REVIEW PROF-1239

# MACROMOLECULES AND PHARMACY;
## COORDINATE COVALENT BONDS BETWEEN CURIOSITY.

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**ABSTRACT...** Curiosity is the nature of man and availability of chance favor the prepared mind to explore the hidden things in the universe. One thought, observation or experience is based for the others. Chemistry is mother of the different disciplines. Macromolecules (carbohydrates, proteins, lipids etc), substitution of different group (R=Alklyl, Aryl etc) in their molecules changes their therapeutic efficacy and pharmacokinetics. Stereoisomerism in macromolecules structures, role of liposome's in penetration of drugs in cosmetics, percentage yield and antibiotics from natural moulds plays an important and significant role in pharmacy. The object is to find out a relationship between curiosity, macromolecules and pharmacy which might be able to clear the concept about mechanism of action of drugs, discovery of the new drugs and to understand pharmacological and adverse effects of drugs. This might be helpful in therapeutic management, follow up and better health care of patients in future.

## INTRODUCTION

Curiosity is one of the most important human traits. Small children constantly ask why?

It was Louis Pasteur, a chemist and microbiologist, who said, "Chance favors the prepared mind." In the history of science and medicine there are many examples of individuals who have made important discoveries because they recognized the value of an unexpected observation. One such example is the use of ultraviolet (UV) light to treat infant jaundice. Infant jaundice is a condition in which the skin and the whites of the eyes appear yellow because of high levels of the bile pigment bilirubin in the blood. Bilirubin is a breakdown product of the oxygen-carrying blood protein hemoglobin. If bilirubin accumulates in the body, it can cause brain damage and death. The immature liver of the baby cannot remove the bilirubin. An observant nurse in England noticed that when jaundiced babies were exposed to sunlight, the jaundice faded. Research based on her observation showed that the UV light changes the bilirubin into another substance that can be excreted. To this day, jaundiced newborns are treated with UV light[1]. The Pap smear test for the early detection of cervical and uterine cancer was also developed because of an accidental observation[2]. Dr. George Papanicolaou, affectionately called Dr. Pap, was studying changes in the cells of the vagina during the stages of the menstrual cycle. In one sample he recognized cells that looked like cancer cells. Within five years, Dr. Pap had perfected a technique for staining cells from vaginal fluid and observing them microscopically for the presence of any abnormal cells. The lives of countless women have been saved because a routine Pap smear showed early stages of cancer[3].

As we get older, our questions become more complex,

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but the curiosity remains. Curiosity is also the basis of the scientific methods. A scientist observes an event, wonders why it happens, and sets out to answer the question.

Dr. Michael Zasloff's curiosity may have lead to the development of an entirely new class of antibiotics. Of all the scientists to observe this remarkable healing, only Zasloff was curious enough to ask whether there were chemicals in the frog's skin that defended the frogs against bacterial infections-a new type of antibiotic. Dr. Zasloff found two molecules in frog skin that can kill bacteria[4]. Both are small proteins. Zasloff named them magainins, from the Hebrew word "for shield". Most of the antibiotics that are now used enter bacteria and kill them by stopping some biochemical process inside the cell.

Magainins are more direct; they simply punch holes in the bacterial membrane, and the bacteria explode. One of the magainins, now chemically synthesized in the laboratory so that no frogs are harmed, may be available to the public in the near future. This magainins can kill a wide variety of bacteria (broad spectrum antibiotic), and it has passed the Phase I human trials. If this compound passes all the remaining tests, it will be used in treating deep infected wounds and ulcers, providing an alternative to traditional therapy. The curiosity that enabled Zasloff to advance the field of medicine also catalyzed the development of chemistry.

