2 Medical Marvels

INTRODUCTION

Medicinal plants and plant-derived medicines are widely used in traditional cultures all over the world. People who use traditional remedies may not understand the scientific rationale for why they work, but know from personal experience that some plants can be highly effective. These plants were probably selected through trial and error.

Traditional medicine often aims to restore balance to the body. In contrast, Western allopathic medicine often uses a well-defined, single chemical entity with specific medicinal properties.

Nevertheless, many of our so-called "modern day" drugs have origins in ancient medicine. Furthermore, there has been a renaissance of awareness in the use of natural "alternative" medicines. The vast array of medicinal plants available from all parts of the world has stimulated much scientific and clinical interest which, in some instances, has provided significant commercial returns.

Each illustration included in Chapter 2 reveals how ancient civilizations survived, thrived and flourished by exploiting local plants. Subsequently, through a combination of trade, conquest, vision and ingenuity, the West successfully absorbed indigenous knowledge into its culture and economy. In more recent times, chemical examination of these plant extracts has led to the identification of many natural product constituents, which provide modern medications of inestimable value to humankind.

Ancient Medicine

Anecdotal and traditional wisdom concerning the use of botanical compounds is documented in the rich histories of traditional Chinese medicine (TCM) and of Ayurvedic medicine from India (and widely practised today in India), and in treatments used by Native Americans. In fact, medicinal plants and plant-derived medicines are widely used in traditional cultures all over the world.

HISTORICAL NOTE: AYURVEDIC MEDICINE

In Sanskrit, ayur means life or living, and veda means knowledge, so Ayurveda may be construed to mean "knowledge of living."

Ayurveda originated in the early civilizations of India some 3,000–5,000 years ago and is mentioned in the Vedas, the ancient religious and philosophical texts which are among the oldest literature surviving in the world.

Ayurveda involves living in harmony with nature and maintaining the human body so that mental and spiritual awareness may be promoted.

The goals of Ayurvedic medicine are prevention as well as promotion of the body's own capacity for maintenance and balance. Ayurvedic physicians claim that their methods help many stress-related, metabolic and chronic conditions. Ayurvedic medicine utilizes diet, purification techniques, herbal and mineral remedies, yoga, breathing exercises, meditation and massage therapy as holistic healing methods.

Historians believe that Ayurvedic ideas were transported from ancient India to China, and were instrumental in the development of Chinese medicine. Ayurvedic medicine is widely practised in modern India today and has been steadily gaining followers in the West.

Records of Ayurvedic medicine are a vast repository of knowledge in the application of herbal extracts to specific health problems, although much of this knowledge is yet to be fully explored and researched by modern scientific methods.

CENTRAL AMERICA'S HUMBLE POTATO!

Abstract: How a humble potato led to the genesis of the birth control pill. Few plants have had a greater impact on modern society. Indigenous to Central America and originally used as a staple food, this humble potato-like tuber contains the natural ingredients which transformed the world through the development of the modern birth control pill bringing about the profound social, cultural and economic impacts of oral contraception.

Natural Products Chemistry

- Steroids
- Hormones, estrogen and progestogen.

Curriculum content

- Hydrocarbons
- Alkanes and cycloalkanes
- Benzene and aromatic compounds
- The profound social, cultural and economic impacts of oral contraception.

Steroids

A steroid contains a characteristic arrangement of four cycloalkane rings, which are joined to each other. The main way in which steroids vary from one another is through the functional groups attached to the four-ring core (Figure 2.1).

Hundreds of distinct steroids are found in plants, animals and fungi. Examples of steroids include the dietary fat, cholesterol, and the sex hormone, testosterone.

Ancient Forms of Contraception

The desire to control contraception goes back to the dawn of culture. Women have risked their health and lives in child birth.

In Egypt, the Kahyn papyrus (1,850 BC) described the use of pessaries. They were made by mixing crocodile dung and selected herbs, which may have led to irritation and infection. However, the presence of a foreign object in the uterus may have

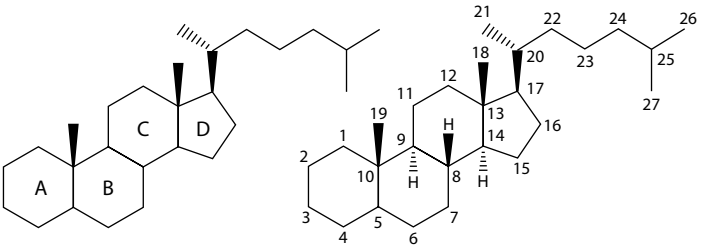


FIGURE 2.1 The carbon skeleton and ring structure of steroids together with the numbering system for steroids.

deterred any union between sperm and egg. (This idea forms the principle in modern times of the contraceptive use of a thin copper coil—the intrauterine device (IUD)). A waxy seal, forming around the cervix, may also have presented a physical barrier to sperm. However, it is unlikely that these early pessaries were entirely effective. Modern pessaries, known as vaginal suppositories, also contain wax-like material, which is infused with a spermicide. In ancient times, men used snake skins as condoms, whereas today, these physical barriers are made of latex or polyurethane.

It is also well documented that for centuries, women have used as an oral contraceptive an extract from the seeds of *Daucus carota* (known also as Queen Anne's Lace or Wild Carrot). The earliest references appear in a work written by the Greek physician, Hippocrates, in the fifth century BC. Modern studies performed on mice reveal that these extracts from the seeds block the production of the important hormone, progesterone (Figure 2.2). Progesterone is essential for pregnancy to occur, as its function is to prepare the uterine endometrium to receive an egg. If the egg does not implant then it will begin to break down and will no longer be viable. If the fertilized egg has been implanted for only a short period, it is believed by some that an extract from the Wild Carrot will cause it to be released. Plants such as Queen Anne's Lace (Wild Carrot) are still used in parts of rural United States as a "morning after" pill.

Another plant extract used as an oral contraceptive is from *Silphium*, a species of Ferula. *Silphium* was an essential item of trade in the ancient North African city of Cyrene where it was so important to the economy that many Cyrenian coins bore a picture of the plant.

Extracts from the plant Pennyroyal (*Hedeoma pulegoides* or *Mentha pulegium*) are also well known for their abortive effects. The extracts cause the uterine muscles to contract promoting menstrual discharge. Finally, the *Asafetida* species of plant has also been reported to have contraceptive and abortive activity. However, none of these plants became significant enough as oral contraceptives to have directly influenced the development of the modern birth control pill.

The Search for the Modern Birth Control Pill: The Hormones, Estrogen and Progesterone

The modern combined oral contraceptive pill, often referred to as the birth control pill, or colloquially as "the pill," is a birth control method that includes a combination of an estrogen and a progestogen. When taken orally every day, these pills

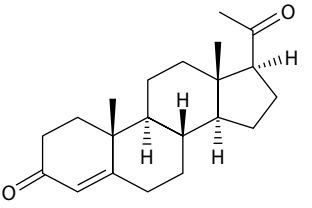


FIGURE 2.2 Chemical structure of progesterone.

inhibit female fertility. They were first approved for contraceptive use in the United States in 1960. They are a very popular form of birth control used by more than 100 million women worldwide, and by almost 12 million women in the United States.

The genesis of the birth control pill derives from the Mexican yam (*Dioscarea villosa* or *Dioscarea barbasco*). This potato is one of the first commercial sources of the key chemicals, known as steroid saponins. The yam is believed to originate from Central America, and approximately 800 *Dioscarea* species are currently known. The wild yam itself has no contraceptive value. Essentially, it provides the starting material from which the steroidal hormones are manufactured by modern technology through a combination of synthetic methods and also microbial transformation. However, in the 1930s, before the discovery of the usefulness of this yam, two important discoveries were made.

Firstly, scientists isolated and determined the structure of small amounts of steroid hormones. They then found that high doses of these hormones, in the form of androgens, estrogens or progesterone, inhibited mammalian ovulation. The isolation of these natural hormones was achieved by research on animal sources and carried out by the major European pharmaceutical companies. Since only small amounts were recovered they were extraordinarily expensive. However, it became immediately apparent that an urgent need for an abundant, reliable and cheap supply of steroids was needed.

Isolation of Natural Diosgenin from the Mexican Yam

In 1939, Professor Russell Marker, at Pennsylvania State University, developed a method of synthesizing progesterone from plant steroids, known as the sapogenins. Initially, he used sarsapogenin from sarsaparilla. However, his chemical route and methodology proved to be far too expensive on a commercial scale.

This finding led to investigation of a variety of Mexican yams, including *Dioscorea mexicana* and *Dioscorea barbasco*, which are found in the rain forests of Veracruz. The tuber (root) of the yam contains the natural chemical called diosgenin (Figure 2.3). This abundant compound could be used as the starting material in the synthesis of hormones on an industrial scale. Diosgenin can be easily converted chemically by opening the rings containing C21 to C27 as shown in Figure 2.1. This is then followed by further degradation of the molecule to reach the structure shown in Figure 2.2.

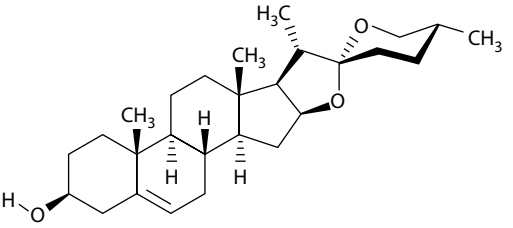


FIGURE 2.3 The chemical structure of diosgenin.

Although by midway through the twentieth century, the stage appeared set for the development of an oral hormonal contraceptive, pharmaceutical companies, universities and governments showed little interest in pursuing further research. At this time in 1944, having developed a synthesis of progesterone from diosgenin from the Mexican yam, Professor Marker left Pennsylvania State University to found a new company, Syntex, in Mexico City. At Syntex, Marker continued to perfect the extraction of the saponins from *Dioscorea mexicana* and then the manufacture of the key hormones. Importantly, due to this achievement, the monopoly of the European pharmaceutical companies was broken, which had until that time controlled production of steroid hormones. As a consequence, the price of progesterone fell dramatically by almost 200-fold over the next 8 years.

Chemical Magic in the Laboratory: Synthesis of Norethindrone

In 1951, the combined brilliance of three extraordinary chemists at Syntex, Carl Djerassi, Luis Miramontes and George Rosenkranz, led to the synthesis of the first oral, highly active progestin, namely, norethindrone (Figure 2.4). It should be noted that this synthetic hormone is a variation of natural progesterone. Furthermore, in

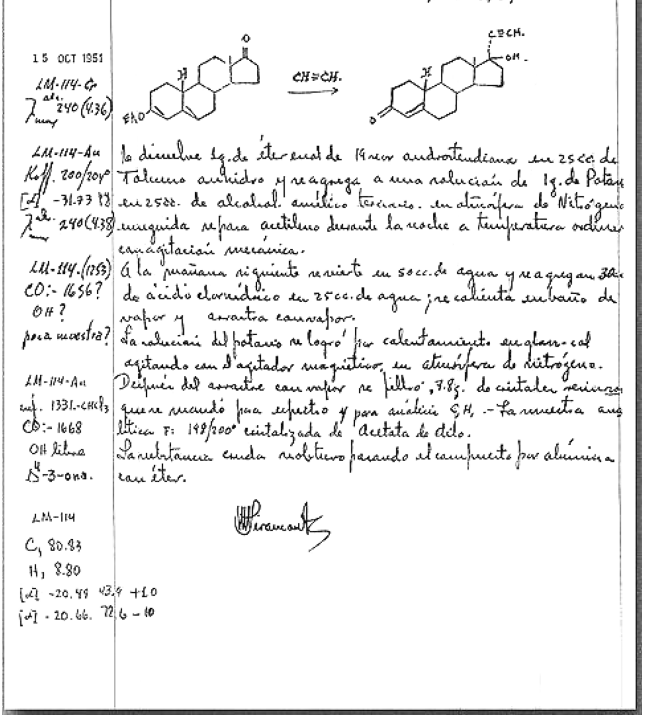


FIGURE 2.4 A copy of the original page from Luis E. Miramontes' laboratory notebook, signed October 15, 1951. (Courtesy of the late Carl Djerassi.)

the following year, at the competing Searle Company in Skokie, Illinois, their chemist, Dr. Frank Colton synthesized the orally active progestin known as norethynodrel (an isomer of norethindrone) followed in 1953 by norethandrolone.

Biological Studies of Progesterone to Prevent Ovulation

Stimulated by a steady supply of research-grade chemical material, important biological studies on the activity of progesterone in inhibiting ovulation progressed rapidly. In early 1951, the reproductive physiologist, Dr Gregory Pincus, who was at the time a leader in hormone research, showed that injection of progesterone suppressed ovulation in rabbits.

