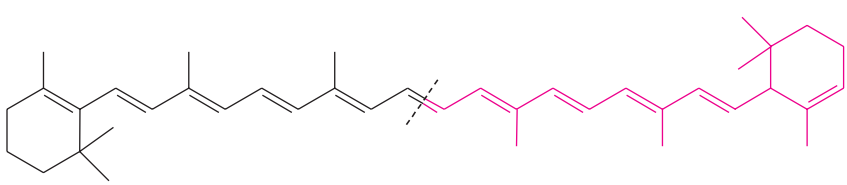
(c) Caryophyllene $\xrightarrow{HCl}$

(d) β-Selinene $\xrightarrow[(2)\ H_2O_2,\ HO^-]{(1)\ BH_3{:}THF\ (2\ equiv.)}$

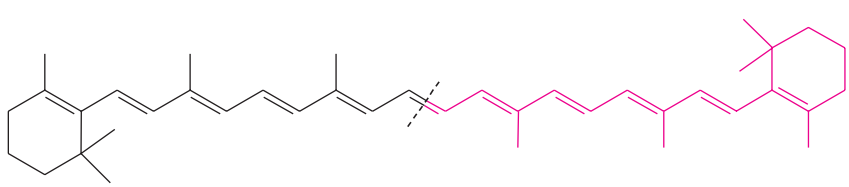
PRACTICE PROBLEM 23.5

What simple chemical test could you use to distinguish between geraniol and menthol?

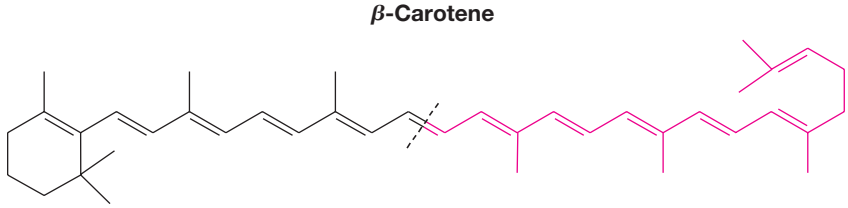
The carotenes are tetraterpenes. They can be thought of as two diterpenes linked in tail-to-tail fashion:



α-Carotene

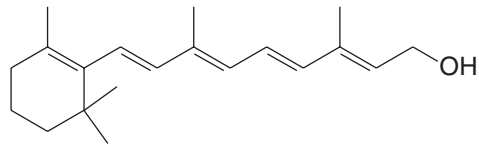


β-Carotene



γ-Carotene

The carotenes are present in almost all green plants. In animals, all three carotenes serve as precursors for vitamin A, for they all can be converted to vitamin A by enzymes in the liver.

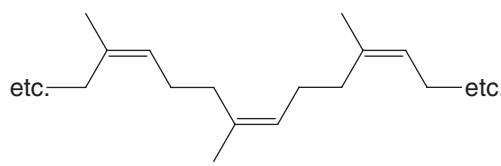


Vitamin A

In this conversion, one molecule of β-carotene yields two of vitamin A; α- and γ-carotene give only one. Vitamin A is important not only in vision but in many other ways as well. For example, young animals whose diets are deficient in vitamin A fail to grow. Vitamin A, β-carotene, and vitamin E ("The Chemistry of ... Antioxidants," Section 10.12) are also important lipid-soluble antioxidants.

23.3A Natural Rubber

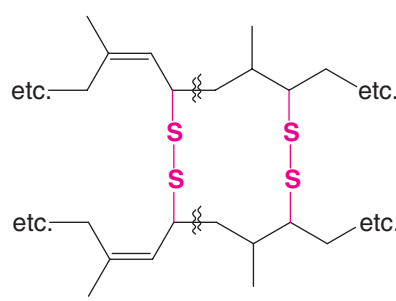
Natural rubber can be viewed as a 1,4-addition polymer of isoprene. In fact, pyrolysis degrades natural rubber to isoprene. Pyrolysis (Greek: *pyros*, a fire, + *lysis*) is the heating of a substance in the absence of air until it decomposes. The isoprene units of natural rubber are all linked in a head-to-tail fashion, and all of the double bonds are cis:



Natural rubber
(*cis*-1,4-polyisoprene)

Ziegler–Natta catalysts (see Special Topic B in *WileyPLUS*) make it possible to polymerize isoprene and obtain a synthetic product that is identical with the rubber obtained from natural sources.

Pure natural rubber is soft and tacky. To be useful, natural rubber has to be *vulcanized*. In vulcanization, natural rubber is heated with sulfur. A reaction takes place that produces cross-links between the *cis*-polyisoprene chains and makes the rubber much harder. Sulfur reacts both at the double bonds and at allylic hydrogen atoms:



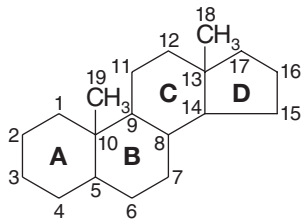
Vulcanized rubber

23.4 STEROIDS

The lipid fractions obtained from plants and animals contain another important group of compounds known as **steroids**. Steroids are important "biological regulators" that nearly always show dramatic physiological effects when they are administered to living organisms. Among these important compounds are male and female sex hormones, adrenocortical hormones, D vitamins, the bile acids, and certain cardiac poisons.

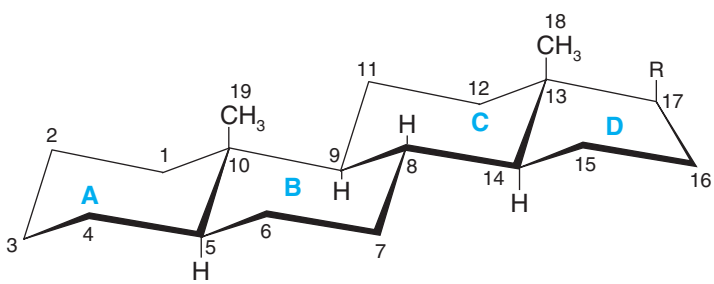
23.4A Structure and Systematic Nomenclature of Steroids

Steroids are derivatives of the following perhydrocyclopentanophenanthrene ring system:

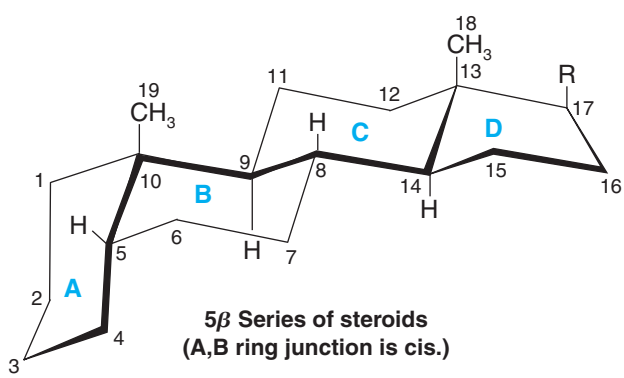


The carbon atoms of this ring system are numbered as shown. The four rings are designated with letters. In most steroids the B,C and C,D ring junctions are trans. The A,B ring junction, however, may be either cis or trans, and this possibility gives rise to two general groups of steroids having the three-dimensional structures shown in Fig. 23.6.

The methyl groups that are attached at points of ring junction (i.e., those numbered 18 and 19) are called **angular methyl groups**, and they serve as important reference points for stereochemical designations. The angular methyl groups protrude above the general plane of the ring system when it is written in the manner shown in Fig. 23.6. By convention, other groups that lie on the same general side of the molecule as the angular methyl groups (i.e., on the top side) are designated ***β* substituents** (these are written with a solid wedge). Groups that lie generally on the bottom (i.e., are trans to the angular methyl groups) are designated ***α* substituents** (these are written with a dashed wedge). When α and β designations are applied to the hydrogen atom at position 5, the ring system in which the A,B ring junction is trans becomes the 5α series; the ring system in which the A,B ring junction is cis becomes the 5β series.



5*α* Series of steroids
(All ring junctions are trans.)



5*β* Series of steroids
(A,B ring junction is cis.)

FIGURE 23.6 The basic ring systems of the 5α and 5β series of steroids.

Helpful Hint

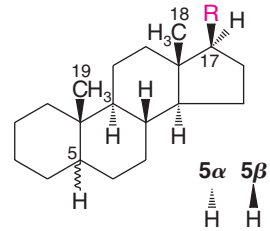
Build handheld molecular models of the 5α and 5β series of steroids and use them to explore the structures of steroids discussed in this chapter.

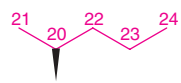
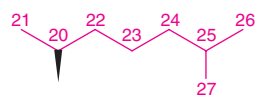
PRACTICE PROBLEM 23.6

Draw the two basic ring systems given in Fig. 23.6 for the 5α and 5β series showing all hydrogen atoms of the cyclohexane rings. Label each hydrogen atom as to whether it is axial or equatorial.

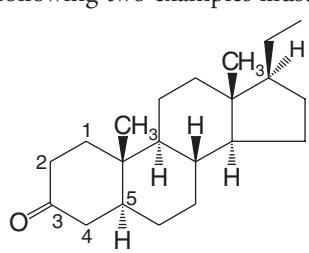
In systematic nomenclature the nature of the R group at position 17 determines (primarily) the base name of an individual steroid. These names are derived from the steroid hydrocarbon names given in Table 23.3.