## PENCILLIN AND ITS DERIVATIVES

The "age of antibiotics" began in 1927-1929, when Alexander Fleming discovered, quite by accident, that a product of the mold Pencillium can kill susceptible bacteria. Penicillin inhibits bacteria growth by interfering with cell wall synthesis[5]. Since Fleming's time, hundreds of antibiotics, which are microbial products that kill or inhibit the growth of susceptible bacteria or fungi, have been discovered? The key to antibiotic therapy is to find a "target" in the microbe, a metabolic process or structure that the human dose not have[6]. In this way the antibiotic will selectively inhibit the disease- causing organism without harming the patient. Many antibiotics disrupt cell membranes. The cell membrane is not an ideal target for antibiotic therapy because all cells, human and bacterial, have membranes[7]. Therefore both types of cells are damaged. Because these antibiotics exhibits a wide range of toxic side effects when ingested, they are usually used to combat infections topically (on body surfaces)[8]. In this way, damage to the host is minimized but the inhibitory effect on the microbe is maximized. These natural penicillins produced by several species of the mold Penicillium, had a number drawbacks. They were effective only against a type of bacteria referred to as gram positive because of a staining reaction based on their cell wall structure. They were also very suspects to destruction by bacterial enzymes called β-lactamases, and some were destroyed by stomach acid and had to be administered by injection. To overcome these problems, chemists have produced semi synthetic pencillins by modifying the core structure. The core of pencillins is 6-aminopencillanic acid, which consists of thiazolidine ring fused to a β-lactam ring. In addition, there is R group bonded via an amide bond to the core structure. The β-lactam ring confers the antimicrobial properties.

However, the R group determines the degree of antibacterial activity, the pharmacological properties, including the types of bacteria against which it is active, and the degree of resistance the β-lactamases exhibited by any particular penicillins antibiotic. These are the properties that must be modified to produce penicillins that are acid resistant, effective with a broad spectrum of bacteria, and β-lactamase resistant.

Chemists simply remove the natural R group by cleaving the amide bond with an enzyme called an amidase. They then replace the R group and test the properties of the "new" antibiotic. Among the resulting semisynthetic penicillins are ampicillin, methicillin, and oxacillin. Polymyxins are antibiotics produced by the bacterium Bacillus polymyxa. They are protein derivatives having one end that is hydrophobic because of an attached fatty acid and the opposite end is hydrophilic. Because of these properties, the polymyins bind to membranes with the hydrophobic end embedded within the membrane, while the hydrophilic end remains outside the cell. As a result, the integrity of the membrane is disrupted, and

leakage of cellular constituents occurs, causing cell death. Although the polymyxins have been found to be useful in treating some urinary tract infections, pneumonias, and infections of burn patients, other antibiotics are now favored because of the toxic effects of the polymyxins on the kidney and central nervous system. Polymyxin B is still used topically and is a available as an over-the-counter ointment in combination with two other antibiotics, neomycin and bacitracin. Two other antibiotics that destroy membranes, amphotericin B and nystatin[9,10,11] are large ring structures that are used in treating serious systemic fungal infections. These antibiotics complexes with ergosterol in the fungal cell membrane, and they disrupt the membrane permeability and cause leakage of cellular constituents[12,13]. Neither is useful in treating bacterial infections because most bacteria have no ergosterol in their membranes[14]. Both amphotericin B[15] and nystatin[16] are extremely toxic and cause symptoms that include nausea and vomiting, fever and chills, anemia, and renal failure. It is easy to understand why the use of these drugs is restricted to treatment of life-threatening fungal diseases.

## Significance of Stereoisomerism

Through the Looking Glass, Lewis Carroll's heroin Alice wonders whether "looking glass milk" would be good to drink. Many biological molecules, such as the sugars, exist as two stereo isomers, enantiomers that are mirror images of one another. Because two mirror-image forms occur, it is rather remarkable that in our bodies and in most of the biological world, only one of the two is found. For instance, the common sugars are members of the L-family. It is not too surprising, then, that the enzymes that break down the sugars and proteins are stereospecific, that is, they recognize only one mirror-image isomer. Knowing this, it can guess that "looking –glass milk" could not be digested by our enzymes and therefore would not be a good source of food for man. It is even possible that it might be toxic to human begins. Pharmaceutical chemists are becoming more and more concerned with the stereo-chemical purity of the drugs that is taken. For examples;

## Thalidomide

In 1960, the drug thalidomide was commonly prescribed in Europe as a sedative. However, during that year, hundreds of women who took thalidomide during pregnancy gave birth to babies with severe birth defects. Thalidomide was a mixture of two enan-tiomers. One is a sedative; the other is a teratogen, a chemical that causes birth defected[17,18].