Also, significantly in this pivotal year, Pincus met with Margaret Sanger, the founder of the American birth control movement (see Historical Note).

HISTORICAL NOTE: THE IMPACT OF MARGARET SANGER

The importance of Margaret Sanger, a nurse and a huge advocate of female contraception, cannot be overlooked. Her crusade to legalize birth control spurred the movement for women's liberation.

Margaret Sanger became acutely aware of the effects of unplanned and unwelcome pregnancy during her work with poor women on the Lower East Side in New York. Sanger had witnessed how her own mother's health had suffered as she bore 11 children. Sanger realized the importance to women's lives and health of the availability of birth control. In 1912, Sanger gave up her nursing work to dedicate herself full time to the distribution of birth control information. However, due to the passage of the Comstock Act of 1873, it was still forbidden to distribute either birth control devices or information. Sanger continued to write articles on health for the Socialist Party paper, "The Call," and published articles: "What Every Girl Should Know" (1916) and "What Every Mother Should Know" (1917). However, she was indicted for "mailing obscenities" and fled to Europe. Eventually, the indictment was withdrawn.

During World War I, Sanger set up the first birth control clinic in the United States yet she was sent to the workhouse for "creating a public nuisance" and was arrested and prosecuted many times. The resulting public outcry helped lead to changes in the law which in turn empowered doctors to give birth control advice to their patients.

In 1927, Sanger helped to organize the first World Population Conference in Geneva.

In 1942, after several organizational mergers and name changes, The Planned Parenthood Federation came into being.

Medical Approval and Social Acceptance

By 1954, studies had advanced on the ovulation-suppressant potential of progestins, which were administered orally. The first medical trials of an oral contraceptive,

later commercially known as Enovid, began in 1956 in Puerto Rico, which led the American Food and Drug Administration (FDA) to approve Enovid for menstrual disorders; and by May 1960, the FDA gave approval for its use as a contraceptive.

Use of the birth control pill varies widely, country by country and by age, education and marital status. One-third of women aged 16–49 in Great Britain use either the combined pill or a progestogen-only version, whereas only 1% of women use the pill in Japan. In Japan, lobbying from the Japan Medical Association prevented the birth control pill from being approved for nearly 40 years. There were concerns: safety of the drug over the long term, and that the use of the pill could lead to diminished use of condoms and thereby to potential for a rise in the rate of sexually transmitted infections. As of 2004, condoms accounted for 80% of birth control use in Japan, which may explain the comparatively low rate of AIDS in the country. By 1999, the pill was finally approved for use in Japan. However, according to estimates, only 1.3% of Japanese females use the pill compared with 15.6% in the United States.

The Profound Social, Cultural and Economic Impacts of Reliable, Oral Contraception

Since the introduction of the oral birth control pill in 1960 and its approval by the FDA, its use has spread rapidly, generating enormous social impact. Since the pill allowed women to have a sexual relationship while pursuing a career, it became a significant factor in a quiet revolution. Many consider it to be the most socially significant medical advance of the twentieth century. The birth control pill has helped women gain more control of their lives and has altered the nature of the nuclear family and life profoundly. Many economists argue that the availability of the birth control pill led directly to an increase in the proportion of women in the labor force and was a key influence in determining the modern economic role of women. It is notable that after the birth control pill was legalized there was a sharp increase in college attendance and in graduation by women. Family planning allowed women to make long-term educational and career plans. The pill offered opportunity to delay the timing of marriage allowing women to invest in education and in other forms of human capital and to become more career oriented.

Owing to the fact that the birth control pill was inexpensive and effective, widespread adoption changed the nature of debate over premarital sex and promiscuity. Never before had sexual activity been so divorced from human reproduction. In this regard, the proliferation of the use of oral contraceptives has required religious authorities to reexamine the relationship between sexuality and procreation.

Transformation: Global Emergence of the Yam

In 1960, two million women were using the pill and over 100,000 Mexican peasants were gathering the raw material used in its production. In order to meet the demand, more than 10 tons of wild yam were removed each week at extraordinarily low prices from the areas around Oaxaca, Veracruz, Tabasco and Chiapas in Mexico. Scientists relied on local indigenous knowledge to cultivate and harvest the plant. Yams made their way from the Mexican jungles to domestic and foreign laboratories and into the

medicine cabinets of millions of women around the world. At the time, little recognition was afforded to Mexican peasants who labored for almost 30 years to collect the yams, yet had no sense of its value in the marketplace or of the importance of their contribution.

Interest in the Mexican yam could no longer be confined within national borders as growing pressure arose from a combination of continued progress in chemistry research, improved pharmaceutical technology and changes in the social and political outlook across the world. The Mexican government eventually established a state-owned company in 1975 to compete with foreign laboratories. Funds were thus secured for the training of scientists and the development of a stronger domestic pharmaceutical industry in Mexico.

Arguably, the indigenous, poor, uneducated yam pickers represented in many respects the antithesis of modernity, but they became an essential link in finally introducing to Mexico a modern, domestic industry-patented medications. In this particular case, an alliance of science and farming practice resulted in a reshuffling of social hierarchy in rural Mexico, and gave real monetary value to an otherwise low-value crop.

Hydrocarbons

Table 2.1 illustrates the general classification of hydrocarbons and provides examples.

Saturated Hydrocarbons

Alkanes

Alkanes are described as saturated hydrocarbon molecules because each carbon atom, which has a valency of four, is bound covalently to four other atoms—either carbon or hydrogen.

Alkane molecules can be in straight chains of carbon atoms (see examples in Table 2.2) or in branched chains.

Cycloalkanes

Cycloalkanes exist too, although they are usually in the form of six-membered carbon rings or larger. Owing to the ring structure, however, some strain exists in the

TABLE 2.1
The General Classification of Hydrocarbons

Hydrocarbons						
Chain			Cyclic			
Saturated	Unsaturated		Carbocyclic		Heterocyclic	
Alkanes	Alkenes	Alkynes	Alicyclic	Aromatic	Alicyclic	Aromatic
Methane	Ethene	Ethyne	Cyclohexane	Benzene	Cyclohexylamine	Pyridine

TABLE 2.2
Examples of Hydrocarbons with the General Formula C_nH_{2n+2}, Known as Alkanes

Formula	Name	Physical Properties	Boiling Point	Melting Point
CH_4	Methane	Colorless gas		
C_2H_6	Ethane	Colorless gas		
C_3H_8	Propane	Colorless gas		
C_4H_{10}	n-Butane	Colorless gas		
C_5H_{12}	n-Pentane	Colorless, volatile liquid	36°C	
$C_{18}H_{38}$	n-Octadecane	White solid		28°C

FIGURE 2.5 The structure of a cyclohexane molecule.

bonds. For instance, flat planar molecules of cyclopropane can be formed, but they are very unstable, whereas in cyclohexane (Figure 2.5) the carbon–carbon bonds are formed at the usual tetrahedral angle of 109.5 degrees. As a consequence, the cyclohexane ring is puckered into what is commonly referred to as either the chair or the boat form.

Owing to the ring structure, cycloalkanes have two fewer hydrogen atoms than the corresponding alkane, and have the general formula C_nH_{2n}. However, the physical and chemical properties of cycloalkanes are scarcely different to those of the corresponding straight chain or branched chain alkane.

Alkanes and cycloalkanes, in gaseous or vapor form, are readily oxidized in the presence of oxygen or air with the release of a great deal of heat energy per mole.

$$C_3H_8 + 5O_2 = 3CO_2 + 4H_2O$$

A mole is defined as the molecular weight of a substance expressed in grams based on the standard of 12 g of carbon 12.

In the presence of a halogen and energized by light, alkanes undergo substitution reactions:

$$CH_4 + Br_2 = CH_3Br + HBr \text{ then } CH_3Br + Br_2 = CH_2Br_2 + HBr$$

and so on to CBr_4.

Crude Oil and Industrial Fractional Distillation

Crude oil or petroleum is a highly complex mixture of alkanes and many other organic compounds. Petroleum is found in underground reservoirs in rock strata

TABLE 2.3
Examples of Oils That Can be Refined by Fractional Distillation

Fraction	Boiling Range	Carbon Atoms per Molecule	Use
Light petroleum	20–90°C	4–6	Solvent
Gasoline (petrol)	100–200°C	8–12	Motor fuel
Paraffin, kerosene	200–300°C	12–16	Diesel fuel
Oil	Above 300°C	More than 25	Lubrication
Bitumen	Solid residue	Large numbers	Road construction

where it was formed by the very slow decomposition of organic matter from plants and animals in the absence of air under the influence of great heat and pressure. The composition of crude oil varies considerably from place to place; some deposits being dominated by straight and branched chain alkanes, whereas other sources contain greater proportions of cyclic alkanes, which often have carbon chain branches.

Crude oil is fractionally distilled and different fractions are collected on an industrial scale (Table 2.3) in oil refineries (Figure 2.6).

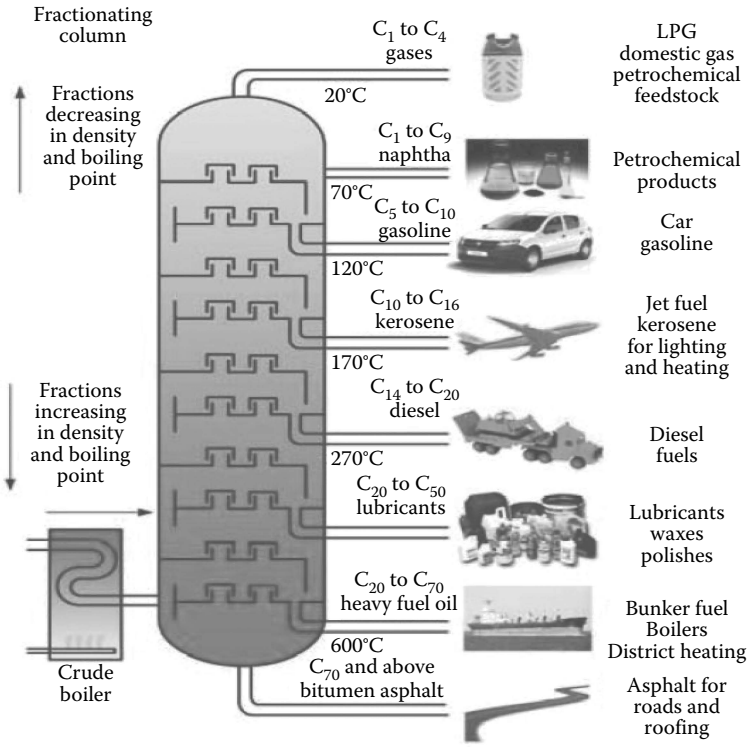


FIGURE 2.6 **(See color insert.)** Diagram of an industrial fractionating column. (With permission under terms of GNU Free Documentation License.)

Benzene and Aromatic Compounds: Physical and Chemical Properties

Benzene is a colorless, volatile liquid, and is a recognized carcinogen.

The molecular formula, C_6H_6, reveals that there is a high percentage of carbon, and that benzene is, to some degree, unsaturated. Indeed, benzene is described as the simplest of the aromatic hydrocarbons.

Studies of the structure of a molecule of benzene have shown that the molecule is in the form of a planar, hexagonal ring of six carbon atoms with the internal angle between them being 120 degrees. This is in marked contrast to the molecular structure of cyclohexane which is discussed earlier in the chapter. The chemical reactivity of benzene is also revealing in that it readily undergoes addition reactions and behaves as a nucleophile in substitution reactions (see also the section on "Tea, from Legend to Healthy Obsession" in Chapter 4 and "A Plant from the East Indies, Camphor" in Chapter 6).

At ordinary temperatures and elevated pressure, benzene can be hydrogenated in the presence of a finely divided catalyst of platinum to produce cyclohexane.

$$C_6H_6 + 3H_2 = C_6H_{12}$$

Another example of an addition reaction involves halogens such as chlorine, which in the presence of the energy source, ultraviolet light, will yield benzene hexachloride.

The replacement of a hydrogen atom in benzene occurs much more readily than the corresponding replacement in an alkane or cycloalkane. In the presence of concentrated nitric and sulfuric acids at about 50°C, benzene will react to give nitrobenzene by nucleophilic substitution.

$$C_6H_6 + HNO_3 = C_6H_5NO_2 + H_2O$$

Halogenation of benzene provides another example of nucleophilic substitution. The reaction takes place in the presence of a catalyst, aluminium chloride, when chlorine is passed through the liquid at room temperature.

$$C_6H_6 + Cl_2 = C_6H_5Cl + HCl$$

Chlorobenzene is known to be the result when a measured increase in weight has occurred.