TABLE 23.3 NAMES OF STEROID HYDROCARBONS

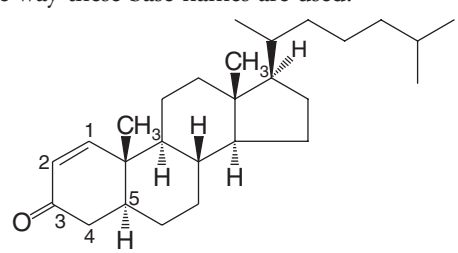


R	Name
H	Androstane
H (with —H also replacing ^{19}—CH_3)	Estrane
	Pregnane
	Cholane
	Cholestane

The following two examples illustrate the way these base names are used:



5α-Pregnan-3-one



5α-Cholest-1-en-3-one

We shall see that many steroids also have common names and that the names of the steroid hydrocarbons given in Table 23.3 are derived from these common names.

PRACTICE PROBLEM 23.7 **(a)** Androsterone, a secondary male sex hormone, has the systematic name 3α-hydroxy-5α-androstan-17-one. Give a three-dimensional formula for androsterone.

(b) Norethynodrel, a synthetic steroid that has been widely used in oral contraceptives, has the systematic name 17α-ethynyl-17β-hydroxy-5(10)-estren-3-one. Give a three-dimensional formula for norethynodrel.

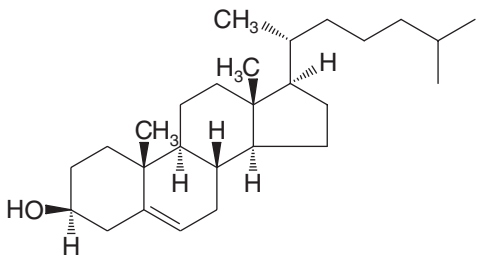
23.4B Cholesterol

Cholesterol, one of the most widely occurring steroids, can be isolated by extraction of nearly all animal tissues. Human gallstones are a particularly rich source.

Cholesterol was first isolated in 1770. In the 1920s, two German chemists, Adolf Windaus (University of Göttingen) and Heinrich Wieland (University of Munich), were responsible for outlining a structure for cholesterol; they received Nobel prizes for their work in 1927 and 1928.*

*The original cholesterol structure proposed by Windaus and Wieland was incorrect. This became evident in 1932 as a result of X-ray diffraction studies done by the British physicist J. D. Bernal. By the end of 1932, however, English scientists, and Wieland himself, using Bernal's results, were able to outline the correct structure of cholesterol.

Part of the difficulty in assigning an absolute structure to cholesterol is that cholesterol contains *eight* tetrahedral chirality centers. This feature means that 2^8, or 256, possible stereoisomeric forms of the basic structure are possible, *only one of which is cholesterol*:



5-Cholesten-3β-ol
(absolute configuration of cholesterol)

Helpful Hint

We saw how cholesterol is biosynthesized in "The Chemistry of . . . Cholesterol Biosynthesis" in *WileyPLUS* materials for Chapter 8.

Designate with asterisks the eight chirality centers of cholesterol. **PRACTICE PROBLEM 23.8**

Cholesterol occurs widely in the human body, but not all of the biological functions of cholesterol are yet known. Cholesterol is known to serve as an intermediate in the biosynthesis of all of the steroids of the body. Cholesterol, therefore, is essential to life. We do not need to have cholesterol in our diet, however, because our body can synthesize all we need. When we ingest cholesterol, our body synthesizes less than if we ate none at all, but the total cholesterol is more than if we ate none at all. Far more cholesterol is present in the body than is necessary for steroid biosynthesis. High levels of blood cholesterol have been implicated in the development of arteriosclerosis (hardening of the arteries) and in heart attacks that occur when cholesterol-containing plaques block arteries of the heart. Considerable research is being carried out in the area of cholesterol metabolism with the hope of finding ways of minimizing cholesterol levels through the use of dietary adjustments or drugs.

It is important to note that, in common language, "cholesterol" does not necessarily refer only to the pure compound that chemists call cholesterol, but often refers instead to mixtures that contain cholesterol, other lipids, and proteins. These aggregates are called chylomicrons, high-density lipoproteins (HDLs), and low-density lipoproteins (LDLs). They have structures generally resembling globular micelles, and they are the vehicles by which cholesterol is transported through the aqueous environment of the body. Hydrophilic groups of their constituent proteins and phospholipids, and cholesterol hydroxyl substituents are oriented outward toward the water medium so as to facilitate transport of the lipids through the circulatory system. Chylomicrons transport dietary lipids from the intestines to the tissues. HDLs (the "good cholesterol") carry lipids from the tissues to the liver for degradation and excretion. LDL ("bad cholesterol") carries biosynthesized lipids from the liver to the tissues (see Fig. 23.7).

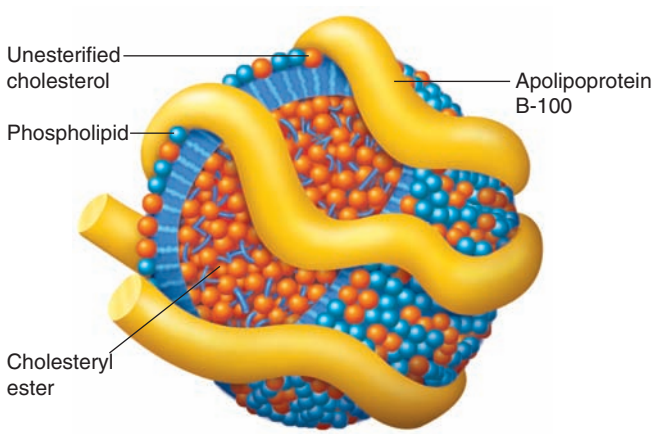
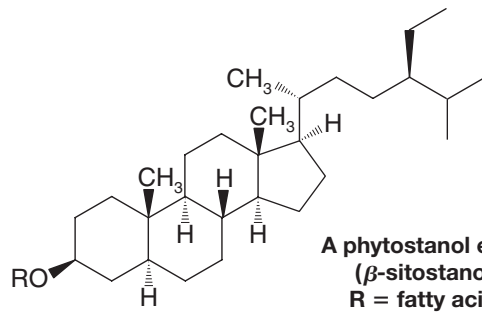


FIGURE 23.7 An LDL showing a core of cholesterol esters and a shell of phospholipids and unesterified cholesterol (hydroxyl groups exposed), wrapped in an apolipoprotein. The phospholipid head groups and hydrophilic residues of the protein support the water compatibility of the LDL particle.
(Reprinted with permission of John Wiley & Sons, Inc., from Voet, D. and Voet, J. G., *Biochemistry*, Second Edition. © 1995 Voet, D. and Voet, J. G.)

Certain compounds related to steroids and derived from plants are now known to lower total blood cholesterol when used in dietary forms approved by the FDA. Called phytostanols and phytosterols, these patented compounds act by inhibiting intestinal absorption of dietary cholesterol. They are marketed as food in the form of edible spreads. An example of a phytostanol is shown here.

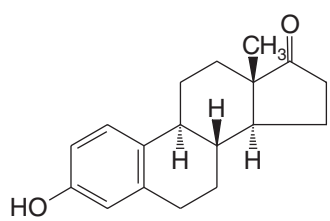


A phytostanol ester (β-sitostanol, R = fatty acid)

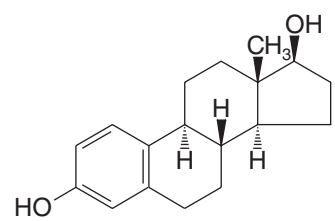
23.4C Sex Hormones

The sex hormones can be classified into three major groups: (1) the female sex hormones, or **estrogens**; (2) the male sex hormones, or **androgens**; and (3) the pregnancy hormones, or **progestins**.

The first sex hormone to be isolated was an estrogen, *estrone*. Working independently, Adolf Butenandt (in Germany at the University of Göttingen) and Edward Doisy (in the United States at St. Louis University) isolated estrone from the urine of pregnant women. They published their discoveries in 1929. Later, Doisy was able to isolate the much more potent estrogen, *estradiol*. In this research Doisy had to extract *4 tons* of sow ovaries in order to obtain just 12 mg of estradiol. Estradiol, it turns out, is the true female sex hormone, and estrone is a metabolized form of estradiol that is excreted.



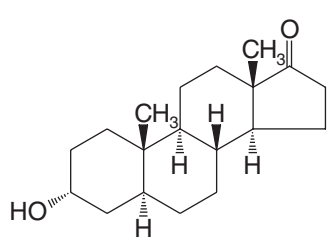
Estrone
[3-hydroxy-1,3,5(10)-estratrien-17-one]



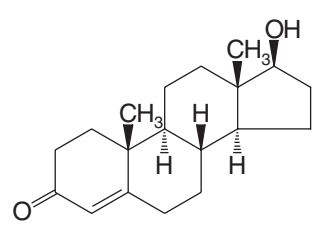
Estradiol
[1,3,5(10)-estratriene-3,17β-diol]

Estradiol is secreted by the ovaries and promotes the development of the secondary female characteristics that appear at the onset of puberty. Estrogens also stimulate the development of the mammary glands during pregnancy and induce estrus (heat) in animals.

In 1931, Butenandt and Kurt Tscherning isolated the first androgen, *androsterone*. They were able to obtain 15 mg of this hormone by extracting approximately 15,000 L of male urine. Soon afterward (in 1935), Ernest Laqueur (in Holland) isolated another male sex hormone, *testosterone*, from bull testes. It soon became clear that testosterone is the true male sex hormone and that androsterone is a metabolized form of testosterone that is excreted in the urine.



Androsterone
(3α-hydroxy-5α-androstan-17-one)



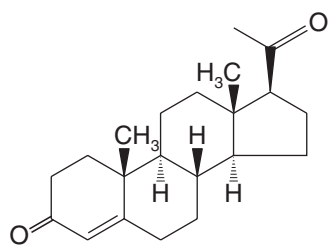
Testosterone
(17β-hydroxy-4-androsten-3-one)

Testosterone, secreted by the testes, is the hormone that promotes the development of secondary male characteristics: the growth of facial and body hair, the deepening of the voice, muscular development, and the maturation of the male sex organs.