## Antihistamines

One of the common side effects of taking antihistamines for colds or allergies is drowsiness. Again, this is the result of the fact that antihistamines are mixtures of enantiomers. One causes drowsiness; the other is a good decongestant.

## Carvone

One enantiomer of the compound carvone is associated with the small of spearmint; the other produces the aroma of caraway seeds or dill.

## Limonene

One mirror-image form of limonene smell like lemons; the other has the aroma of oranges.

## Ibuprofen

The pain reliever ibuprofen is currently sold as a mixture or enantiomers, but one is a much more effective analgesic than the other[19].

Taste, smell, and the biological effects of drugs in the body all depend on the Stereo chemical from of compounds and their interactions with cellular enzymes or receptors. As a result chemists are actively working to devise methods of separating the isomers in pure form. Alternatively, methods of conducting stereospecific synthesis that produce only one stereo-isomer are being sought. By preparing pure stereo-isomers, the biological activity of a compound can be much more carefully controlled this will lead to safer medications[20].

## Opiate: Biosynthesis and Mutant Poppy

Hippocrates, the Father of Medicine, left us the first record of the therapeutic use of opium (460 B.C). Although not recorded, it is probably true that the addictive properties of opium were recognized soon

thereafter. The opium poppy (Papaver somniferum) is cultivated, legally and illegally, in many parts of the world. The flowers vary in color from white to deep red, but it is the seed pod that is sought after. In the seed pod is a milky fluid that contains morphine and codeine, and a small amount of an opioid called thebaine. The juice is extracted from the unripe seed pods and dried, and the opium alkaloids are extracted and purified. In the legal pharmaceutical world, morphine and codeine are used to ease pain and spasmodic coughing[21].

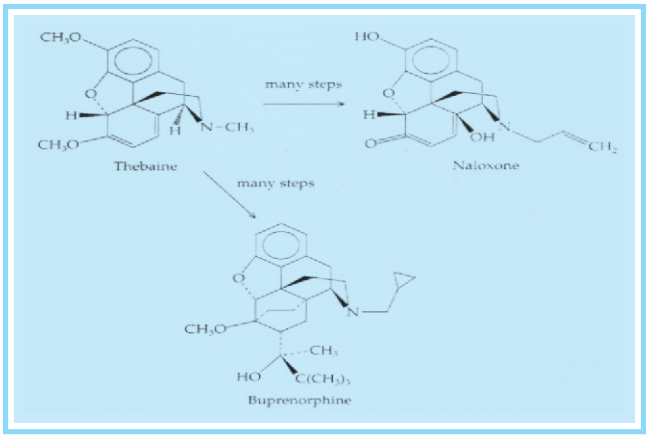
Thebaine is used as a reactant in pharmaceutical synthesis to produce a number of synthetic opioid compounds with a variety of biological effects[22]. These include the analgesics oxycodone (brand name Oxycontin), oxymorphone, and nalbuphine, naloxone, which is used to treat opioid overdosage; naltrexone, which is useful in helping people with narcotic or alcohol addictions to remain drug free; and buprenorphine, which is useful in the treatment of opiate addiction because it prevents withdrawal symptoms[23]. Approximately 40% of the world's legal opium poppies are grown on the Australian island state of Tasmania. This is big business, and the industry has developed an active research program to study the biochemical pathway for the synthesis of morphine and codeine. The pathway begins with the amino acid tyrosine, the same amino acid that is the initial reactant for the synthesis of dopamine and epinephrine.

7 steps 6 steps 3steps 1step
Tyrosine[24] →Reticuline →Thebaine →Codeine →Morphine

Through seven chemical reactions, tyrosine is converted to reticuline. Another six reaction convert reticuline to thebaine. Three chemical modifications convert thebaine to codeine, which undergoes an ester hydrolysis to produce morphine. In the course of studies, researchers produced a mutant strain of poppy that cannot make morphine or codeine, but does produce high levels of thebaine. "Norman, "for No" Morphine, "has been the most common strain of poppy grown in Tasmania since 1997. The mutation that causes Norman to produce high levels of thebaine is an alteration in one of the enzymes that catalyzes the conversion of thebaine to codeine.