The Friedel–Crafts reaction is an important example of a nucleophilic substitution which provides a very useful synthetic pathway in organic chemistry. Catalyzed by aluminium chloride, benzene can undergo alkylation or acylation to produce an alkyl benzene (such as toluene) or an acyl benzene (such as acetophenone).

$$C_6H_6 + CH_3Cl = C_6H_5 \cdot CH_3 + HCl$$

$$C_6H_6 + CH_3 \cdot CO \cdot Cl = C_6H_5 \cdot CO \cdot CH_3 + HCl$$

Reference to the sections on "Europe Solves a Headache" in Chapter 2, and "Morphine: A Two-Edged Sword" in Chapter 5, is also advised for more reading on alkylation.

Finally, mention must also be made of the violent oxidation reaction between benzene vapor and ozone, or indeed between any hydrocarbon and ozone, which ultimately yields carbon dioxide and water. This property of ozone has crucial consequences in the upper atmosphere of the Earth where hydrocarbon pollutants, arising from aircraft at high altitude or from upward diffusion of propellant gases from aerosol cans or refrigeration systems in use in the lower atmosphere, have caused serious reduction in the partial pressure of ozone—commonly referred to as the ozone hole. A key property of ozone is that it absorbs high energy, short wavelength ultraviolet radiation. If ultraviolet radiation is not reduced in intensity to natural levels at the surface of the Earth, it can cause serious damage to plant and animal life.

Theory of the Molecular Structure of Benzene

The structure of benzene with a molecular formula of C_6H_6 has always presented something of a problem. If the molecule were linear, that would suggest that benzene ought to have a similar degree of unsaturation to that of ethyne or acetylene, but benzene is much less reactive in addition and substitution reactions. It is more stable than anyone would expect at first sight. In 1865, Kekule was the first person to suggest a cyclic structure which might be based on a hybrid of resonant forms (Figure 2.7). This idea has been reinforced somewhat by theory in quantum mechanics.

Modern spectroscopic studies of the benzene molecule indicate unequivocally a planar, regularly hexagonal molecule with C–C–C and C–C–H bond angles of 120 degrees. These facts, together with the relative stability of benzene, compared to alkenes and alkynes, have led to the acceptance of a molecular orbital theory in which the p electron orbitals of neighboring carbon atoms overlap one another, thus allowing electrons to pass around the ring above and below the plane of the ring. These are the delocalized electrons which are considered responsible for the aromatic character of benzene and larger compounds containing benzene as a building block. As noted in the section on "Tobacco: A Profound Influence on

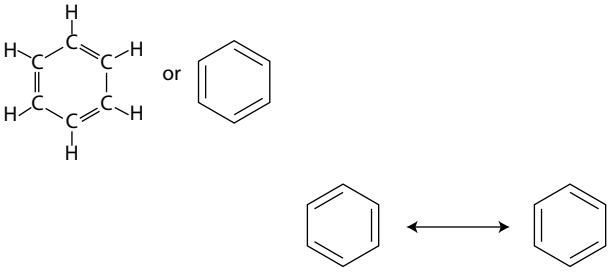


FIGURE 2.7 Kekule's theory of benzene, the structures of resonant hybrids.

FIGURE 2.8 The delocalized electron structure representing a molecule of benzene.

the World" in Chapter 5, some heterocyclic compounds, such as pyridine, pyrrole and thiophen, are also aromatic for the same reason—the delocalization of electrons around a ring molecule, above and below its plane (Figure 2.8).

While Kekule's structures are not quite consistent with physical and chemical evidence, they are still used today in depicting possible mechanisms of reactions of benzene derivatives, especially when hydrogen atoms in the ring are substituted in the ortho- and para-positions. An example of this behavior is found in the molecule of phenol, which behaves as a weak acid in aqueous solution and reacts much more easily than benzene does in electrophilic substitution reactions involving the 2 and 4 positions (ortho and para) in the carbon ring (see also the section on "Tea, from Legend to Healthy Obsession" in Chapter 4 for more on phenol).

Summary of the Characteristics of Aromatic Compounds

a. Aromatic compounds burn in air with a luminous, smoky flame, due to the high proportion of carbon in the molecule.
b. These compounds are somewhat less reactive toward oxidation and reduction than alkenes and alkynes.
c. They do not undergo addition reactions very readily.
d. Aromatic compounds behave as weak nucleophiles, and are readily involved in substitution reactions with electrophiles.

QUESTIONS

1. Give an account of the process of refining petroleum making sure to explain the science involved in each step including fractional distillation and cracking.
2. All manufactured goods have a carbon footprint. Choose an example of a product and explain how the carbon footprint of the product arises from start to end, from the conversion of raw materials to the finished product appearing in the shops.
3. Taking as an example the steroid, diosgenin, describe the range of chemical reactions which, in principle, you would expect to arise from the functional groups present; an ether-like linkage, a carbonyl group, a cyclohexane ring and a degree of unsaturation in the molecule. Describe any limitations in practice.
4. Give a full account of the implications of the high reactivity of introduced hydrocarbons with naturally occurring ozone in the stratosphere of the Earth's atmosphere. Explain what international measures have been

undertaken to reduce the release of hydrocarbons to counteract depletion of the ozone layer.

5. Ozone can appear as a pollutant at low level in the Earth's atmosphere (or troposphere) in the presence of strong sunlight resulting in a photochemical smog which is injurious to human health. Explain carefully all of the factors involved, and especially the chemistry, which give rise to this phenomenon in developed countries of the world.
6. Compare and contrast the physical and chemical properties of cyclohexane and benzene.
7. Draw together the evidence for the delocalized ring structure of benzene molecules and relate this to the Kekule model of resonant hybrids, and also to modern molecular orbital theory.
8. The simplest polycyclic aromatic hydrocarbon is naphthalene, $C_{10}H_8$, which is a white crystalline solid. It is the main constituent of mothballs. Given the knowledge of benzene, draw a delocalized structure of a molecule of naphthalene and describe the range of chemical properties you would expect naphthalene to have.

REFERENCES

J. W. Goldzieher and H. W. Rudel. 1974. How the oral contraceptives came to be developed. *The Journal of the American Medical Association* 230(3):421–425.

G. Pincus. 1958. The hormonal control of ovulation and early development. *Postgraduate Medicine* 24(6):654–660.

SUGGESTED FURTHER READING

N. Applezwei. 1962. *Steroid Drugs vii–xi*. Pages 9–83. McGraw-Hill.

R. Cooper, G. Nicola. 2014. *Natural Products Chemistry: Sources, Separations and Structures*. CRC Press, Taylor & Francis Group.

C. Djerassi. 2001. *This Man's Pill Reflections on the 50th Birthday of the Pill*. Pages 11–62. Oxford University Press.

J. M. Riddle. 1992. *Contraception and Abortion from the Ancient World to the Renaissance*. Page 28 and references therein. Harvard University Press.

E. W. Straus, A. Strauss. 2006. *Medical Marvels: 100 Greatest Advances in Medicine*. Pages 139–143. Prometheus Books.

EUROPE SOLVES A HEADACHE! EMERGENCE OF ASPIRIN

Abstract: The use of willow bark to relieve symptoms of the ague by riverbank communities led to the eventual development of the great miracle drug, aspirin, by the German pharmaceutical giant, Bayer Company.

Natural products chemistry

- Salicylic acid and aspirin.

Curriculum content

- Carboxylic acids
- Phenol and the hydroxyl group in an aromatic ring
- Acetylation of the hydroxyl group of salicylic acid to form aspirin.

Salicin and Salicyclic Acid

The active ingredient in willow bark is salicin (Figure 2.9) which is converted naturally within the human body into salicylic acid. Salicin is a glycoside that is revealed when it is hydrolyzed to salicylic alcohol and glucose (see also the sections on "Global Aloe" and "A Steroid in Your Garden" in Chapter 6 for more about glycosides).

The molecular structure of salicylic acid is shown in Figure 2.10. This molecule is an example of a bifunctional organic compound, whereby the chemical reactivity may be due to either the carboxylic acid group or the phenolic group or both.

Carboxylic Acids

Carboxylic acids contain the carboxyl functional group –COOH, and examples are shown in Table 2.4. Nomenclature, as usual, follows the name of the stem of the corresponding alkane or benzene with the suffix *oic* applied. There are, of course, straight chain carboxylic acids with branched chain isomers, molecules with two or more carboxylic functional groups and aromatic carboxylic acids.

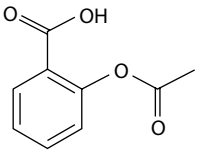


FIGURE 2.9 Chemical structure of salicin.

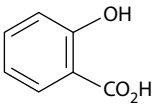


FIGURE 2.10 Molecular structure of salicylic acid.

TABLE 2.4
Examples of Simple Organic Carboxylic Acids

HCOOH	Methanoic acid (unsystematic name, formic acid)
$CH_3 \cdot COOH$	Ethanoic acid (unsystematic name, acetic acid)
$CH_3 \cdot CH_2 \cdot COOH$	Propionic acid
$CH_3 \cdot CH_2 \cdot CH_2 \cdot COOH$	Butanoic acid (unsystematic name, butyric acid)
$CH_2Cl \cdot CH(CH_3) \cdot COOH$	3-Chloro-2-methyl butanoic acid
$C_6H_4(COOH)_2$	Benzene dicarboxylic acid (informal name, phthalic acid)

Methanoic acid (b.p. 100°C) and ethanoic acid (b.p. 118°C) are both volatile liquids at ambient temperature and pressure and have pungent smells. The other acids are generally colorless crystalline solids.

Owing to the electronegativity of oxygen atoms relative to those of hydrogen, the hydroxyl bond is polar. This fact accounts for a number of the properties of carboxylic acids, especially those of low molecular mass where the hydrocarbon moiety in the molecule is less influential.

Due to the influence of hydrogen bonding in the liquid state or in aqueous solution, the lighter aliphatic acids are quite soluble in cold water, while aromatic acids are only sparingly soluble under the same conditions.

As the name of the class strongly suggests, these compounds

- Are acidic in aqueous solution
- Form organic salts readily in dilute solutions of inorganic bases
- Displace carbon dioxide from inorganic alkali metal carbonates
- Form ammonium salts or amides with ammonium hydroxide
- Combine with alcohols to form esters (catalyzed in aqueous solution by an inorganic acid).

More on the formation, properties and uses of esters is to be found in the section "A Steroid in Your Garden" in Chapter 2.

Phenol and Phenolic Compounds

Phenol (Figure 2.11) consists of a benzene ring in which one of the hydrogen atoms has been replaced by a hydroxyl group. More on the properties and uses of phenol and phenolic compounds is to be found in the section "Tea: From Legend to Healthy Obsession!" in Chapter 4.

Phenolic molecules dissolve sparingly in water as the polar hydroxyl group is able to form hydrogen bonds with water molecules. More importantly though, because of

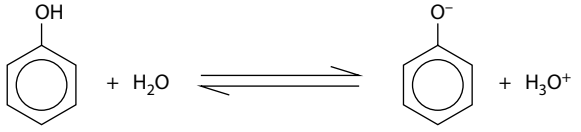


FIGURE 2.11 Partial dissociation of phenol in aqueous solution involving ions and the molecule in equilibrium.

stabilization of the anion through the delocalization of electrons over the benzene ring, the hydroxyl group in phenol partially dissociates in aqueous solution to form phenoxide anions and hydrogen cations.

As a consequence, the molecules and ions are in dynamic equilibrium and aqueous solutions of phenol have the properties of a weak acid:

- Reacting with strong bases to form a salt and water
- Unable to react with weaker bases such as sodium carbonate.

Even though phenol is different from aliphatic alcohols in many ways, phenol will form esters with a carboxylic acid. As carboxylic acids are weak acids themselves, the reaction is slow, but as an example, may be speeded up acceptably by using either an acyl chloride, such as ethanoyl chloride, or alternatively and more safely, ethanoic anhydride. Phenyl ethanoate would be the product.

$$CH_3 \cdot COCl + C_6H_5 \cdot OH = CH_3 \cdot COO \cdot C_6H_5 + HCl$$

Phenol is an important building block found in many natural products. Ease of electrophilic substitution (see Glossary) in the ortho- and/or para-positions (also known as the 2 and 4 carbon positions) of the aromatic ring is a notable chemical property of phenol. The directing effect of the hydroxyl group is so strong in phenol that in a chemical preparation it is often difficult to control the reaction to just monosubstitution.

The second main type of reaction which phenol undergoes involves replacement of the hydroxyl group by a carboxyl group, or by an ether linkage, or by a methyl or acetyl group.