Testosterone and estradiol, then, are the chemical compounds from which "maleness" and "femaleness" are derived. It is especially interesting to examine their structural formulas and see how very slightly these two compounds differ. Testosterone has an angular methyl group at the A,B ring junction that is missing in estradiol. Ring A of estradiol is a benzene ring and, as a result, estradiol is a phenol. Ring A of testosterone contains an α,β-unsaturated keto group.

PRACTICE PROBLEM 23.9

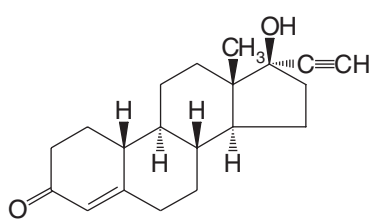
The estrogens (estrone and estradiol) are easily separated from the androgens (androsterone and testosterone) on the basis of one of their chemical properties. What is that property, and how could such a separation be accomplished?



Progesterone
(4-pregnene-3,20-dione)

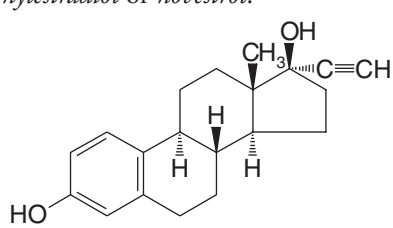
Progesterone is the most important *progestin* (pregnancy hormone). After ovulation occurs, the remnant of the ruptured ovarian follicle (called the *corpus luteum*) begins to secrete progesterone. This hormone prepares the lining of the uterus for implantation of the fertilized ovum, and continued progesterone secretion is necessary for the completion of pregnancy. (Progesterone is secreted by the placenta after secretion by the corpus luteum declines.)

Progesterone *also suppresses ovulation*, and it is the chemical agent that apparently accounts for the fact that pregnant women do not conceive again while pregnant. It was this observation that led to the search for synthetic progestins that could be used as oral contraceptives. (Progesterone itself requires very large doses to be effective in suppressing ovulation when taken orally because it is degraded in the intestinal tract.) A number of such compounds have been developed and are now widely used. In addition to norethynodrel (see Practice Problem 23.7), another widely used synthetic progestin is its double-bond isomer, *norethindrone*:



Norethindrone
(17α-ethynyl-17 β-hydroxy-4-estren-3-one)

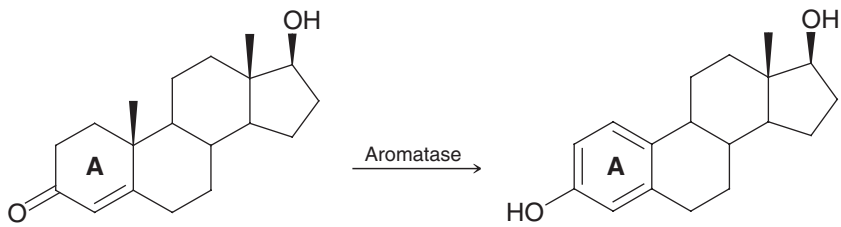
Synthetic estrogens have also been developed, and these are often used in oral contraceptives in combination with synthetic progestins. A very potent synthetic estrogen is the compound called *ethynylestradiol* or *novestrol*:



Ethynylestradiol
[17α-ethynyl-1,3,5(10)-estratriene-3,17β-diol]

THE CHEMISTRY OF... The Enzyme Aromatase

Look at the structures for testosterone and estradiol below. Testosterone is the primary male sex hormone, or **androgen**. It is the hormone that promotes the development of secondary male characteristics at puberty, such as muscular development and the maturation of the male sex organs. Estradiol is the primary **estrogen**. Estrogens promote the development of secondary female characteristics that occur at the onset of puberty and regulate the reproductive cycle. A significant molecular difference between the two hormones is the presence of a benzene ring in the female sex hormone.



Testosterone **Estradiol**

Aromatase is an enzyme that converts the male sex hormone, testosterone, into the female sex hormone, estradiol. In the course of this transformation, ring A of testosterone is converted to a benzene ring in estradiol.

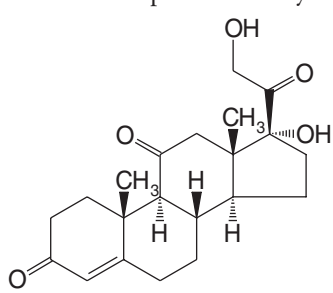
Estrogen is essential for male behaviors. This may seem counterintuitive. However, during fetal development, testosterone produced in the male fetus interacts with aromatase in the fetal brain, where it is converted to estrogen. There is mounting evidence that this locally produced estrogen (which interacts with estrogen receptors in the brain) is responsible for male behavior. In fact, mutant male mice deficient in aromatase activity display a profound deficit in male sexual behavior.

In women who have not reached menopause the main source of estradiol is the ovaries. After menopause, aromatase turns testosterone, produced by the adrenal glands, into estradiol.

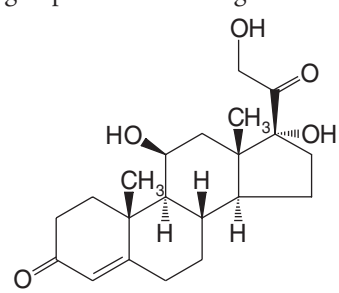
Certain breast cancers require estrogen to grow. Aromatase inhibitors, because they block the synthesis of estrogen, are a new class of drugs used in the treatment of breast cancer in postmenopausal women.

23.4D Adrenocortical Hormones

At least 28 different hormones have been isolated from the adrenal cortex, part of the adrenal glands that sit on top of the kidneys. Included in this group are the following two steroids:



Cortisone
(17α,21-dihydroxy-4-pregnene-3,11,20-trione)



Cortisol
(11β,17α,21-trihydroxy-4-pregnene-3,20-dione)

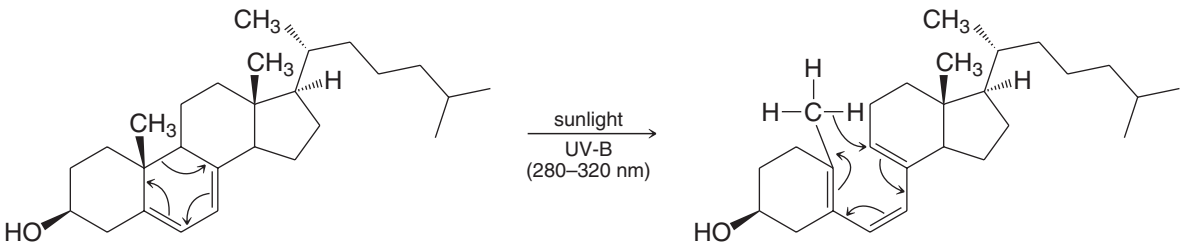
Most of the adrenocortical steroids have an oxygen function at position 11 (a keto group in cortisone, for example, and a β-hydroxyl in cortisol). Cortisol is the major hormone synthesized by the human adrenal cortex.

The adrenocortical steroids are apparently involved in the regulation of a large number of biological activities, including carbohydrate, protein, and lipid metabolism; water and electrolyte balance; and reactions to allergic and inflammatory phenomena. Recognition, in 1949, of the anti-inflammatory effect of cortisone and its usefulness in the treatment of rheumatoid arthritis led to extensive research in this area. Many 11-oxygenated steroids are now used in the treatment of a variety of disorders ranging from Addison's disease to asthma and skin inflammations.

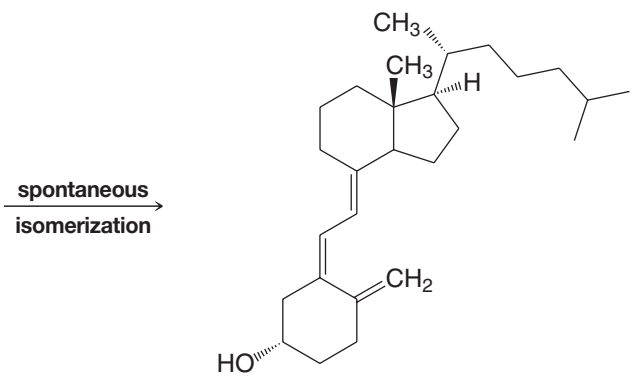
23.4E D Vitamins

The demonstration, in 1919, that sunlight helped cure rickets—a childhood disease characterized by poor bone growth—began a search for a chemical explanation.

Subsequent investigations showed that D vitamins were involved, and eventually it became known that one of several D vitamins, called vitamin D_3, is the curative factor. Vitamin D_3 is formed in the skin from 7-dehydrocholesterol by two reactions. In the first reaction (below), ultraviolet light in the UV-B range (280–320 nm, which can penetrate the epidermal layer) brings about a 6-electron conrotatory electrocyclic reaction (see Special Topic H, *WileyPLUS*) to produce pre-vitamin D_3. Following this event, a spontaneous isomerization (by way of a [1,7] sigmatropic hydride shift) produces vitamin D_3 itself.



7-Dehydrocholesterol **Pre-vitamin D_3**



Vitamin D_3

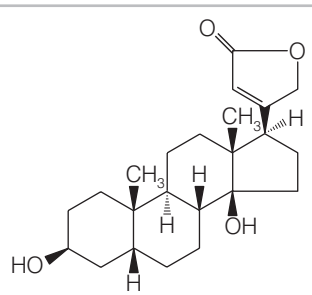
Vitamin D_3 is required for good health because it is essential in the process by which calcium (as Ca^{2+}) is absorbed from the intestine so as to allow for proper bone growth.