Since it can't converted into codeine, large amounts of thebaine accumulate in the seed pods. Synthetic opioids, such as naloxone[25, 26] and buprenorphine[27] and others mentioned above, have become much more important commercially than codeine and morphine.

The economic value of Norman is that it produces large amounts of the starting material for the synthesis of these synthetic opioids. Consider the drug formulation "Suboxone" a combination of buprenorphine and naloxone, calms the addicts craving for opiates and yet posses little risk of being abused[28]. Buprenorphine or "bupe" works by binding to the same receptors in the brain to which heroin binds, but the drug is only a partial heroin agonist. As a result, buprenorphine is much less additive than methadone and make it easier for them to withdraw from the drug after a few months. Because addicts don't get high from Suboxone, it is much less likely than methadone to be stolen and sold illegally. It has the added advantage that its effects are longer lasting than those of methadone; so addicts need only one pill every two or three days. In addition, because naloxone is an opioid antagonist, it causes instant withdrawal symptoms if an addict tries to inject Suboxone for a high[29]. As a result, Suboxone can be given to addicts to be taken at home, rather than being dispensed only at clinics, as methadone is. With all of these features, Suboxone begins to sound like a miracle drug.



## Liposomes—Pharmaceutical and Biomedical Significance

Liposomes were discovered by Dr. Alec Bangham in 1961. During his studies on phospholipids and blood clotting, it was found that when phospholipids and water are mixed, tiny phospholipids bilayer sacs, called liposome's, are formed spontaneously. Since that first observation, liposomes have been developed as efficient delivery system for everything from anti-tumor and antiviral drugs, to the hair-loss therapy minoxidil[30]. If a drug is included in the solution during formation of liposomes, the phospholipids will form a sac around the solution. In this way the drug becomes encapsulated within the phospholipids sphere. This liposome's can be injected intravenously or applied to body surfaces. Sometimes scientists include hydrophilic molecules in the surface of the liposome. This increases the length of time that they will remain in circulation in the bloodstream. These so- called stealth liposomes are being used as carry anticancer drugs, such as doxorubicin and mitoxantrone[31].

Liposomes are also being used as carriers for the antiviral drugs, such as AZT and ddC that are used to treat human immunodeficiency virus infection. A clever trick to help target the drug-carrying liposome is to include an antibody on the surface of the liposome. These antibodies are proteins designed to bind specifically to the surface of a tumor cell. Upon attaching to the surface of the tumor cell, the liposome "membrane" fuses with the cell membrane. In this way the deadly chemicals are delivered only to those cells targeted for destruction. This helps to avoid many of the unpleasant side effects of chemotherapy treatment that occur when normal healthy cells are killed by the drug. Another application of liposomes is in the cosmetics industry. Liposome's can be formed that encapsulate a vitamin, herbal agent, or other nutritional element. When applied to the skin, the liposome's pass easily through the outer layer of dead skin, delivering their contents to the living skin cells beneath.

As with the pharmaceutical liposome's, these liposome's, sometimes called cosmeceuticals, fuse with skin cells. Thus, they directly deliver the beneficial cosmetic agent directly to the cells that can benefit the most. Since their accidental discovery forty years ago, much has been learned about the formation of liposome's and ways to engineer them for more efficient delivery of their contents.

This is another example of the marriage serendipity, an accidental discovery, with scientific research and technological application i.e; (coordinate covalent bond between curiosity, macromlecules and pharmacy). As the development of new types of liposomes continues, it can expect that even more ways will be found to improve the human condition[32].

## Pharmaceutical Chemistry: Practical Significance of Percent Yield

In recent years the major pharmaceutical industries have introduced a wide variety of new drugs targeted to cure or alleviate the symptoms of a host of diseases that afflict humanity. The vast majority of these drugs are synthetic; they are made in a laboratory or by an industrial process. These substances are complex molecules that are patiently designed and constructed from relatively simple molecules in a series of chemical reactions.