More on the properties and uses of phenol and phenolic compounds is to be found in the section "Tea: From Legend to Healthy Obsession!" in Chapter 4.

Acetylation of the Hydroxyl Group of Salicylic Acid to Form Aspirin

Acetylsalicylic acid, commonly known as aspirin, may be prepared in the laboratory by substitution of the hydrogen atom of the phenol group of salicylic acid with an acetyl group (Figure 2.12). Further reference should also be made to the section titled "Morphine: A Two-Edged Sword" in Chapter 5 where the acetylation reaction is examined closely. Substitution of the phenol group may be achieved under anhydrous conditions using an acyl chloride, ethanoyl chloride, or preferably by using an acid anhydride, ethanoic anhydride, since the hazardous by-product, gaseous hydrogen chloride, is avoided.

Aspirin is a colorless crystalline solid (melting point 135°C), which is soluble in water. The drug is a well known as an analgesic (pain killer) and as a pyretic (reduces

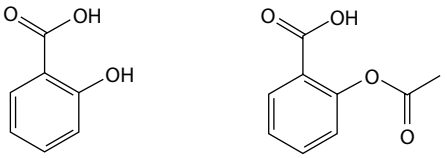


FIGURE 2.12 Salicylic acid and acetylsalicylic acid commonly known as aspirin.

fever or body temperature). Besides aspirin, another derivative of salicylic acid deserves mention. Methyl salicylate, or oil of wintergreen, occurs in many plants. Owing to its fragrant smell, methyl salicylate is used in perfumery.

HISTORICAL NOTE

From the earliest times, it was known that the chewing of the bark of the willow tree, *Salix alba*, reduced fever and inflammation. The ancient Greek physician, Hippocrates, is recorded as having recognized its therapeutic benefits.

In 1763, the Reverend Edmund Stone of Chipping Norton, Oxfordshire, England, read an obscure paper to the Philosophical Society of London entitled "An Account of the Success of the Bark of the Willow in the Cure of Agues." Later, he wrote about this lecture in a letter to the Right Honourable George, Earl of Macclesfield, who was the President of the Royal Society at the time.*

In the 1800's, pharmacists created salicylic acid in its acetylated form (acetylsalicylic acid)—more commonly known by its brand name, Aspirin. Aspirin was first isolated and synthesized by Felix Hoffmann, a chemist with the German company, Bayer, and marketed in 1897. The most widely used drug in the world continues to be Aspirin which remarkably has remained essentially unchanged for over 2,500 years.

* *Philosophical Transactions* 1683–1775. 53(1763):195–200. Published by the Royal Society.

QUESTIONS

1. Give the systematic names and molecular structures of the isomers of pentanoic acid.
2. Name the three isomers of benzene dicarboxylic acid, and give their structural formulae.
3. Give the systematic names of oxalic acid, $(COOH)_2$; lactic acid, $CH_3 \cdot CH(OH) \cdot COOH$; tartaric acid, $[CH(OH) \cdot COOH]_2$; benzoic acid, $C_6H_5 \cdot COOH$; and cinnamic acid, $C_6H_5 \cdot CH{:}CH \cdot COOH$.
4. Explain the origin of hydrogen bonding in carboxylic acids, and the nature of dimers in glacial ethanoic acid. Account, in turn, for the differences in the physical properties of low molecular weight carboxylic acids, high molecular weight carboxylic (fatty) acids and aromatic carboxylic acids.
5. Knowing the properties of a carboxylic acid and phenol, describe in full the chemistry of salicylic acid given that it is an example of a bifunctional organic compound.
6. Give examples of plants which are sources of oil of wintergreen, and explain how it is extracted and used commercially.
7. In phenol, the ortho- and para-positions in the carbon ring have been revealed in this section. Identify the *meta* position in the ring.
8. Explain why the OH group in phenol has such a strong directing effect within the carbon ring in reactions involving electrophiles.

REFERENCE

'Philosphical Transactions' 1683–1775, Vol. 53 (1763), pp. 195–200. *Published by the Royal Society.*

SUGGESTED FURTHER READING

D. Jeffreys. 2004. *Aspirin, Story of a Wonder Drug.* Bloomsbury.
C. C. Mann, M. L. Plummer. 1991. *Aspirin Wars.* A. A. Knopf.
E. W. Straus, A. Strauss. 2006. *Medical Marvels: 100 Greatest Advances in Medicine.* Prometheus Books.

ATTACKING MALARIA: A SOUTH AMERICAN TREASURE (BUT NOT GOLD) AND A CHINESE MIRACLE

Abstract: The huge cultural and economic impact of an extract from cinchona bark upon European colonization of tropical and subtropical regions of the world can scarcely be exaggerated.

Spanish colonists learned about cinchona from the native South Americans, brought the plant back to Europe and, as a consequence, reduced the spread of malaria. Later, scientists discovered how to isolate and refine the active biological ingredient, now known by the name, quinine.

Another botanical miracle emerged in recent times in China where initially secret research led to the development of a new antimalarial drug called artemisinin.

Natural products chemistry

- Quinine
- Artemisinin.

Curriculum content

- Carbon—oxygen bonds in organic compounds
- Oxygen—oxygen bonds in organic compounds
- Peroxides.

Malaria

Malaria is a vector-borne disease transmitted by the bite of a female mosquito infected with single-celled (protozoan) parasites (known as plasmodium). The tiny parasites pass through the blood stream of the human victim and travel to the liver where they mature and reproduce before affecting the whole body by attacking red blood cells. Symptoms of malaria typically include headache, feverishness and fatigue. If not treated, malaria can cause death. The areas in the world most associated with malaria are shown in red in Figure 2.13.

Two major drugs are employed in the fight against malaria, and both originate directly from natural products; quinine from the bark of the cinchona tree found in South America; artemisinin from the leaves of *Artemisia annua* native to China. The latter discovery is particularly important, as the effectiveness of drugs based solely on quinine has gradually diminished as the infecting parasites have developed resistance to the quinine-based drugs. Subsequently, artemisinin has become the treatment of choice for malaria. However, the World Health Organization (WHO) called for cessation in the use of single doses of artemisinin in 2006 in favor of combinations of artemisinin together with another malaria drug in order to reduce the risk of the parasites developing resistance. Thus, artemisinin is usually combined with a synthetic derivative of quinine known as chloroquinine. In this dual dose, the drugs reinforce one another in addressing malaria in that they have complementary roles; the former is quick acting whilst the latter reduces inflammation. However, it remains to be seen whether the strategy of combination therapy will be entirely successful in the management of malaria.

FIGURE 2.13 (See color insert.) Parts of the world where malaria is endemic are shown in red on the map from the 2013 Global Malaria Mapper. (Courtesy of the World Health Organization (WHO), http://www.who.int/malaria/publications/world_malaria_report/global_malaria_mapper/en/)

Cinchona

Cinchona is an evergreen shrub or small tree indigenous to the high Andes of South America.

The botanical name of the genus Cinchona was given by Linnaeus in 1742 from the Indian name, *Quinaquina,* derived from the Quechua language of Ecuador, Peru and Bolivia. The Quechua people used an extract from the bark as a relaxant for muscles to combat extreme cold in the high mountains. It was also noticed that the extract had a favourable impact on malaria. Later use of an extract from the bark of the cinchona tree led to significant reduction in malaria among the ranks of conquistador invaders, and helped strengthen the might of Spain for generations. Because of its medicinal property, Spanish colonists brought the shrub back to Europe around the early 1600s. Later research expeditions left from France, The Netherlands and Great Britain. Eventually, the Dutch and British cultivated cinchona for this "mysterious extract" in the East Indies and in the Indian subcontinent, respectively.

Isolation of Quinine

This substance was first isolated in 1820 by Pierre Pelletier from the bark of the cinchona shrub. He separated a yellow gum with a bitter taste, which he called quinine. However, the exact chemical structure presented in Figure 2.14 was not fully elucidated until much later. Even today, quinine is still recognized as one of the most effective drugs in the treatment of malaria although details of the mechanism of its disruption of the life cycle of the plasmodium parasite are not understood.

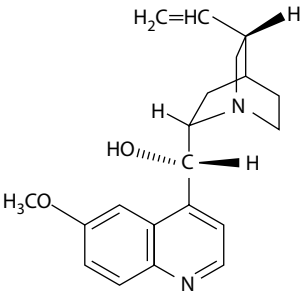


FIGURE 2.14 The structure of quinine, the antimalarial drug from the cinchona bark.

The quinine molecule has two distinctive parts; an aromatic component and an amine component. As a consequence, quinine

- Is soluble in water at room temperature to give an alkaline solution (pH 8.8)
- Readily forms salts with strong acids, examples being quinine sulphate and quinine hydrochloride.

Synthesis of Quinine in the Laboratory

The famous and brilliant British chemist, William Perkin, tried to synthesize quinine in 1856 but was unsuccessful. Eventually, quinine was synthesized in 1944. Quinine was the first drug from a natural product to be synthesized although the route was so complex it could not be made into a commercial success. Consequently, quinine is still obtained directly from the cinchona bark. Nowadays, quinine is chemically modified synthetically to make quinine derivatives, which are even more powerful as antimalarial drugs.

However, it should be remembered that Perkin's persistence in the early research of 1856 led remarkably to the discovery and production of a mauve-colored compound, which he established as a derivative of aniline. Inadvertently, he had fashioned the world's first synthetic dye, which became the basis of the entire aniline dye industry. For more on dyes, see the section on "Woad (Isatis tinctoria) and Indigo" in Chapter 7.

Uses of Quinine

Beyond its application as an antimalarial drug, quinine is widely utilized in the modern drinks industry. By repute, British administrators and army personnel working for the colonial service in the Indian subcontinent during the nineteenth century dissolved their bitter-tasting antimalarial treatment or tonic (quinine) in gin (a solution of ethanol in water). Henceforward, gin and tonic became established as a fashionable and well-liked alcoholic drink. In the English speaking world, tonic water is appreciated as a mixer for cocktails especially those based on gin or vodka.

To this day, the bitter taste of quinine is used in dilute solution to produce what is known and sold as "tonic water." Quinine, or a quinine salt such as quinine

hydrochloride, is dissolved in a small quantity in citrus drinks in order to enhance the flavor of soft drinks such as bitter lemon and bitter lime.

Artemisinin

More recently, a new and completely different antimalarial miracle drug, artemisinin, has been extracted from the leaves of *Artemisia annua* which grows in China and is shown in Figure 2.15. The discovery led to the award of the Nobel Prize in 2015 (see Historical Note).

HISTORICAL NOTE

The plant, *Artemisia annua*, has been used by Chinese herbalists for over two millennia. An extract was believed to have been used in the treatment of skin diseases and malaria. The antimalarial property of the extract was first specifically described in the fourth century within the classic Chinese text, *The Handbook of Prescriptions for Emergencies.*

In the 1960s, a research program was set up by the Chinese army to find an adequate treatment for malaria. By 1972, artemisinin had been discovered in the leaves of *Artemisia annua*. Screening of over 5,000 traditional plants (TCMs) revealed that artemisinin was the most effective drug in dealing with malaria parasites in a patient. Owing to the secret nature of the research program, however, the work was not given until recently the full international recognition it deserved. Today the world is a grateful and beneficial recipient of chemical derivatives based on artemisinin. A share of the 2015 Nobel Prize for Medicine or Physiology was awarded to the Chinese scientist, Youyou Tu for her discovery of the anti-malarial properties of artemisinin.

Artemisinin (Figure 2.16) has a complex structure including a six-membered lactone ring (for more on lactones see the section titled "A Steroid in Your Garden." The structure also contains an unusual peroxide linkage, which is believed to be involved in the antimalarial effectiveness of the drug and may also account for its relatively rapid medical action compared to quinine. WHO recognizes that artemisinin is very effective in the prevention and treatment of malaria even in cases where the parasite responsible is resistant to quinine. To avoid the possibility of drug resistance to artemisinin treatment, WHO recommends a combination therapy of artemisinin and quinine derivatives, respectively.

Carbon–Oxygen Single Bonds and Oxygen–Oxygen Single Bonds in Organic Compounds

The electronegativity of carbon and oxygen atoms is similar arising from the fact that they are close to each other in atomic structure and position in the periodic table.

FIGURE 2.15 (See color insert.) *Artemisia annua* (annual wormwood). (Taken from R. Cooper and G. Nicola. 2014. *Natural Products Chemistry: Sources, Separations and Structures*. CRC Press, Taylor & Francis Group.)