Various factors can cause a deficiency of sunlight and therefore of vitamin D_3, including one's geographic latitude and the season of the year. Sunlight levels are lower in extreme northern and southern latitudes, and are much lower in winter, so much so that for these conditions dietary guidelines in many countries call for supplemental D_3 for children and older persons. Other factors that can affect vitamin D_3 production in the skin are skin coloration, cloud cover, and the use of sunscreens.

23.4F Other Steroids

The structures, sources, and physiological properties of a number of other important steroids are given in Table 23.4.

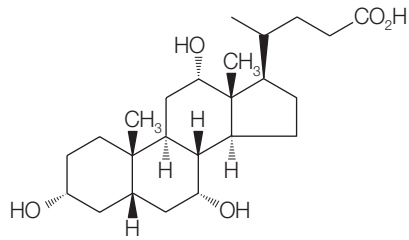
TABLE 23.4 OTHER IMPORTANT STEROIDS



Digitoxigenin

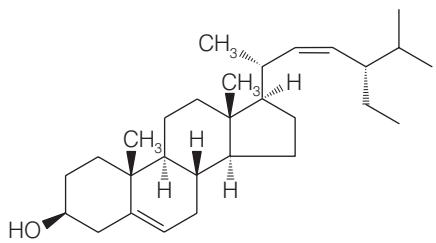
Digitoxigenin is a cardiac aglycone that can be isolated by hydrolysis of digitalis, a pharmaceutical that has been used in treating heart disease since 1785. In digitalis, sugar molecules are joined in acetal linkages to the 3-OH group of the steroid. In small doses digitalis strengthens the heart muscle; in larger doses it is a powerful heart poison. The aglycone has only about one-fortieth the activity of digitalis.

(continues on next page)



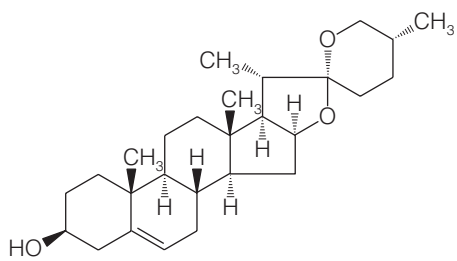
Cholic acid

Cholic acid is the most abundant acid obtained from the hydrolysis of human or ox bile. Bile is produced by the liver and stored in the gallbladder. When secreted into the small intestine, bile emulsifies lipids by acting as a soap. This action aids in the digestive process.



Stigmasterol

Stigmasterol is a widely occurring plant steroid that is obtained commercially from soybean oil. β-Sitostanol (a phytostanol, esters of which inhibit dietary cholesterol absorption) has the same formula except that it is saturated (C5 hydrogen is α).

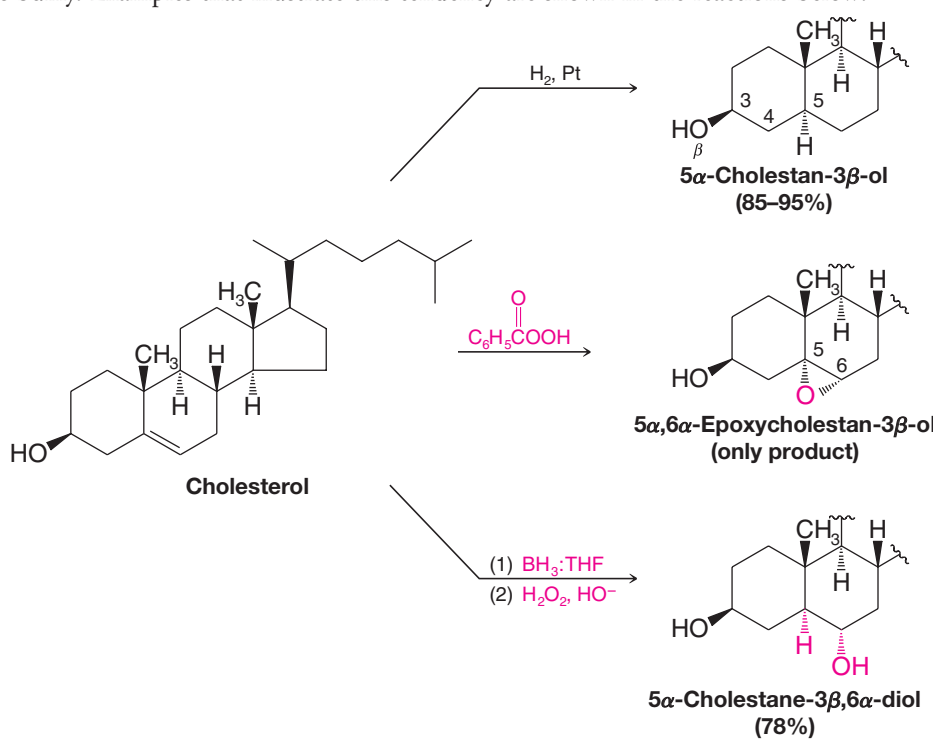


Diosgenin

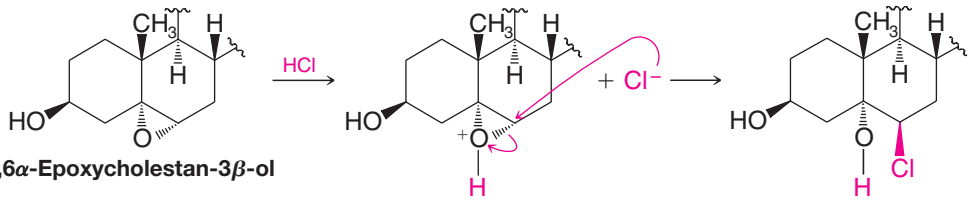
Diosgenin is obtained from a Mexican vine, *cabeza de negro*, genus *Dioscorea*. It is used as the starting material for a commercial synthesis of cortisone and sex hormones.

23.4G Reactions of Steroids

Steroids undergo all of the reactions that we might expect of molecules containing double bonds, hydroxyl groups, ketone groups, and so on. While the stereochemistry of steroid reactions can be quite complex, it is often strongly influenced by the steric hindrance presented at the β face of the molecule by the angular methyl groups. Many reagents react preferentially at the relatively unhindered α face, especially when the reaction takes place at a functional group very near an angular methyl group and when the attacking reagent is bulky. Examples that illustrate this tendency are shown in the reactions below:



When the epoxide ring of 5α,6α-epoxycholestan-3β-ol (see the following reaction) is opened, attack by chloride ion must occur from the β face, but it takes place at the more open 6 position. Notice that the 5 and 6 substituents in the product are *diaxial* (Section 8.13):



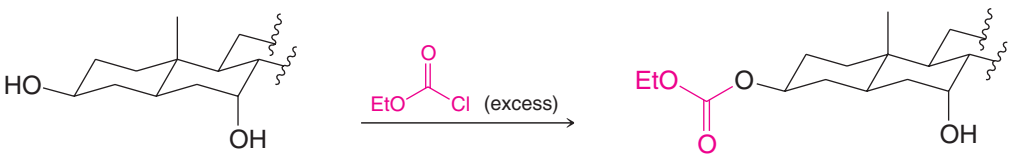
5α,6α-Epoxycholestan-3β-ol

PRACTICE PROBLEM 23.10

Show how you might convert cholesterol into each of the following compounds:

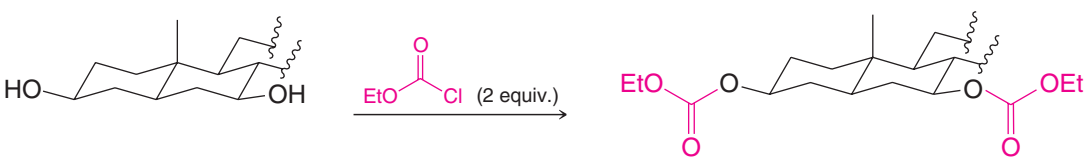
(a) 5α,6β-Dibromocholestan-3β-ol **(b)** Cholestane-3β,5α,6β-triol **(c)** 5α-Cholestan-3-one **(d)** 6α-Deuterio-5α-cholestan-3β-ol **(e)** 6β-Bromocholestane-3β,5α-diol

The relative openness of equatorial groups (when compared to axial groups) also influences the stereochemical course of steroid reactions. When 5α-cholestane-3β,7α-diol (see the following reaction) is treated with excess ethyl chloroformate (EtOCOCl), only the equatorial 3β-hydroxyl becomes esterified. The axial 7α-hydroxyl is unaffected by the reaction:



5α-Cholestane-3β,7α-diol **(only product)**

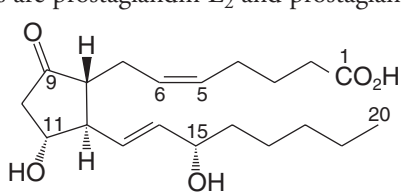
By contrast, treating 5α-cholestane-3β,7β-diol with excess ethyl chloroformate esterifies both hydroxyl groups. In this instance, both groups are equatorial:



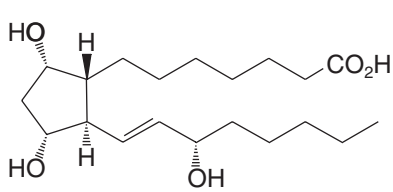
5α-Cholestane-3β,7β-diol **(only product)**

23.5 PROSTAGLANDINS

One very active area of research has concerned a group of lipids called **prostaglandins**. Prostaglandins are C_{20} carboxylic acids that contain a five-membered ring, at least one double bond, and several oxygen-containing functional groups. Two of the most biologically active prostaglandins are prostaglandin E_2 and prostaglandin $F_{1\alpha}$:



Prostaglandin E_2 (PGE_2)



Prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$)

Helpful Hint

These names for the prostaglandins are abbreviated designations used by workers in the field; systematic names are seldom used for prostaglandins.