A series of ten to twenty "steps," or sequential reactions, is not unusual to put together a final product that has the proper structure, geometry and reactivity for efficacy against a particular disease. Although a great deal of research occurs to ensure that each of these steps in the overall process is efficient (having a large percent yield), the overall process is still very inefficient (low percent yield). This inefficiency, and the research needed to minimize it, at least in part determine the cost and availability o both prescription and over-the- counter preparations. Consider a hypothetical five-step sequential synthesis. If each step has a percent yield of 80% our initial impression might be that this synthesis is quite efficient. However, on closer inspection we find quite the contrary to be true. The overall yield of the five-step reaction is the product of the decimal fraction of the percent yield of each of the sequential reactions.

So, if the demical fraction corresponding to 80% is 0.80:
0.80 x 0.80 x 0.80 x 0.80 x 0.80 x = 0.33
Converting the decimal fraction to percentage:
0.33 x 100% = 33% yield

Many reactions are considerably less than 80% efficient, especially those that are used to prepare large molecules with complex arrangements of atoms. Imagine a more realistic scenario in which one step is only 20% efficient (a 20% yield) then the other four steps are 50%, 60%, 70%, and 80% efficient. Repeating the calculation with these numbers (after conversion to a decimal fraction):
0.20 x 0.50 x 0.60 x 0.70 x 0.80 x = 0.0336.

Converting the decimal fraction to a percentage: 0.0336 x100% = 3.36% yield a very inefficient process. If we apply this logical to a fifteen- or twenty-step synthesis we gain some appreciation of the difficulty of producing modern pharmaceutical products. Add to this the challenge of predicting the most appropriate molecular structure that will have the desired biological effect and be relatively free of side effects. All these considerations give new meaning to the term “wonder drug” that has been attached to some of the more successful synthetic products.

## Acquired Immune Deficiency Disease (AIDS)

In 1981 the Centers for Disease Control in Atlanta, Georgia, recognized a new disease syndrome, acquired immune deficiency syndrome (AIDS). The syndrome is characterized by an impaired immune system, a variety of opportunistic infections and cancer, and brain damage that results in dementia. It soon becomes apparent that the disease was being transmitted by blood and blood products, as well as by sexual conduct[33].

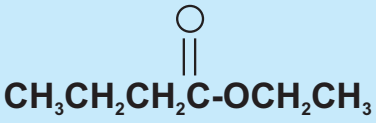
The earliest drugs that proved effective in the treatment of HIV infections all inhibited replication of the genetic material of the virus[34]. While these treatments were initially effective, prolonging the lives of many, it was not long before viral mutants resistant to these drugs began to appear. Clearly, a new approach was needed[35] (Curiosity). In 1989, it was revealed, a three-dimensional structure of the HIV protease. This enzyme is necessary for viral replication because the virus has an unusual strategy for making all of its proteins. Rather than make each protein individually, it makes large “polyproteins” that must then be cut by the HIV protease to form the final proteins required for viral replication. The enzyme protease was essential for HIV replication, and it was decided to engineer a substance that would inhibit the enzyme by binding irreversibly to the active site, in essence plugging it up. Researchers knew the primary structure (amino acid sequence) of the HIV protease from earlier nucleic acid sequencing studies (coordinate bond with macromolecules). By 1989 a very complete picture of the three-dimensional nature of the molecule was obtained by X-ray crystallography[36]. Putting all of this information into a sophisticated computer modeling program, protease could be looked from any angle. The location of each of the R groups of each of the amino acids in the active site. This kind of information allowed the scientists to design molecules that would be complementary to the shape and charge distribution of the enzyme active site-in-other words, structural analogs of the normal protease substrate (coordinate bond with pharmacy). It was not long before to produce several drugs for the HIV protease inhibitor[37]. But, there are many tests that a drug candidate must pass before it can be introduced into the market as safe and effective. Candidate drugs would bind effectively to the HIV protease and block its function, thereby inhibiting virus replication[38].

Properties such as the solubility, the efficiency of absorption by the body, the period of activity in the body, and the toxicity of the drug candidates all had to be determined. By 1996 there were three protease inhibitors available to combat HIV infection[39]. There are currently seven of these drugs on the market. In many cases development and testing of a drug candidate can take up to fifteen years[40]. In the case of the first HIV protease inhibitors, the first three drugs were on the market in less than eight years[41]. This is an urgent need for HIV treatments and the technology that should be available to attack the problems[42].