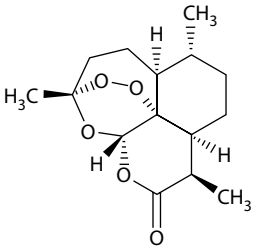


FIGURE 2.16 Molecular structure of artemisinin.

Consequently, carbon–oxygen single bonds are covalent and strong with little charge separation or dipole effect.

In contrast, the peroxide link formed by a single covalent bond between two oxygen atoms, O–O, is relatively weak by comparison with a single C–O bond. We all know that chains, however long, are only as strong as the weakest link because that is the point where a break is most likely to occur. Physically and chemically, the molecules of peroxide compounds are unstable, since they are likely to break at the weakest point, the single O–O bond, resulting in the release of free radicals (see Glossary), which are highly reactive and destructive to tissues in the human body.

The instability of organic peroxide compounds may be further contrasted with the great stability of ethers where the strength of the single C–O–C covalent bonds

results in a family of substances, which is relatively stable with little chemistry. These compounds are often volatile liquids at ambient temperature and pressure due to an absence of hydrogen bonding between adjacent molecules. For more on ethers, see the section on "Maca from the High Andes in South America" in Chapter 4.

Furthermore, the stability of C–O single bonds should not be confused with the reactivity of C═O double bonds, which are somewhat strained physically, and weakly dipolar, leading to the extensive chemistry of the large families of organic compounds, which contain the C═O double bond; namely, aldehydes, carboxylic acids, esters and ketones. This book provides many references to the diverse chemistry of each of these families of organic compounds, which are covered extensively in the sections on "Asian Staple: Rice," "A Plant from the East Indies, Camphor," "A Steroid in Your Garden," "Morphine: A Two-Edged Sword" and "Europe Solves a Headache."

The Peroxide Link and the Peroxide Bridge in Artemisinin

A peroxide is a compound containing the link of two oxygen atoms joined together by a single covalent bond as in hydrogen peroxide, H_2O_2, or in a generalized organic peroxide, R′.O.O.R″. The peroxide bond is weak, which renders peroxide compounds unstable, hence they readily decompose to form highly reactive free radicals, R′O and R″O. Owing to this instability, hydrogen peroxide and organic peroxides are found in strictly limited quantities in the natural environment.

Owing to their property as a bleaching agent, peroxide compounds are used in detergents and in cosmetic colorant treatments for human hair. In the laboratory and in some industrial pharmaceutical processes, organic peroxides are utilized to good effect as intermediates or building blocks in step-wise and lengthy preparations.

It is interesting to note that the firefly produces a small amount of the peroxide, 1,2-dioxetane (Figure 2.17), which decays spontaneously to produce electronically excited molecules of acetaldehyde. As each molecule returns to the ground electronic state, a quantum of visible light is released—an instance of chemiluminescence. Quaint glow sticks produced for human entertainment have 1,2-dioxethanedione, C_2O_4, embedded within them, which slowly breaks down in a similar way to yield carbon dioxide and emission of light.

A more sobering consideration is the care required in the storage of liquid organic compounds in the laboratory—particularly ethers. When ether is stored in a Winchester bottle (see Glossary) with some air inevitably enclosed and in the presence of light, unstable peroxides will form very slowly over a period of time measured in months, rendering the bottle somewhat explosive and hazardous to use. This effect is counteracted simply by keeping ether over potassium hydroxide which destroys the peroxide impurity as it develops.

FIGURE 2.17 1,2-Dioxetane also called 1,2-dioxacyclobutane.

QUESTIONS

1. Explain the chemical properties of quinine by reference to its molecular structure.
2. Give an account of the behavior of the peroxide link seen in artemisinin, and relate this to the properties of free radicals in organic chemistry.
3. Explain why peroxides are so unstable.
4. Potassium hydroxide is added to ethers when they are stored in order to avoid peroxide formation. Can you explain how this precaution avoids the risk of accumulation of dangerously explosive peroxides?
5. Give an account of the different chemistry of each of the three C–O bonds in artemisinin.
6. Give a full account of the implications of the high reactivity of introduced hydrocarbons with naturally occurring ozone in the stratosphere of the Earth's atmosphere. Explain what international measures have been undertaken to reduce the release of hydrocarbons to counteract depletion of the ozone layer.
7. Ozone can appear as a pollutant at low levels in the Earth's atmosphere (or troposphere) in the presence of strong sunlight resulting in a photochemical smog, which is injurious to human health. Explain carefully the chemistry, which gives rise to this phenomenon in developed countries of the world.

REFERENCES

J. Jaramillo-Arango. 1949. A critical review of the basic facts in the history of cinchona. *Journal of the Linnean Society of Botany* 351:272–309.

G. Stork et al. 2001. The first stereo-selective total synthesis of quinine. *Journal of the American Chemical Society* 123(14):3239–3242.

R. B. Woodward and W. E. Doering. 1944. The total synthesis of quinine. *Journal of the American Chemical Society* 66(5):849.

SUGGESTED FURTHER READING

R. Cooper and G. Nicola. 2014. *Natural Products Chemistry: Sources, Separations and Structures*. CRC Press, Taylor & Francis Group.

H. Hobhouse. 2015. *Seeds of Change. Six Plants that Transformed Mankind*, Pages 3–50. Counterpoint.

A STEROID IN YOUR GARDEN

Abstract: There is a very important medicine growing in your garden! In Western medicine, the drug known as digitalis has been exploited for its medicinal qualities for many years. Digitalis is obtained from the roots and seeds of the foxglove. In fact, the foxglove contains several important but highly toxic, chemically related steroidal glycosides.

Natural products chemistry

- Cyclic esters—known as lactones
- Lactones as building blocks in nature.

Curriculum content

- The hydroxyl functional group in alcohols (primary, secondary, and tertiary)
- The carboxy functional group in esters.

The Foxglove and Digoxigenin

The foxglove (Figure 2.18) (Latin name: *Digitalis purpurea*) is a wild plant, a native of the woodland margin in temperate climes, which is often cultivated in domestic gardens for its ornamental value.

Foxglove, including the roots and seeds, contains chemicals known as cardiac glycosides. One of these chemicals has the common name digitalis or its chemical

FIGURE 2.18 **(See color insert.)** Foxglove (*D. purpurea*). (Taken from R. Cooper and G. Nicola. 2014. *Natural Products Chemistry: Sources, Separations and Structures*. CRC Press, Taylor & Francis Group.)

name, digoxigenin (Figure 2.19). This compound is composed of two distinctive building blocks, which occur frequently in the natural world; the carbon skeleton of a steroid (see the section on "Central America's Humble Potato!" in Chapter 2) and that of the five-membered cyclic ester (RCOOR) known as a lactone represented in Figures 2.20 through 2.22, as examples.

Digitalis is an example of a drug derived from a plant used by folklorists and herbalists although it is difficult today to determine what amounts of active drug were present in those early herbal preparations. An extract of digitalis was used for the first time in 1785 as the modern era of therapeutic science was beginning. William Withering, a Fellow of the Royal Society, was a physician actively engaged at a hospital in Birmingham, England. He published "An Account of the Foxglove

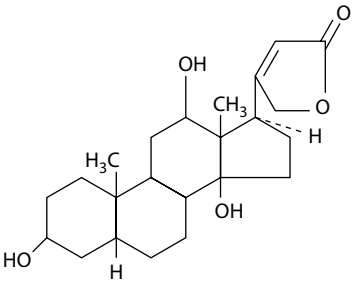


FIGURE 2.19 Molecular structure of digoxigenin.

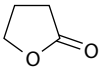


FIGURE 2.20 The structure of 4-hydroxybutyric acid lactone, also known as γ-hydroxybutyric acid lactone.

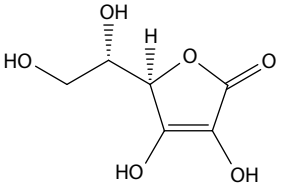


FIGURE 2.21 The structure of vitamin C, also known as ascorbic acid.

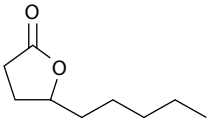


FIGURE 2.22 Chemical structure of γ-nonalactone.

and Some of Its Medicinal Uses," which contained notes on the medical effects of digitalis on congestive heart failure, characterized by low heart output. He had learned of the folk remedies used by people in Shropshire, UK, where he had grown up. Digitalis is used to control a slow heart rate and to strengthen the contraction of heart muscles, thereby producing a stronger pulse. However, digitalis is very toxic and must be administered carefully. An overdose can easily be fatal. It can still be prescribed for those patients who suffer from atrial fibrillation (an erratic heartbeat), especially if they also have congestive heart problems.

A modern application of digoxigenin is in the field of analysis called immunohistochemical staining (IHS). The technique is widely employed in molecular biology to visually reveal the presence of antigens causing abnormality in cells, as in cancerous tumors, and was first reported in the scientific literature by Coons et al. (1941). IHS has proved to be an excellent means of detecting the protein belonging to an antigen within body tissue—especially in neuroscience, where tumors may be located precisely within nerve tissue and brain cells.

Esters Are Formed from Alcohols and Acids

The alcohols are a class of organic substances forming a homologous series with the general formula $C_nH_{2n+1}OH$ containing the characteristic functional group: the hydroxyl. They are rarely found in a free state in nature although a little may be present in over-ripe fruit. The individual names of alcohols are derived by adding the suffix, ol, to the name of the corresponding alkane, thus: methanol, CH_3OH; ethanol, C_2H_5OH; propanol, C_3H_7OH, etc. Where isomerism occurs in propanol and in succeeding members of the series, the position of the hydroxyl group in the longest carbon chain is indicated by inserting a number before the "ol."

Thus, there are three types of alcohol; primary, secondary and tertiary, depending on the chemical environment of the carbon atom to which the hydroxyl is bonded.

$$\text{Primary } R' \cdot CH_2OH$$

$$\text{Secondary } R'R'' \cdot CHOH$$

$$\text{Tertiary } R'R''R''' \cdot COH$$

There is a marked difference between alkanes and alcohols with regard to boiling point and solubility in water. The difference arises unambiguously from the ability of hydroxyl groups to form hydrogen bonds by electrostatic attraction due to their dipolar nature. This molecular association has the effect of increasing molecular weight. Even the alcohols of lowest molecular weight are colorless liquids at normal temperature and pressure. As the alkyl moiety increases in proportion in the molecules of larger members of the series, so the influence of the hydroxyl group declines and physical properties relate more closely to those of the alkanes.

Alcohols undergo two types of chemical reaction directly arising from the hydroxyl group, which may break at the hydrogen–oxygen bond or at the carbon–oxygen bond.

Dehydration of ethanol occurs when the vapor is passed slowly at 200°C over a finely divided catalyst, aluminum oxide. Diethyl ether ($CH_3CH_2 \cdot O \cdot CH_2CH_3$) is the product formed from the breaking of the hydroxyl bond.

$$2C_2H_5OH = CH_3 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_3 + H_2O$$

However, at a higher temperature of 300°C, ethene is formed as the stronger hydroxyl bond is removed.

$$C_2H_5OH = CH_2CH_2 + H_2O$$

This reaction provides a renewable synthetic pathway in the chemical industry to alkenes and polymers from a feedstock of ethanol produced by the fermentation of glucose obtained from commercially grown plants such as sugarcane.

A primary alcohol may be oxidized through an aldehyde as an intermediate to form a carboxylic acid.

$$R \cdot CH_2 \cdot OH + \text{'O'} = R \cdot CHO + \text{'O'} = R \cdot COOH$$

A typical oxidizing agent for the reaction, which is performed under reflux conditions, is acidified potassium dichromate solution.

Esters are formed by the elimination of water from a reaction between an alcohol and a carboxylic acid, for example:

$$C_3H_7OH + CH_3 \cdot CO \cdot OH = CH_3 \cdot CO \cdot OC_3H_7 + H_2O$$

The reaction is effected by gently refluxing the reagents in the presence of a small quantity of a mineral acid, sulfuric or hydrochloric, as a catalyst.

Properties and Uses of Esters

Esters are formed from alcohols and carboxylic acids, whose properties are fully described in the section titled "Europe Solves a Headache!" and reinforced in "Morphine: A Two-Edged Sword."

The protocol for naming esters parallels that for the naming of salts in inorganic chemistry. Since esters are made from an alcohol and an acid, the alkyl group from the alcohol comes first and the acid stem second.

While esters can be made synthetically in the laboratory, esters occur naturally in many different flowers and fruits. Indeed, ethyl ethanoate smells strongly of the confection known as pear drops.

Esters have a sweet, fruity aroma, which serves well for applications in the perfume industry. Esters are also used as a flavoring agent in the processed food and soft drinks industries.