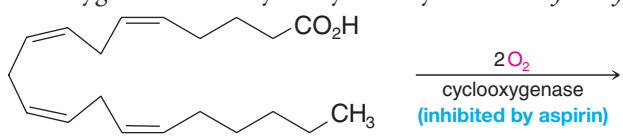
The 1982 Nobel Prize in Physiology or Medicine was awarded to S. K. Bergström and B. I. Samuelsson (Karolinska Institute, Stockholm, Sweden) and to J. R. Vane (Wellcome Foundation, Beckenham, England) for their work on prostaglandins.

Prostaglandins of the E type have a carbonyl group at C9 and a hydroxyl group at C11; those of the F type have hydroxyl groups at both positions. Prostaglandins of the 2 series have a double bond between C5 and C6; in the 1 series this bond is a single bond.

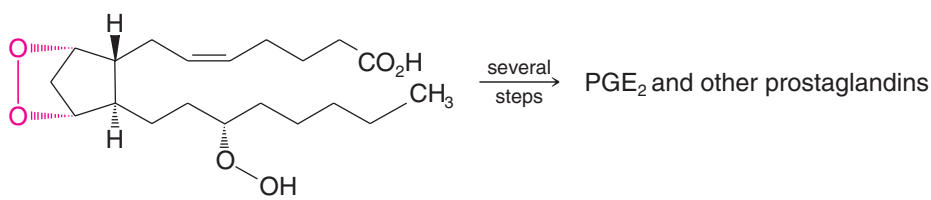
First isolated from seminal fluid, prostaglandins have since been found in almost all animal tissues. The amounts vary from tissue to tissue but are almost always very small. Most prostaglandins have powerful physiological activity, however, and this activity covers a broad spectrum of effects. Prostaglandins are known to affect heart rate, blood pressure, blood clotting, conception, fertility, and allergic responses.

The finding that prostaglandins can prevent formation of blood clots has great clinical significance, because heart attacks and strokes often result from the formation of abnormal clots in blood vessels. An understanding of how prostaglandins affect the formation of clots may lead to the development of drugs to prevent heart attacks and strokes.

The biosynthesis of prostaglandins of the 2 series begins with a C_{20} polyenoic acid, arachidonic acid, an omega-6 fatty acid. (Synthesis of prostaglandins of the 1 series begins with a fatty acid with one fewer double bond.) The first step requires two molecules of oxygen and is catalyzed by an enzyme called *cyclooxygenase*:



Arachidonic acid

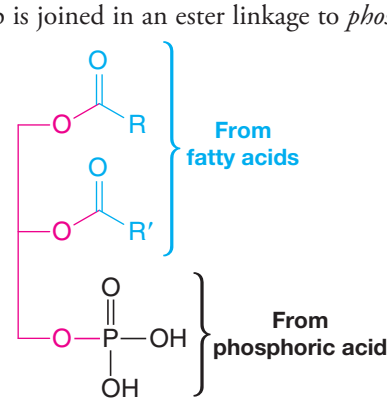


PGG_2
(a cyclic endoperoxide)

The involvement of prostaglandins in allergic and inflammatory responses has also been of special interest. Some prostaglandins induce inflammation; others relieve it. The most widely used anti-inflammatory drug is ordinary aspirin (see Section 21.8). Aspirin blocks the synthesis of prostaglandins from arachidonic acid, apparently by acetylating the enzyme cyclooxygenase, thus rendering it inactive (see the previous reaction). This reaction may represent the origin of aspirin's anti-inflammatory properties. Another prostaglandin (PGE_1) is a potent fever-inducing agent (pyrogen), and aspirin's ability to reduce fever may also arise from its inhibition of prostaglandin synthesis.

23.6 PHOSPHOLIPIDS AND CELL MEMBRANES

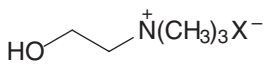
Another large class of lipids are those called **phospholipids**. Most phospholipids are structurally derived from a glycerol derivative known as a *phosphatidic acid*. In a phosphatidic acid, two hydroxyl groups of glycerol are joined in ester linkages to fatty acids and one terminal hydroxyl group is joined in an ester linkage to *phosphoric acid*:



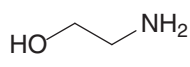
A phosphatidic acid
(a diacylglyceryl phosphate)

23.6A Phosphatides

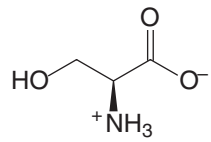
In *phosphatides*, the phosphate group of a phosphatidic acid is bound through another phosphate ester linkage to one of the following nitrogen-containing compounds:



Choline



2-Aminoethanol (ethanolamine)

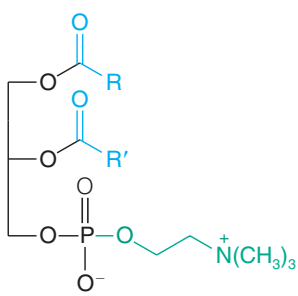


L-Serine

The most important phosphatides are the **lecithins, cephalins, phosphatidylserines**, and **plasmalogens** (a phosphatidyl derivative). Their general structures are shown in Table 23.5.

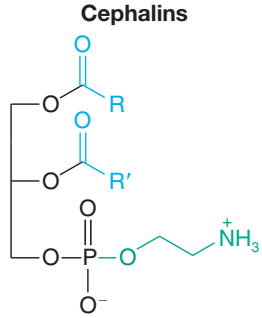
TABLE 23.5 PHOSPHATIDES

Lecithins



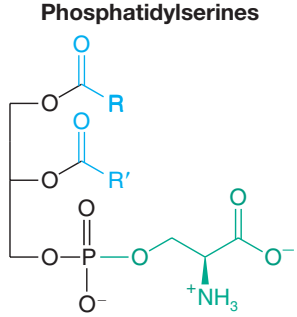
(from choline)
R is saturated and R′ is unsaturated.

Cephalins



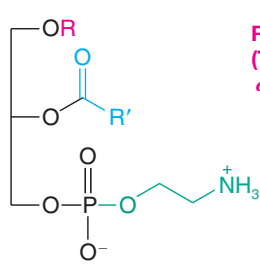
(from 2-aminoethanol)

Phosphatidylserines



(from L-serine)
R is saturated and R′ is unsaturated.

Plasmalogens



(from 2-aminoethanol) or —$OCH_2CH_2N^+(CH_3)_3$ (from choline)
R′ is an unsaturated fatty acid.

R is —CH=CH$(CH_2)_nCH_3$ (This linkage is that of an α,β-unsaturated ether.)

Phosphatides resemble soaps and detergents in that they are molecules having both polar and nonpolar groups (Fig. 23.8*a*). Like soaps and detergents, too, phosphatides "dissolve" in aqueous media by forming micelles. There is evidence that in biological systems the preferred micelles consist of three-dimensional arrays of "stacked" bimolecular micelles (Fig. 23.8*b*) that are better described as **lipid bilayers**.

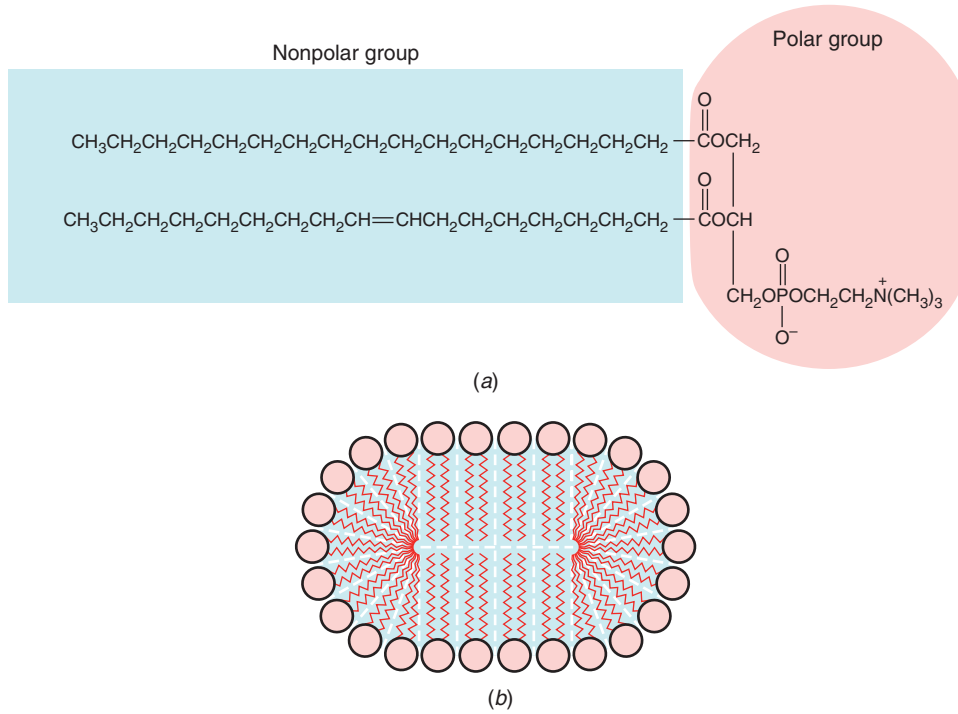


FIGURE 23.8 (*a*) Polar and nonpolar sections of a phosphatide. (*b*) A phosphatide micelle or lipid bilayer.

The hydrophilic and hydrophobic portions of phosphatides make them perfectly suited for one of their most important biological functions: they form a portion of a structural unit that creates an interface between an organic and an aqueous environment. This structure (Fig. 23.9) is located in cell walls and membranes where phosphatides are often found associated with proteins and glycolipids (Section 23.6B).