## Chemistry of flavor and Fragrance:

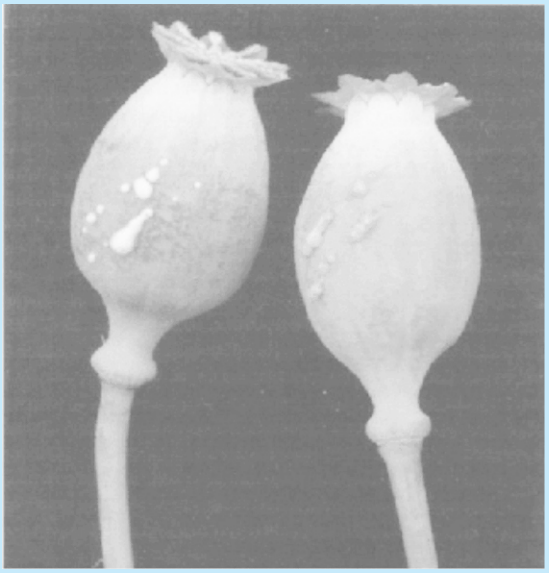
| Name of fruit | Flavor is due to |
|---|---|
| Pineapple: | Ethyl butanoate (Ethyl butyrate) |
| Raspberries: | Isobuty methanoate (Isobutyl formate) |
| Banana: | 3-Methylbutyl ethanoate (Isoamyl acetate) |
| Oranges: | Octyl ethanoate (Octyl acetate) |
| Apricot: | Pentyl butnoate (Pentyl butyrate) |
| Apple: | Methyl butnaote (Methyl butyrate) |
| Strawberries: | Methyl thiobutanoate (Methyl thiobutyrate) (A thioester in which sulfur replace oxygen) |

**Pineapple**



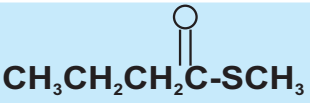
$CH_3CH_2CH_2C\text{-}OCH_2CH_3$

Ethyl butanoate
(ethyl butyrate)



**Poppy**

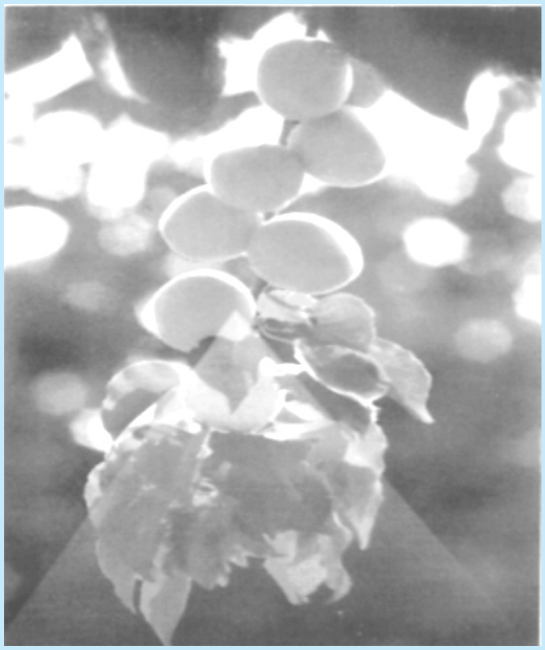
**Strawberries**

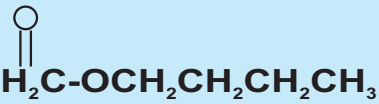


$CH_3CH_2CH_2C\text{-}SCH_3$

Methyl thiobutanoate
(methyl thoibutyrate)
(a thioester In which sulfur replaces oxygen)