Owing to the presence of the carboxyl group, esters tend to be polar molecules, so even those of low molecular weight are liquids. These esters find application as a

solvent for printing ink where their characteristic smell is noticeable when marker pens are applied by a reader to highlight text on paper.

Esters are also applied in the cosmetics industry where they are used as the medium in which the active ingredients of creams and soothing or healing salve are dissolved or suspended. Furthermore, esters contribute to the aesthetic feel of the product on the skin.

Introducing Cyclic Esters Known as Lactones

The name of the class, lactone, arises from the intramolecular dehydration of lactic acid, $CH_3CH\ (OH) \cdot COOH$. The Latin name for sour milk is *lactis* owing to the presence of lactic acid. A lactone (Figure 2.20) is a cyclic ester which can be formed from an intramolecular reaction as the condensation product of an alcohol group –OH and a carboxylic acid group –COOH. Lactones are characterized by a closed ring consisting of two or more carbon atoms and a single oxygen atom with one of the carbon atoms being part of a ketone functional group, typical of an ester (see the top right of the structure of digoxigenin in Figure 2.19).

Individual lactones are named according to the precursor carboxylic acid

• Aceto	Two carbon atoms
• Propio	Three carbon atoms
• Butyro	Four carbon atoms
• Valero	Five carbon atoms
• Capro	Six carbon atoms

The nomenclature of lactones involves one further refinement. The first carbon atom along the chain of the parent molecule from the carbon atom in the COOH group is labeled alpha (α), the second beta (β) and so on.

Lactone molecules with three or four-membered rings are physically strained and, as a consequence, are quite reactive. In contrast, lactones with five or six-membered rings are relatively straightforward to prepare and are much more stable.

Lactones as Building Blocks in Nature

Lactone rings occur widely in nature as building blocks within larger molecules, which form a part of neurotransmitters, or of various enzymes, or of ascorbic acid also known as vitamin C (Figure 2.21).

Vitamins

The term, vitamin, is derived from "vitamine"—a compound word formed from vital and amine.

Currently, there are 13 recognized vitamins: vitamins A to E, including a range of B vitamins, and vitamin K.

Vitamins fall into two broad categories. The fat-soluble vitamins, vitamins A, D, E and K, can be stored by our bodies in the liver or in fatty tissues. They are stored

until they are required, which consequently means they generally do not need to be ingested as frequently. Water-soluble vitamins, on the other hand, are not stored in the body. As such, they must be a regular part of the diet in order to avoid deficiency.

Vitamins are vital for good human health: they are an important part of our diet. They perform a range of roles in the body. For example, a number of the B vitamins are important for making red blood cells and in the metabolism of a variety of compounds during digestion. Others have uses in more specific parts of the body; for example, vitamin A is important for good eyesight, whilst vitamin K plays a major role in the clotting of blood. Conversely, deficiencies of vitamins can also have effects; a lack of vitamin C can lead to scurvy, the bane of sailors before the role of vitamin C was understood. A lack of vitamin K can cause bleeding problems, which is why newborn babies are immediately given a dose containing the vitamin to prevent potential brain damage.

Vitamin C, Ascorbic Acid

Vitamin C is an essential nutrient for sound human health. Vitamin C is a primary metabolite that is directly involved in normal growth, development and reproduction. Also, it plays a role as a redox agent and catalyst in a broad array of biochemical reactions and processes. Vitamin C acts as a reducing agent donating electrons to various enzymatic and nonenzymatic reactions.

Vitamin C is found in fresh vegetables and fruits, and is also present in animal organs such as the liver, kidney and brain. Owing to its antioxidant properties, vitamin C has been widely used as a food additive to prevent or limit oxidation.

HISTORICAL NOTES ON VITAMIN C

A work published in 1753 suggested that citrus fruits (limes) contained certain compounds that could treat scurvy. Scurvy became an endemic disease between the seventeenth and nineteenth centuries because of insufficient dietary intake of fresh fruit and vegetables. Today, we know that vitamin C has the ability to cure and prevent scurvy.

The discovery of vitamin C began in the late sixteenth century when French explorers were saved from effects of scurvy by drinking a tea made from the arbor tree during long sea voyages. Later, it was noted that lemon juice could prevent people from getting scurvy. By 1734, it had been concluded that people who did not eat fresh vegetables and greens would get the disease—a clear risk for sailors denied access due to a long sea voyage in the days of sail. All seamen were thus provided with citrus fruits. The famous British naval captain, James Cook, routinely supplied his men with limes during long voyages of exploration and hydrographic survey in the late eighteenth century. In fact, the practice was commonplace in the Royal Navy of the time so much so that the American term for the British, "limeys," arises from it. These observations led to important breakthroughs in the understanding of scurvy through experiments involving guinea pigs and became one of the first examples of the

use of animal models to study disease. The first chemists to isolate vitamin C, ascorbic acid, were Svirbely and Szent-Gyorgyi for which they received the Nobel Prize for Medicine in 1937. The approach takes advantage of the acidic functional groups present in the molecule since ion-exchange resins are used to remove the acidic cations of vitamin C from aqueous solution. When a dilute solution of a strong acid is eluted through the resin as a second step, the anions of the strong acid are retained and vitamin C or ascorbic acid is released.

The first synthesis of vitamin C was achieved by Haworth and Hirst, and also resulted in the award of the Nobel Prize for Chemistry in 1937. Mass production of vitamin C by the Swiss pharmaceutical giant, Hoffmann-La Roche, came 20 years later.

Commercial Uses of Lactones

As is the case with chain or branched chain esters, some lactones, since they are cyclic esters, are used for flavoring processed foods and drinks and as fragrances particularly when specific aromas are required. For instance, γ-nonalactone, presented in Figure 2.22, smells of coconut.

Artemisinin, a complex lactone, is employed in the prevention and treatment of malaria—see the section on "Attacking Malaria: A South American Treasure and a Chinese Miracle."

Gibberellins are another group of complex diterpenoid molecules, some of which have a lactone bridge completing one of the four rings. Gibberellins are worthy of mention, because they are plant hormones, which regulate growth by stimulating plants to grow tall (or to remain short in the absence of them). They also regulate the flowering and ripening of fruit. Gibberellins continue to be the subject of intense research interest due to their ability to increase crop yields.

QUESTIONS

1. Name the following alcohols; $CH_3CH(OH)\cdot CH_3$; $CH_3\cdot CH_2\cdot CH_2\cdot CH_2OH$; $CH_3\cdot CH_3\cdot CH\cdot CH_2OH$; $CH_3\cdot CH(OH)\cdot CH_2\cdot CH_3$; $CH_3\cdot CH_3\cdot CH_3\cdot COH$. Identify the primary, secondary and tertiary alcohols.
2. Give an account of the uses of different alcohols, giving emphasis to ethanol, and their value as feedstock for a variety of industrial processes.
3. Compare and contrast the oxidation of primary, secondary and tertiary alcohols.
4. Given knowledge of the chemistry of esters, describe and give examples of the kinds of reactions lactones will undergo.
5. Three- and four-membered ring lactones are quite reactive, whereas lactones with five- or six-membered rings are much more stable. What is the reason for this in physical terms?
6. What is a vitamin?
7. Give the structure of a gibberellin and point out the important functional groups in the molecule.

REFERENCES

A. H. Coons, H. J. Creech, R. N. Jones. 1941. Immunological properties of an antibody containing a fluoroscein group. *Proceedings of the Society for Experimental Biology and Medicine* 47:200–202.

J. MacMillan. 2001. Occurrence of gibberellins in vascular plants, fungi, and bacteria. *Journal of Plant Growth Regulation* 20(4):387–442.

SUGGESTED FURTHER READING

G. F. Ball. 2004. *Vitamins: Their Role in the Human Body*. John Wiley & Sons.

R. Cooper, G. Nicola. 2014. *Natural Products Chemistry: Sources, Separations and Structures*. CRC Press, Taylor & Francis Group.

M. B. Davies, J. Austin, D. A. Partridge. 1991. *Vitamin C: Its Chemistry and Biochemistry*. Royal Society of Chemistry, paperback series.

R. B. Rucker, J. Zempleni, J. Suttie, D. McCormick, Eds. 2007. *Handbook of Vitamins*, 4th edition. Taylor & Francis.

AFRICA'S GIFT TO THE WORLD

Abstract: The Madagascan periwinkle becomes Africa's great gift to the world. A chain of serendipitous events led the Eli Lily Pharmaceutical Company, based in the United States, to isolate the drug, vinblastine, which is still used today in the fight against childhood leukemia.

Natural products chemistry

- Vincristine and vinblastine
- Alkaloids and indoles
- Isolation of chemicals from plants.

Curriculum content

- Aromatic chemistry with a nitrogen atom within an organic ring
- Indole, and alkaloids.

Discovery of the Periwinkle Plant and Its Properties

Periwinkle, also known as *Catharanthus rosea,* is a tropical perennial, often grown as an annual in temperate climates. The African plant was found only in Madagascar (Figure 2.23).

It was first described in the mid-eighteenth century. In 1757, the Madagascan periwinkle was brought to Europe as an ornamental plant and was cultivated in

FIGURE 2.23 Madagascar, Island off East Africa. (Courtesy of One World Nations Online, http://www.nationsonline.org/oneworld/madagascar.htm)

European gardens. By the late eighteenth century, widespread distribution throughout the tropics led to its adoption as a medicinal plant wherever it became established

- In Cuba and in Puerto Rico, an infusion of flowers together with a few drops of alcohol (ethanol) added was used as an eyewash for infants.
- In Latin America, the leaf tea has been used as a gargle for sore throat and laryngitis.
- In India, the fresh juice squeezed from the leaves was used for wasp stings.
- In Vietnam, herbalists use the leaf and stem tea as a treatment for everything from menstrual difficulties to malaria.
- In Asian cultures, South Africa and Caribbean islands, periwinkle tea was useful as a folk cure for diabetes.

In the early twentieth century, patent medicines containing periwinkle were touted as a cure for diabetes. "Vinculin" was sold in Great Britain while "Convinca" was sold in South Africa, but both were later shown to have no genuine medical influence in reducing levels of blood sugar. Despite this, consumption of the Madagascan periwinkle as a spurious remedy for diabetes continued and remarkably, led scientists to use the plant as the source for the development of an antileukemia drug.

Indole is an important building block for many naturally occurring alkaloids, which include significant, complex, chemical compounds extracted from the Madagascan periwinkle. Both indole and the indoles as a family of compounds are described in more detail in the sections titled "Maca from the High Andes in South America" in Chapter 4 and "Woad and Indigo" in Chapter 7.

Serendipity

Probably more drugs have been developed through a serendipitous approach by scientists than through planned attack. Educated observation of abnormal events can be further investigated. However, the discovery of the exquisitely complex chemicals from the Madagascan periwinkle was serendipitous. Rather than an inspirational, Archimedean moment of "Eureka," the two active, naturally occurring chemicals extracted from the Madagascan periwinkle were developed from research and careful observation. These compounds were eventually made commercially and sold as drugs. They were called Velban and Oncovin and were developed by a U.S. pharmaceutical company based in Indiana: the Eli Lily Company.

Traditional Madagascan healers used the periwinkle for treating diabetes, which led Western scientists to collect samples of the plant and subsequently to study the plant extract further. Eventually, using sophisticated chemical and biological techniques and some luck, they discovered its anticancer properties quite by accident. Further research led them to isolate and characterize two of the most important chemicals in the plant as cancer-fighting medicines. The chemicals were given the names, vincristine and vinblastine. Today, vinblastine has helped increase the chance of surviving childhood leukemia from 10% to 95%, while vincristine is used to treat Hodgkin's disease. This is a cancer of the lymph tissue, which is found in the liver and in bone marrow and elsewhere, and is expressed in the number of white blood cells.

Thomas Hodgkin described the symptoms in 1832 (see Glossary).

Angela's Story

One medical miracle is the story of little Angela, who, at seven years old, survived childhood leukemia, a form of cancer that up until recent times was almost always fatal. Angela and her family will always be grateful to the doctors who helped her on the road to recovery. As part of her treatment, the doctors prescribed the very special drug derived from the periwinkle called vinblastine, which was central to the chemotherapy that cured her of leukemia. Without the Madagascan periwinkle, she probably would not have survived. Angela endured more than 2 years of medical treatment. Her curly locks of hair fell out, and she remained thin and fragile, yet she bravely went to school. Her class teacher and the class children were so inspired by her courage that they all decided to shave their heads so Angela did not feel different in the classroom. Without vinblastine, her illness could have been fatal and she has every chance of full recovery.