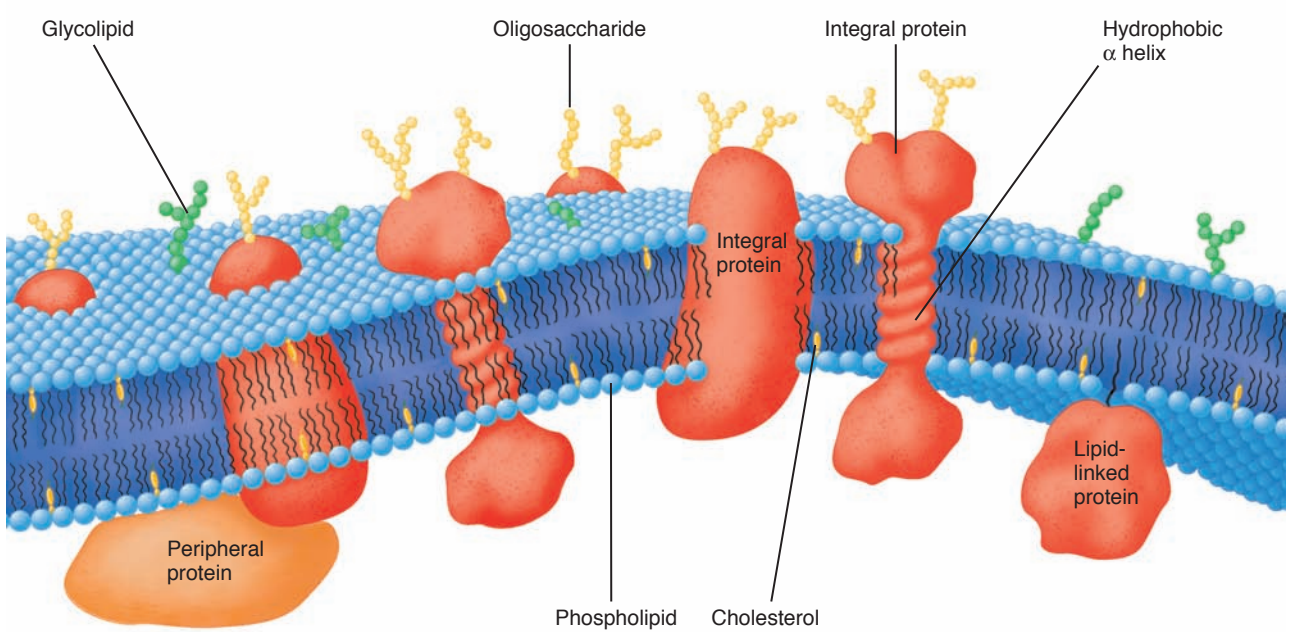


FIGURE 23.9 A schematic diagram of a plasma membrane. Integral proteins (*red-orange*), shown for clarity in much greater proportion than they are found in actual biological membranes, and cholesterol (*yellow*) are embedded in a bilayer composed of phospholipids (*blue spheres with two wiggly tails*). The carbohydrate components of glycoproteins (*yellow beaded chains*) and glycolipids (*green beaded chains*) occur only on the external face of the membrane.

PRACTICE PROBLEM 23.11

Under suitable conditions all of the ester (and ether) linkages of a phosphatide can be hydrolyzed. What organic compounds would you expect to obtain from the complete hydrolysis of (see Table 23.5) **(a)** a lecithin, **(b)** a cephalin, and **(c)** a choline-based plasmalogen? [*Note:* Pay particular attention to the fate of the α,β-unsaturated ether in part (c).]

THE CHEMISTRY OF... STEALTH® Liposomes for Drug Delivery

The anticancer drug Doxil (doxorubicin) has been packaged in STEALTH® liposomes that give each dose of the drug extended action in the body. During manufacture of the drug it is ensconced in microscopic bubbles (vesicles) formed by a phospholipid bilayer and then given a special coating that masks it from the immune system. Ordinarily, a foreign particle such as this would be attacked by cells of the immune system and degraded, but a veil of polyethylene glycol oligomers on the liposome surface masks it from detection. Because of this coating, the STEALTH® liposome circulates through the body and releases its therapeutic contents over a period of time significantly greater than the lifetime for circulation of the undisguised drug. Coatings like those used for STEALTH® liposomes may also be able to reduce the toxic side effects of some drugs. Furthermore, by attaching specific cell recognition "marker" molecules to the polymer, it may be possible to focus binding of the liposomes specifically to cells of a targeted tissue. One might be tempted to call a targeted liposome a "smart stealth liposome."

23.6B Derivatives of Sphingosine

Another important group of lipids is derived from **sphingosine**; the derivatives are called **sphingolipids**. Two sphingolipids, a typical *sphingomyelin* and a typical *cerebroside*, are shown in Fig. 23.10.

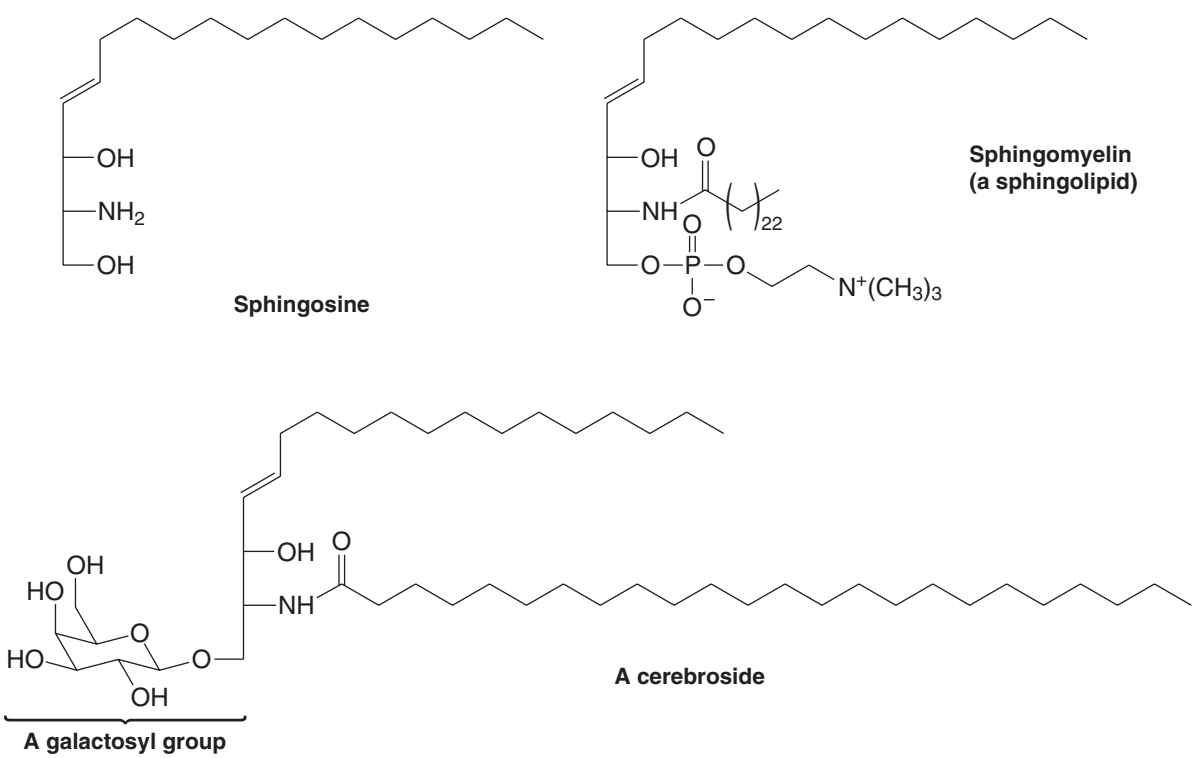


FIGURE 23.10 A sphingosine and two sphingolipids.

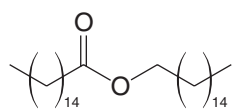
On hydrolysis, sphingomyelins yield sphingosine, choline, phosphoric acid, and a C_{24} fatty acid called lignoceric acid. In a sphingomyelin this last component is bound to the $-NH_2$ group of sphingosine. The sphingolipids do not yield glycerol when they are hydrolyzed.

The cerebroside shown in Fig. 23.10 is an example of a **glycolipid**. Glycolipids have a polar group that is contributed by a *carbohydrate*. They do not yield phosphoric acid or choline when they are hydrolyzed.

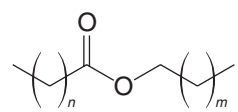
The sphingolipids, together with proteins and polysaccharides, make up **myelin**, the protective coating that encloses nerve fibers or **axons**. The axons of nerve cells carry electrical nerve impulses. Myelin has a function relative to the axon similar to that of the insulation on an ordinary electric wire (see the chapter opening vignette).

23.7 WAXES

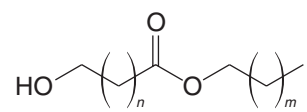
Most **waxes** are esters of long-chain fatty acids and long-chain alcohols. Waxes are found as protective coatings on the skin, fur, and feathers of animals and on the leaves and fruits of plants. Several esters isolated from waxes are the following:



Cetyl palmitate (from spermaceti)



***n* = 24 or 26; *m* = 28 or 30 (from beeswax)**



***n* = 16–28; *m* = 30 or 32 (from carnauba wax)**

[SUMMARY OF REACTIONS OF LIPIDS]

The reactions of lipids represent many reactions that we have studied in previous chapters, especially reactions of carboxylic acids, alkenes, and alcohols. Ester hydrolysis (e.g., saponification) liberates fatty acids and glycerol from triacylglycerols. The carboxylic acid group of a fatty acid can be reduced, converted to an activated acyl derivative such as an acyl chloride, or converted to an ester or amide. Alkene functional groups in unsaturated fatty acids can be hydrogenated, hydrated, halogenated, hydrohalogenated, converted to a vicinal diol or epoxide, or cleaved by oxidation reactions. Alcohol functional groups in lipids such as terpenes, steroids, and prostaglandins can be alkylated, acylated, oxidized, or used in elimination reactions. All of these are reactions we have studied previously in the context of smaller molecules.