**Apricots**

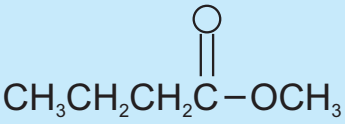




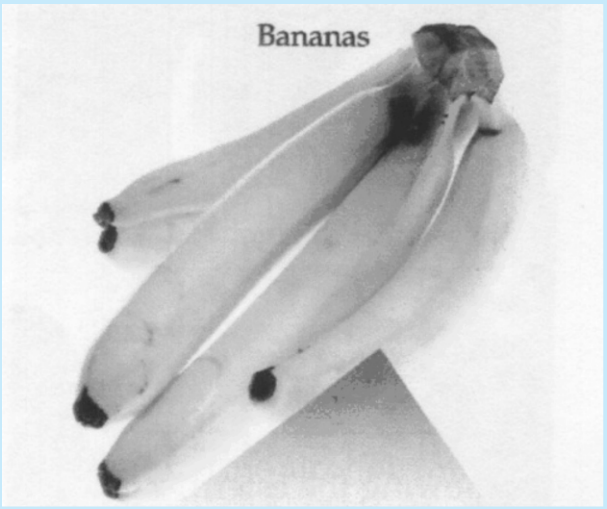
$CH_3CH_2CH_2C\text{-}OCH_2CH_2CH_2CH_3$

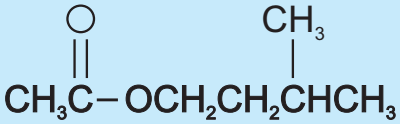
Pentyl butanoate
(pentyl butyrate)

## Apples



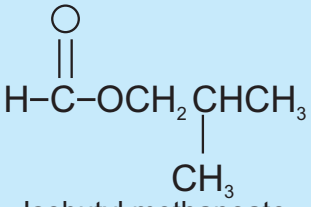
Methyl butanoate
(methyl butyrate)



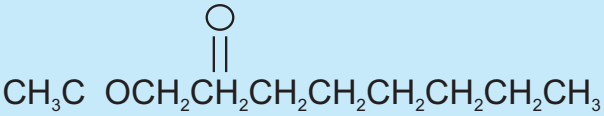
3-Methylbutyl ethanoate
(isoamyl acetate)

## Raspberries



Isobutyl methanoate
(isobutyl formate)

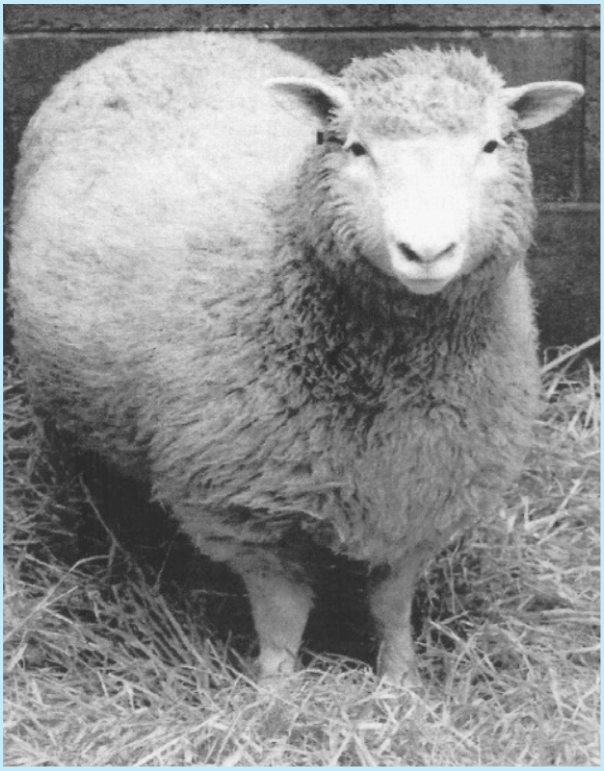
## Oranges



Octyl ethanoate
(octyl acetate)

## Genetic Engineering

Most of the tools are assembled and needed for a cloning experiment that must decide which gene is to be cloned. For example cloning of the β-globin genes for normal and sickle cell hemoglobin. The bacteria are able to transcribe and translate the cloned DNA and produce valuable products for use in medicine and other fields.[43, 44, 45]



Dolly the most famous sheep in the world produced by cloning technique

A lot of work is required to develop coordinate covalent bonds between macromolecules and Pharmaceutics to produce new drugs which might be helpful for management, preventive measures, and treatment to relieve the mankind from the drastic effects of ailments.



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