Modern Research and Therapeutic Value

In the 1950s, the scientists, Robert Noble and Charles Beer at the University of Western Ontario in Canada discovered that extracts of the Madagascan periwinkle destroyed white blood cells. However, they had begun research on this plant based on folklore reports of antidiabetic activity from a surgeon, Dr. C. D. Johnson living in Jamaica. The results of their research on the discovery of novel anticancer activity found in the chemical extracts were presented in March 1958 in a research symposium at the New York Academy of Science. Their paper had been submitted at the last minute by invitation of the conference organizer, and was the last of the evening's presentations. The symposium ran late and the Canadians presented their findings at midnight! The audience had by then dwindled to just a few listeners—mostly members of a team of researchers from the Eli Lily drug company.

During this period, Eli Lily was testing and screening hundreds of plant extracts each year in search of biological activity which might lead to the development of a new drug. Natural products chemist, Dr. Gordon H. Svoboda (1922–1994) at Eli Lily, had added the Madagascan periwinkle to the list of research subjects based on reports of use of periwinkle products for the treatment of diabetes in the Philippines during the Second World War. Independently of the Canadians, an extract of the plant was submitted for assay, and Svoboda learned in early 1958 that the extract exhibited very high potency in anticancer tests. So, at the time that the Canadians' paper was presented in the spring of 1958, neither the Canadian research group nor the Eli Lily researchers knew of each other's work on the same plant. However, both groups had observed that their respective plant extracts lowered white blood cell counts in laboratory animals whilst they were looking for antidiabetic effects. Since leukemia involves a proliferation of white blood cells, both teams made observations leading to the deduction that an agent which reduced the number of white blood cells might have potential value in the treatment of leukemia. From an extract of the plant, another scientist, Charles Beer, isolated one specific chemical compound. He named the active compound, vincristine, which was also reported in a scientific paper in

1958 at a cancer research symposium. Needless to say, the Eli Lily research team was extremely interested in this Canadian researcher's work on the Madagascan periwinkle.

After an initial meeting, agreement on collaboration between the Eli Lily Company and the Canadian researchers was secured.

Thus, the race was on!

In March 1961, vincristine was approved by the United States FDA as a chemotherapeutic agent for the treatment of Hodgkin's disease. Even more importantly, a second chemical compound, vinblastine, was isolated by Dr. Svoboda from the Madagascan periwinkle. In July 1963, this drug was approved in the United States for the treatment of childhood leukemia.

Within 2 years of the discovery of the compounds and their antitumor activity and approval as new drugs, Eli Lily had to secure and develop a significant supply of Madagascan periwinkle in order to make production commercially viable. This meant rapid development of farming operations. The extraction of just 1 g of vinblastine from the Madagascan periwinkle required 2,000 lbs of dried leaves. It should be noted that the chemical structures of these compounds are complex. Laboratory synthesis is tedious and expensive, so natural supplies remain the best source.

Tens of thousands of cancer patients, especially those suffering with leukemia and lymphomas, have benefited from the drugs derived from this remarkable medicinal plant, the Madagascan periwinkle, better known to many in tropical climates as a weed, and to the American gardener, as an easy-to-grow ornamental. Serendipity led to an educated guess, and the hunch turned out to be correct.

The Alkaloids, Vincristine and Vinblastine

Although extracts of the Madagascan periwinkle had been used as a folk remedy for centuries, scientific studies were only carried out in the 1950s. Research revealed that extracts from the plant contained up to 70 different alkaloids, many of which are active on metabolic systems in humans. Alkaloids are very common natural compounds produced by a large variety of organisms including bacteria, fungi, green plants and animals. More examples of alkaloids are to be found in the sections on "Morphine: A Two-Edged Sword," "Coffee, Wake Up and Smell the Aroma" and "Cocaine."

Two alkaloids of particular interest isolated from the Madagascan periwinkle were vincristine and vinblastine. The alkaloids are very similar to one another as their chemical structures are very closely aligned (see Figure 2.24).

Vincristine has the empirical formula $C_{46}H_{56}N_4O_{10}$. Vincristine contains many functional groups familiar to the student chemist: carbonyl groups, hydroxyl groups, carboxylic groups, aromatic rings and an indole ring. Despite this, structurally and chemically, vincristine and other alkaloids are extremely complex compounds.

Vincristine and vinblastine are so similar that they differ by only one carbonyl group, present in an aldehyde functional group in the former, which is to be compared with a methyl group in the corresponding location in the latter. Can you spot the difference in Figure 2.24?

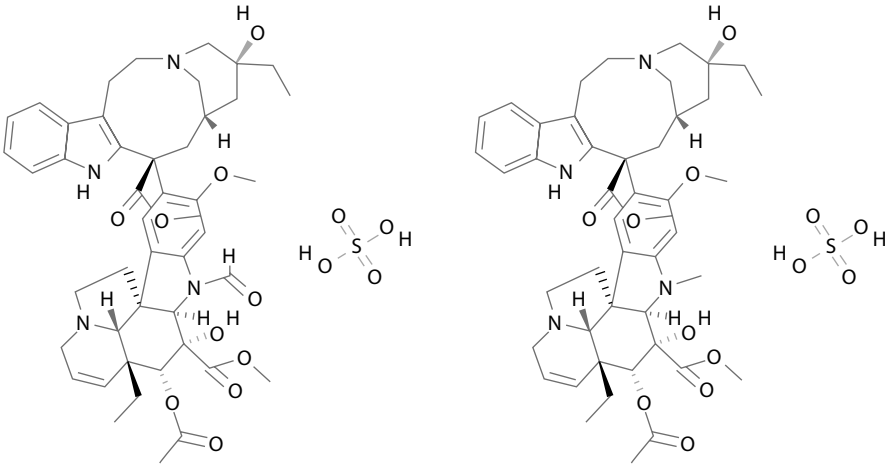


FIGURE 2.24 Vincristine (left) and vinblastine (right) in the form of the sulfate salt. (PubMed. http://pubchem.ncbi.nlm.nih.gov/compound/Vincristine_sulfate)

Furthermore, it should be noted that indole is an important building block for many naturally occurring alkaloids which include significant, complex chemical compounds extracted from the Madagascan periwinkle. Both indole and the indoles as a family of compounds are described in the section titled "Woad and Indigo," in Chapter 7.

Isolation of Vincristine and Vinblastine from Plants

Fractional Distillation

In order to isolate vincristine and vinblastine from the source plant, much research had to be undertaken to find solvents which could dissolve these alkaloids. Thereafter, the first step in the process of extraction involves simply immersing the plant in the solvent. After filtration, the spent plant material is discarded and the solution retained. Then, the solution is concentrated by reducing the volume of solvent which is achieved by fractional distillation. Distillation of the solution leads to the collection of a fraction, which is finally refined by chromatography to yield a pure sample of vincristine.

Chromatography is treated in the section on "An Asian Staple: Rice," while fractional distillation is described in the section titled "Central America's Humble Potato." Furthermore, the process of steam distillation is described in the section on "European Lavender."

Acid–Base Extraction

Alkaloids almost always contain at least one basic nitrogen atom so they can also be purified from crude extracts by acid–base extraction which is a process elaborated upon further in the sections dealing with the decaffeination of coffee and zwitterions, "Coffee: Wake Up and Smell the Aroma" and in "Maca from the High Andes in South America."

QUESTIONS

1. What property allows mixtures to be separated by fractional distillation
   - Density
   - Boiling point or
   - Type of bonding?
2. Explain hydrogen bonding in water and organic liquids, and how it influences density and boiling point.
3. Whenever possible, why is melting point rather than boiling point used to check the purity of a sample of an organic substance?
4. From the structure of vinblastine, point out the indole subunits.
5. Explain simply, in terms of functional groups, the type of reactions you would expect vinblastine to undergo. Draw attention to any complications, which may arise from the polyfunctional nature of the molecule.
6. Give examples of other organic compounds, which have the indole group as a building block, and briefly describe their properties and commercial value.
7. Unlike most amines, indole is weakly basic as only very strong acids such as hydrochloric acid are able to protonate the nitrogen atom. Explain why indole differs from amines in this way.
8. Explain why the acid–base extraction is a useful technique in the purification of vinblastine and vincristine?

REFERENCE

J. Duffin. 2002. Poisoning the spindle: Serendipity and discovery of the anti-tumor properties of the Vinca alkaloids. *Part 1: Pharmacy in History* 44(2):64–76 and *Part 2: Pharmacy in History* 44(3):105–119.

SUGGESTED FURTHER READING

M. Iwu. 2014. *Handbook of African Medicinal Plants*, 2nd edition. CRC Press.

A. D. Osseo-Asare. 2014. *Bitter Roots. The Search for Healing Plants in Africa*. Pages 31–52. University of Chicago Press.

SAVING THE PACIFIC YEW TREE

Abstract: The amazing story of a natural product, paclitaxel (commercially known as Taxol®), which was isolated from a yew tree in the 1960s as an anticancer agent. The development of Taxol was allowed to languish for years due to the issue of a lack of sustainable natural sources. Eventually, the full force of a joint effort by industry and government led to the successful commercialization of the Pacific yew and production of the drug through a process involving fermentation and semisynthesis.

Natural products chemistry

- Terpenes in nature
- Paclitaxel (Taxol).

Curriculum content

- Isomers
- Stereochemistry and chirality
- Nuclear magnetic resonance (NMR) spectroscopy.

The Nature of Paclitaxel

Paclitaxel (Figure 2.25a) is a terpenoid which was first isolated from the bark of Pacific yew trees (*Taxus brevifolia).* Terpenes are hydrocarbons. Terpenes, which contain additional functional groups are known as terpenoids (see also the section on "A Plant from the East Indies, Camphor" in Chapter 6).

HISTORICAL PERSPECTIVE

The compound, Taxol, was discovered in 1971 by Monroe and Wall who were seeking anticancer agents. Remarkably, many more years were to pass before further study at the National Cancer Institute (NCI) in the USA proceeded to clinical trials. The NCI showed great reluctance to pursue Taxol because its isolation was extremely difficult. The bark of the yew tree produced only small amounts of compound and, once stripped of its bark, the tree dies.

However, the program gained momentum due to efforts of Dr. Matthew Suffness at NCI who found Taxol to be very active against melanoma. In 1978, it was also revealed that Taxol had the capability to cause considerable regression in mammary tumors.

In the early 1980s, NCI approached industry for support and Bristol Myers Squibb decided to develop Taxol into a clinically tested drug. New research showed that Taxol could be obtained from the needles of the yew tree—ecologically much better than extraction from bark. Subsequently, Taxol was discovered as a fungal metabolite, which provided the opportunity for large-scale production from fermentation.

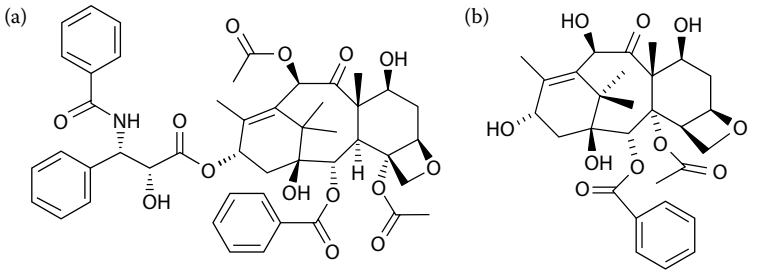


FIGURE 2.25 (a) Paclitaxel and (b) 10-DAB.

Medical Value of Paclitaxel

Paclitaxel was approved by the FDA for treatment of drug-resistant ovarian and breast cancers, and is also used in the treatment of lung cancer. Subsequently, it has become a major research tool of study in cancer therapy. Paclitaxel works by inhibiting mitosis: as the cells are unable to multiply, tumors are unable to grow.

Modern-Day Preparation of Paclitaxel

Today, the preparation of paclitaxel involves an elegant combination of measures. Large amounts of a precursor compound are isolated, which is followed by an additional semisynthetic step to yield the final product. The source of the precursor is the English yew, *Taxus baccata*. The precursor, 10-deacetyl baccatin (10-DAB) (Figure 2.25b), is available from the needles of the tree in large quantity. The difference between 10-DAB and paclitaxel is simply that 10-DAB has no ester side chain. The prepared side chain is attached to the C-13 hydroxyl group of 10-DAB to obtain paclitaxel on a large scale. In this manner, paclitaxel is manufactured by semisynthetic production from a natural precursor.

Terpenes and Isoprene as a Building Block in Nature

Terpenes are a class of compounds which are common in nature. They are also described in the section on "Cannabis and Marijuana" in Chapter 5, and in the section on "A Plant from the East Indies, Camphor" in Chapter 6.