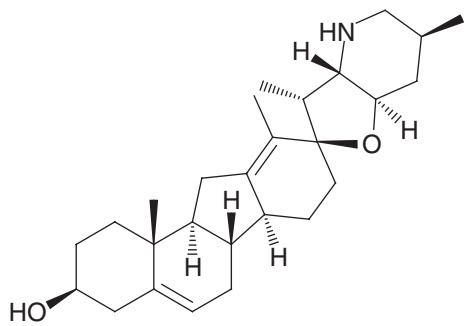
[WHY Do These Topics Matter?

MYTHS TURNED INTO REALITY

Greek and Roman mythologies include stories of giant creatures known as cyclops that have a single eye in the center of their forehead. Homer's *Odyssey*, for example, describes an encounter between the hero Odysseus and a cyclops named Polyphemus. What is amazing, however, is that these tales may well have a grain of truth.

After World War II, sheep farmers in Idaho encountered a number of lambs with a consistent set of strange birth defects, including underdeveloped brains and a single eye located right in the center of their foreheads, exactly as described for the mythical creatures. The cause of this condition, which took over a decade to unravel, was discovered by a diligent scientist who lived with the sheep for a number of summers and cataloged their behaviors, particularly their diets. What proved key was the observation

that during periods of drought the grazing sheep moved higher into the hills and ate corn lilies instead of grass. These flowers, it turns out, produce the nitrogen-containing steroid shown below that is now named cyclopamine for its effects. Though seemingly harmless to adult sheep, it stunts the development of embryonic lambs and produces cyclops-like abnormalities. The effect is the same in other organisms as well. What is perhaps more amazing, however, is that not all the effects of this molecule are harmful. In fact, it may well be a future cancer therapy.



Cyclopamine

Starting in the late 1990s, scientists at a number of pharmaceutical, biotechnology, and academic laboratories determined just how cyclopamine impacts developing embryos. The compound acts on a critical signaling pathway called hedgehog, blocking its function and leading to abnormal development of the brain and other organs in the fetus. In adults, the hedgehog signaling pathway continues to play an important role, largely in controlling the division of adult stem cells for proper maintenance and regeneration of organ tissues. If the genes in the pathway become abnormal, many deadly cancers can result due to uncontrolled cellular division. It is this knowledge that led to the idea that cyclopamine could be a cancer therapy. Since it can block hedgehog functioning, it could potentially prevent cell division when the pathway is not operating normally. This theory is currently showing promise, with both cyclopamine and related analogs being able to combat pancreatic cancer and basal cell carcinoma in a number of human clinical trials. Thus, out of myth has come not only reality, but potentially an even more important discovery pertinent to treating a major human disease.

To learn more about these topics, see:

1. Heretsch, P.; Tzagkaroulaki, L.; Giannis, A. "Cyclopamine and Hedgehog Signaling: Chemistry, Biology, Medical Perspectives" in *Angew. Chem Int. Ed*. **2010**, *49*, 3418–3427.

SUMMARY AND REVIEW TOOLS

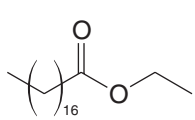
The study aids for this chapter include a narrative summary of reactions of lipids (after Section 23.7), and key terms and concepts, which are highlighted in bold, blue text within the chapter, defined in the Glossary at the back of the book, and which have hyperlinked definitions in the accompanying *WileyPLUS* course (www.wileyplus.com).

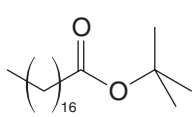
PROBLEMS

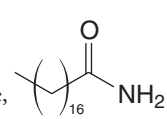
Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

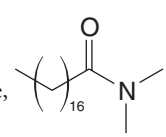
GENERAL REACTIONS

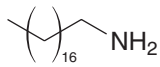
23.12 How would you convert stearic acid, $CH_3(CH_2)_{16}CO_2H$, into each of the following?

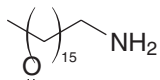
(a) Ethyl stearate,  (two ways)

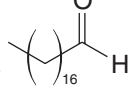
(b) *tert*-Butyl stearate, 

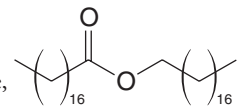
(c) Stearamide, 

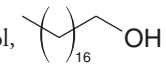
(d) *N,N*-Dimethylstearamide, 

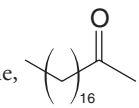
(e) Octadecylamine, 

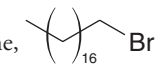
(f) Heptadecylamine, 

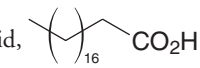
(g) Octadecanal, 

(h) Octadecyl stearate, 

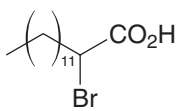
(i) 1-Octadecanol,  (two ways)

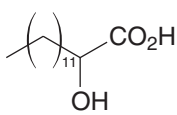
(j) 2-Nonadecanone, 

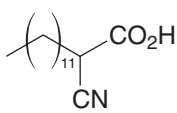
(k) 1-Bromooctadecane, 

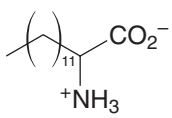
(l) Nonadecanoic acid, 

23.13 How would you transform tetradecanal into each of the following?

(a) 

(b) 

(c) 

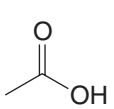
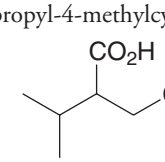
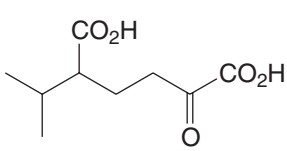
(d) 

23.14 Using palmitoleic acid as an example and neglecting stereochemistry, illustrate each of the following reactions of the double bond:
(a) Addition of bromine **(b)** Addition of hydrogen **(c)** Hydroxylation **(d)** Addition of HCl

23.15 When oleic acid is heated to 180–200 °C (in the presence of a small amount of selenium), an equilibrium is established between oleic acid (33%) and an isomeric compound called elaidic acid (67%). Suggest a possible structure for elaidic acid.

23.16 When limonene (Section 23.3) is heated strongly, it yields 2 mol of isoprene. What kind of reaction is involved here?

23.17 Gadoleic acid ($C_{20}H_{38}O_2$), a fatty acid that can be isolated from cod-liver oil, can be cleaved by hydroxylation and subsequent treatment with periodic acid to $CH_3(CH_2)_9CHO$ and $OHC(CH_2)_7CO_2H$. **(a)** What two stereoisomeric structures are possible for gadoleic acid? **(b)** What spectroscopic technique would make possible a decision as to the actual structure of gadoleic acid? **(c)** What peaks would you look for?

23.18 α-Phellandrene and β-phellandrene are isomeric compounds that are minor constituents of spearmint oil; they have the molecular formula $C_{10}H_{16}$. Each compound has a UV absorption maximum in the 230–270 nm range. On catalytic hydrogenation, each compound yields 1-isopropyl-4-methylcyclohexane. On vigorous oxidation with potassium permanganate, α-phellandrene yields  and  A similar oxidation of β-phellandrene yields  as the only isolable product. Propose structures for α- and β-phellandrene.

ROADMAP SYNTHESES

23.19 Vaccenic acid, a constitutional isomer of oleic acid, has been synthesized through the following reaction sequence:

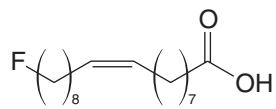
$$\text{1-Octyne} + NaNH_2 \xrightarrow[NH_3]{\text{liq.}} \mathbf{A}\ (C_8H_{13}Na) \xrightarrow{ICH_2(CH_2)_7CH_2Cl} \mathbf{B}\ (C_{17}H_{31}Cl) \xrightarrow{NaCN} \mathbf{C}\ (C_{18}H_{31}N) \xrightarrow{KOH,\ H_2O} \mathbf{D}\ (C_{18}H_{31}O_2K) \xrightarrow{H_3O^+} \mathbf{E}\ (C_{18}H_{32}O_2) \xrightarrow[BaSO_4]{H_2,\ Pd} \text{vaccenic acid}\ (C_{18}H_{34}O_2)$$

Propose a structure for vaccenic acid and for the intermediates **A–E**.