Terpenes are present in tree resin from which turpentine can be extracted. Indeed, the very name, terpene, is derived from the word turpentine. Terpenes are major biochemical building blocks within nearly every living creature. Steroids, for example, are derivatives of the terpene known as squalene. Terpenes and terpenoids are also the primary constituents of the oils of many types of plants and flowers. These oils are used widely as natural flavor additives for food, as fragrances in perfumery, and in both traditional and alternative medicines such as aromatherapy (see the section concerning "Exotic Potions, Lotions and Oils" in Chapter 6).

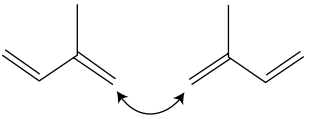
Terpenes are polymeric compounds made up of a number of isoprene molecules, namely 2-methyl-1,3-butadiene, with a molecular formula $CH_2C\,(CH_3) \cdot CH \cdot CH_2$, which have a short five-carbon chain. Because all terpenes share a common building

block, isoprene, terpenes can be categorized by the number of isoprene units they include. The simplest molecule is a two-isoprene unit called a monoterpene which has 10 carbon atoms. Examples of derivatives of monoterpenes are camphor and menthol, which help clear mucus from sinuses when a person is suffering from a cold, and pinene, which is used in wood varnish.

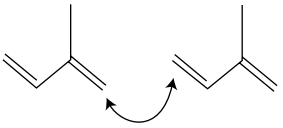
Isomers

Linkage between two isoprene molecules can occur in different ways involving either the "head" or "tail" of the molecule to form three distinct structural sequences, which have the same empirical formula. As a consequence, each of these structurally different molecules has distinct chemistry. Each structurally different molecule is known as an isomer.

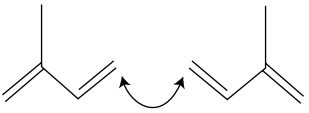
Here is an isomer being formed from the head-to-head or 1–1 link



while this link is called a head-to-tail or 1–4 link



A rare linkage is called a tail-to-tail or 4–4 link



Isomers and Stereochemistry

Physical rotation around the axis of a carbon–carbon double bond is not physically possible, as the double bond is structurally rigid. This gives rise to stereochemistry because the relative orientation of the groups within a molecule can also give rise to different isomers.

trans-1,2-dichloroethene *cis*-1,2-dichloroethene

FIGURE 2.26 An example of two isomers: *trans* (opposite) and *cis* (same). (Taken from R. Cooper and G. Nicola. 2014. *Natural Products Chemistry: Sources, Separations and Structures*. CRC Press, Taylor & Francis Group.)

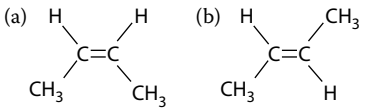


FIGURE 2.27 Stereoisomerism in alkenes. (a) *cis*-2-Butene and (b) *trans*-2-butene.

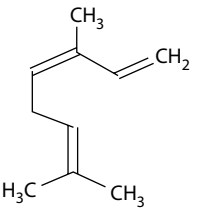


FIGURE 2.28 Structure of ocimene.

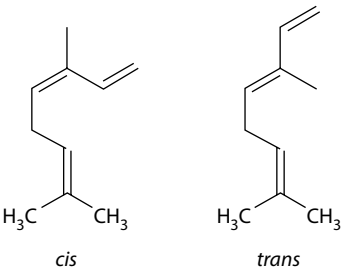


FIGURE 2.29 The geometric isomers of ocimene.

The stereochemistry of carbon–carbon double bonds is usually called *cis* and *trans* isomerism, but is also known as geometric isomerism (Figure 2.26). The terms *cis* means "on the same side" and *trans* means "across."

An alternative, the E–Z notation, makes it possible to deal with more complex cases. Look at the atoms or groups attached to each of the carbon atoms in the double bond in the example below for E- and Z-butene (Figure 2.27). When the two methyl groups are on the same side of the C=C, the isomer is described as Z, from the German word for together, *zusammen*. If not it is E, from the German word for opposite, *entgegen*.

Ocimene (Figure 2.28) is another example of a compound, which has geometric isomers found in the *cis* and *trans* configurations (Figure 2.29). It is extracted as an essential oil from the popular herb, basil (*Ocimum tenuiflorum*). Ocimene is classified as a linear terpene and possesses a pleasant odor and so finds application in perfumery.

Isomers and Chirality

The term chiral is used, in general, to describe an object, which is not superimposable on its mirror image. Human hands are an example. No matter how our two

hands are orientated, it is impossible for all the major features of both hands to coincide in space. This difference in symmetry becomes obvious if a left-handed glove is placed on a right-handed glove.

The concept of chirality is extremely important in chemistry too. Each mirror image of a chiral molecule is a special type of isomer known as an enantiomer. A pair of enantiomers is often designated as "right-handed" and "left-handed." Molecular chirality is of considerable interest in stereochemistry, especially in organic chemistry and biochemistry, where molecules can be large and complex. Spatial relationships between functional groups in different, large or complex molecules can fundamentally determine vital aspects of chemical interaction (see also the fascinating entry on the significance of the chirality of proteins and enzymes in the section on "Foods of the Fertile Crescent: Ancient Wheat" in Chapter 3).

A simple example of a chiral molecule arises in a tetrahedral molecule in which all four substituents are different, for example, fluoro chloro bromo methane, CHFClBr.

An enantiomer is a chiral molecule which also has the property of rotating the plane of polarized light. If the rotation of light is clockwise (as seen by a viewer toward whom the light is traveling), the enantiomer is labeled (+). Its mirror image is labeled (–). This property helps scientists to study chirality and enantiomers.

Nuclear Magnetic Resonance (NMR) Spectroscopy and Molecular Structure

The impact of NMR spectroscopy on organic chemistry has been substantial. NMR spectroscopy is frequently used by chemists and biochemists to investigate the structure and, hence, the properties of organic molecules from small to large and complex, such as proteins or nucleic acids or carbohydrates.

The technique relies on the phenomenon of NMR. Only nuclei having an odd number of protons or neutrons give a signal. Research often exploits the magnetic properties of the nuclei of the hydrogen atom ^{1}H, usually referred to as a proton in this context, and an isotope of carbon, ^{13}C, which is about 1% abundant compared to the common isotope, ^{12}C.

A spinning charged atomic nucleus generates a tiny magnetic field. When an external magnetic field is applied, the difference between two energy levels (ΔE) is resolved arising from two possible directions of spin. The nuclei of some atoms align with the magnetic field while other nuclei line up against it.

Irradiation of the sample with energy in the radio-frequency band which corresponds to this small difference will cause excitation of those nuclei in the lower energy state (with the field) to the higher energy state. Resonant absorption of energy occurs at a frequency characteristic of the NMR-active atom, ^{1}H or the isotope of carbon, ^{13}C. The spinning nuclei, which lie against the applied magnetic field, will, of course, radiate energy at this frequency when they return to the ground or lower energy state in which the spinning nuclei are aligned with the field.

However, the magnetic field around a nucleus is also influenced slightly by the magnetic effects of the electrons present in other atoms within the molecule and most importantly by the distribution of the other atoms in the molecule. This, of course,

is determined by the structure of the molecule. The energy difference between the spin states of the NMR-active nucleus is therefore, affected by the structure, which in turn, alters the exact frequency of absorption of energy by a nucleus in a given externally applied magnetic field strength. Analysis of a spectrum of absorption signals from NMR-active nuclei (such as a proton or the isotope of carbon, ^{13}C) can, in expert hands, reveal details of molecular structure including isomerism (see the section on "Foods of the Fertile Crescent: Ancient Wheat" in Chapter 3, for the application of NMR spectroscopy to the understanding of the structure of proteins and enzymes). As there are fewer sharp absorption peaks in ^{13}C NMR spectra, they are usually more straightforward to interpret than proton spectra. Each functional group in organic chemistry, such as C–C, C═C, C–O, C═O, C–Cl, C–N, CNO, CHO, COOH or aromatic carbon rings, can be identified in ^{13}C NMR spectra from their distinctive chemical shift.

Fine details of the location of hydrogen atoms in a molecule can also be obtained from proton NMR spectroscopy as shown in the spectrum of ethanol below.

The chemical shift of the ^{1}H nuclei is the difference between its resonant frequency of absorption of energy and the frequency of absorption of proton nuclei in a standard such as tertramethyl silane, which is set at zero on the NMR scale. The chemical shift of each group of protons, whether those present in CH_3, CH_2 or OH in this instance, is influenced by the charged electrons in their immediate proximity, in other words, by the electrons in the functional group of which they are a part of.

The signals from protons in the methyl and methylene groups are, in turn, split into multiple peaks or multiplets due to coupling with the spin of hydrogen atoms on adjacent carbon atoms. Spin–spin coupling is used to interpret NMR proton spectra through what is simply called the n + 1 rule, where n is the number of hydrogen

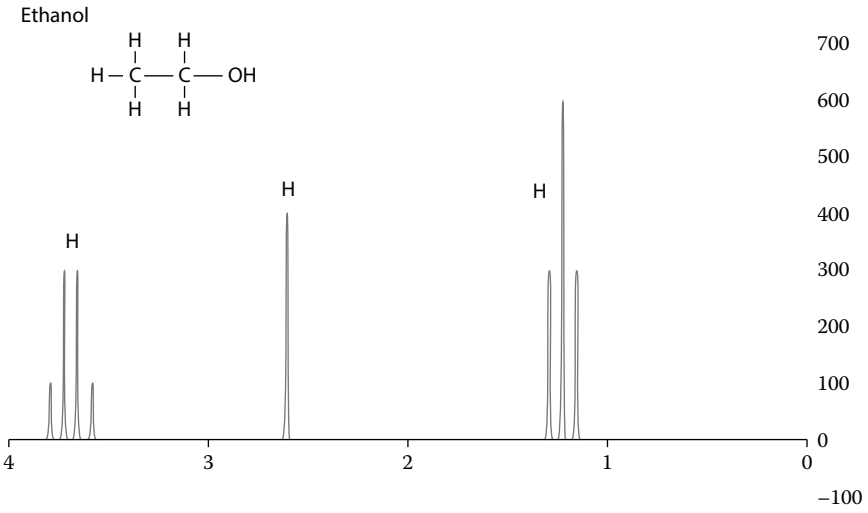


FIGURE 2.30 (See color insert.) ^{1}H NMR spectrum of ethanol. (Taken from R. Cooper and G. Nicola. 2014. *Natural Products Chemistry: Sources, Separations and Structures.* CRC Press, Taylor & Francis Group.)

atoms on the adjacent carbon atoms. As an illustration in Figure 2.30 we show the ^{1}H NMR spectrum of ethanol.

When a peak in a proton NMR spectrum is split into two multiples, then there is one hydrogen atom on the neighboring carbon atoms.

When a peak in a proton NMR spectrum is split into three multiples, then there are two hydrogen atoms on the neighboring carbon atoms.

When a peak in a proton NMR spectrum is split into four multiples, then there are three hydrogen atoms on the neighboring carbon atoms.

QUESTIONS

1. Although the structure of a molecule of paclitaxel appears complex, its characteristics will be influenced by the functional groups present. Identify those functional groups and their chemical properties.
2. How might an ester side chain be added at C-13, and what complications would you anticipate?
3. Which of the following exhibit(s) geometric isomerism
   - But-2-ene
   - But-2-yne
   - Phthalic acid based on a benzene ring with formula $C_6H_4(COOH)_2$?
4. Compare and contrast the chemical and physical properties of two structural isomers, namely ethanol and dimethyl ether.
5. Explain why spin–spin coupling is not observed in ^{13}C NMR spectra.
6. Applying the n + 1 rule to the multiplets present in the proton NMR spectrum of ethanol shown in Figure 2.30, identify the signals from distinct hydrogen atoms in the CH_3, CH_2 and OH functional groups.
7. Explain in each case why tetramethylsilane, $(CH_3)_4Si$, or deuterated chloroform, $CDCl_3$, may be used as a standard in proton NMR spectroscopy.
8. Give an account of the value of NMR to society in general given its application in approaches to health scanning undertaken in hospitals.

REFERENCES

A seminal paper describing the isolation and structure of the anticancer compound Taxol from the Pacific yew:

M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail. 1971. Plant antitumor agents. VI. The isolation and structure of Taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. *Journal of the American Chemical Society* 93:2325–7.

Key papers describing the chemical synthesis of Taxol:

R. A. Holton et al. 1994. First total synthesis of Taxol. Functionalization of the B ring. *Journal of the American Chemical Society* 116:1597–1598.

K. C. Nicolaou et al. 1994. Total synthesis of Taxol. *Nature* 367(6464):630.