23.20 ω-Fluorooleic acid can be isolated from a shrub, *Dechapetalum toxicarium*, that grows in Africa. The compound is highly toxic to warm-blooded animals; it has found use as an arrow poison in tribal warfare, in poisoning enemy water supplies, and by witch doctors "for terrorizing the native population." Powdered fruit of the plant has been used as a rat poison; hence ω-fluorooleic acid has the common name "ratsbane." A synthesis of ω-fluorooleic acid is outlined here. Give structures for compounds **F–I**:

1-Bromo-8-fluorooctane + sodium acetylide ⟶ **F** ($C_{10}H_{17}F$) $\xrightarrow[(2)\ I(CH_2)_7Cl]{(1)\ NaNH_2}$

G ($C_{17}H_{30}FCl$) $\xrightarrow{NaCN}$ **H** ($C_{18}H_{30}NF$) $\xrightarrow[(2)\ H_3O^+]{(1)\ KOH}$ **I** ($C_{18}H_{31}O_2F$) $\xrightarrow[Ni_2B\ (P\text{-}2)]{H_2}$



ω-Fluorooleic acid
(46% yield, overall)

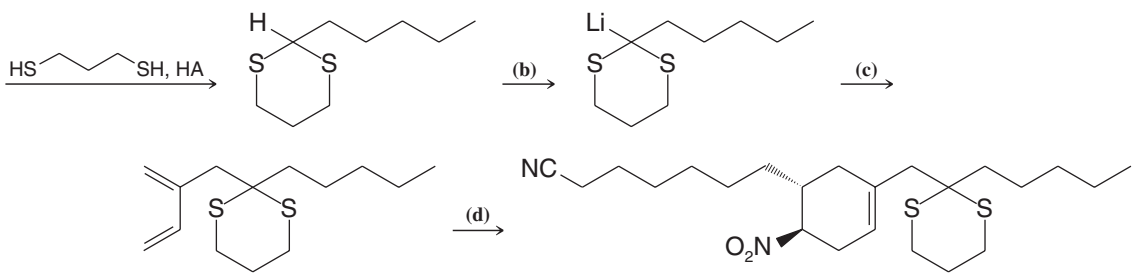
23.21 Give formulas and names for compounds **A** and **B**:

5α-Cholest-2-ene $\xrightarrow{C_6H_5\overset{O}{\overset{\|}{C}}OOH}$ **A** (an epoxide) $\xrightarrow{HBr}$ **B**

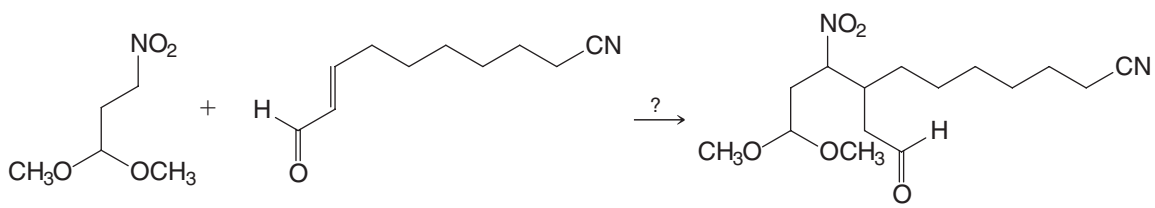
(*Hint*: **B** is not the most stable stereoisomer.)

23.22 The initial steps of a laboratory synthesis of several prostaglandins reported by E. J. Corey (Section 7.15B) and co-workers in 1968 are outlined here. Supply each of the missing reagents:

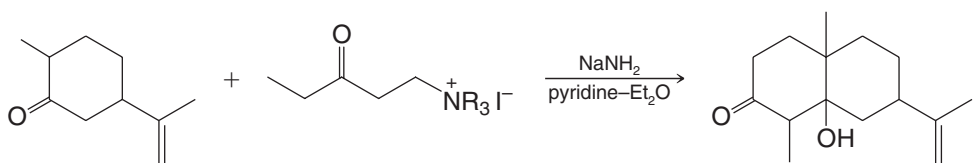
(a)



(e) The initial step in another prostaglandin synthesis is shown in the following reaction. What kind of reaction—and catalyst—is needed here?

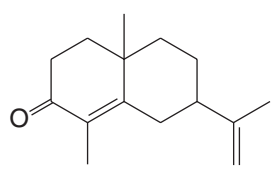


23.23 A useful synthesis of sesquiterpene ketones, called *cyperones*, was accomplished through a modification of the following Robinson annulation procedure (Section 19.7B). Write a mechanism that accounts for each step of this synthesis.



Dihydrocarvone

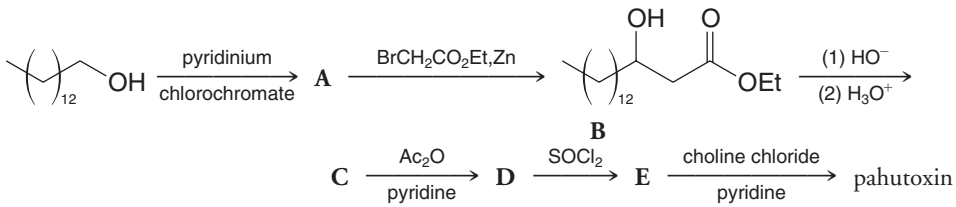
HA, heat



A cyperone

CHALLENGE PROBLEMS

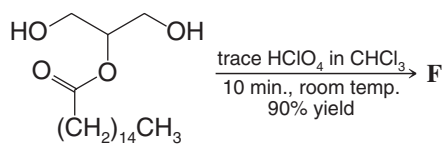
23.24 A Hawaiian fish called the pahu or boxfish (*Ostracian lentiginosus*) secretes a toxin that kills other fish in its vicinity. The active agent in the secretion was named pahutoxin by P. J. Scheuer, and it was found by D. B. Boylan and Scheuer to contain an unusual combination of lipid moieties. To prove its structure, they synthesized it by this route:



Compound	Selected Infrared Absorption Bands (cm^{-1})
A	1725
B	3300 (broad), 1735
C	3300–2500 (broad), 1710
D	3000–2500 (broad), 1735, 1710
E	1800, 1735
Pahutoxin	1735

What are the structures of **A**, **C**, **D**, and **E** and of pahutoxin?

23.25 The reaction illustrated by the equation below is a very general one that can be catalyzed by acid, base, and some enzymes. It therefore needs to be taken into consideration when planning syntheses that involve esters of polyhydroxy substances like glycerol and sugars:



Spectral data for **F**:

MS (*m/z*): (after trimethylsilylation): 546, 531

IR (cm^{-1}): 3200 (broad), 1710

^{1}H NMR (δ) (after exchange with D_2O): 4.2 (d), 3.9 (m), 3.7 (d), 2.2 (t), and others in the range 1.7 to 1

^{13}C NMR (δ): 172 (C), 74 (CH), 70 (CH_2), 67 (CH_2), 39 (CH_2), and others in the range 32 to 14

(a) What is the structure of product **F**?

(b) The reaction is intramolecular. Write a mechanism by which it probably occurs.

LEARNING GROUP PROBLEMS

1. Olestra is a fat substitute patented by Procter and Gamble that mimics the taste and texture of triacylglycerols (see "The Chemistry of…Olestra and Other Fat Substitutes" in Section 23.2B). It is calorie-free because it is neither hydrolyzed by digestive enzymes nor absorbed by the intestines but instead is passed directly through the body unchanged. The FDA has approved olestra for use in a variety of foods, including potato chips and other snack foods that typically have a high fat content. It can be used in both the dough and the frying process.

(a) Olestra consists of a mixture of sucrose fatty acid esters (unlike triacylglycerols, which are glycerol esters of fatty acids). Each sucrose molecule in olestra is esterified with six to eight fatty acids. (One undesirable aspect of olestra is that it sequesters fat-soluble vitamins needed by the body, due to its high lipophilic character.) Draw the structure of a specific olestra molecule comprising six different naturally occurring fatty acids esterified to any of the available positions on sucrose. Use three saturated fatty acids and three unsaturated fatty acids.

(b) Write reaction conditions that could be used to saponify the esters of the olestra molecule you drew and give IUPAC and common names for each of the fatty acids that would be liberated on saponification.

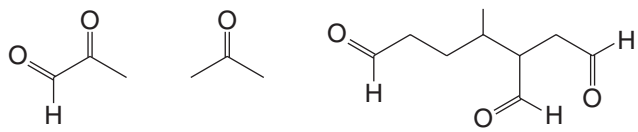
(c) Olestra is made by sequential transesterification processes. The first transesterification involves reaction of methanol under basic conditions with natural triacylglycerols from cottonseed or soybean oil (chain lengths of C_8–C_{22}). The second transesterification involves reaction of these fatty acid methyl esters with sucrose to form olestra. Write one example reaction, including its mechanism, for each of these transesterification processes used in the synthesis of olestra. Start with any triacylglycerol having fatty acids like those incorporated into olestra.

2. The biosynthesis of fatty acids is accomplished two carbons at a time by an enzyme complex called fatty acid synthetase. The biochemical reactions involved in fatty acid synthesis are described in Special Topic E (*WileyPLUS*). Each of these biochemical reactions has a counterpart in synthetic reactions you have studied. Consider the biochemical reactions involved in adding each $-CH_2CH_2-$ segment during fatty acid biosynthesis (those in Special Topic E that begin with acetyl-S-ACP and malonyl-S-ACP, and end with butyryl-S-ACP). Write laboratory synthetic reactions using reagents and conditions you have studied (not biosynthetic reactions) that would accomplish the same sequence of transformations (i.e., the condensation–decarboxylation, ketone reduction, dehydration, and alkene reduction steps).

3. A certain natural terpene produced peaks in its mass spectrum at *m/z* 204, 111, and 93 (among others). On the basis of this and the following information, elucidate the structure of this terpene. Justify each of your conclusions.

(a) Reaction of the unknown terpene with hydrogen in the presence of platinum under pressure results in a compound with molecular formula $C_{15}H_{30}$.

(b) Reaction of the terpene with ozone followed by dimethyl sulfide produces the following mixture of compounds (1 mol of each for each mole of the unknown terpene):



(c) After writing the structure of the unknown terpene, circle each of the isoprene units in this compound. To what class of terpenes does this compound belong (based on the number of carbons it contains)?

4. Draw the structure of a phospholipid (from any of the subclasses of phospholipids) that contains one saturated and one unsaturated fatty acid.

(a) Draw the structure of all of the products that would be formed from your phospholipid if it were subjected to complete hydrolysis (choose either acidic or basic conditions).

(b) Draw the structure of the product(s) that would be formed from reaction of the unsaturated fatty acid moiety of your phospholipid (assuming it had been released by hydrolysis from the phospholipid first) under each of the following conditions:

(i) Br_2

(ii) OsO_4, followed by $NaHSO_3$

(iii) HBr

(iv) Hot alkaline $KMnO_4$, followed by H_3O^+

(v) $SOCl_2$, followed by excess CH_3NH_2