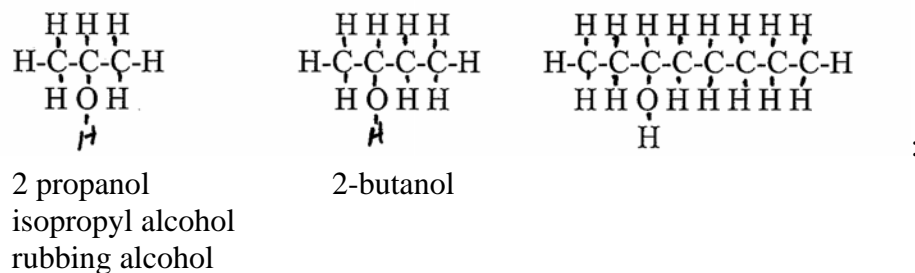
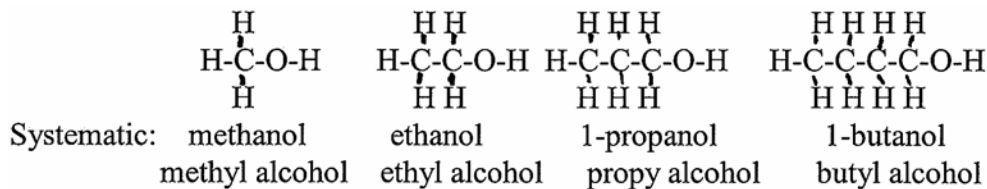


CHAPTER 6

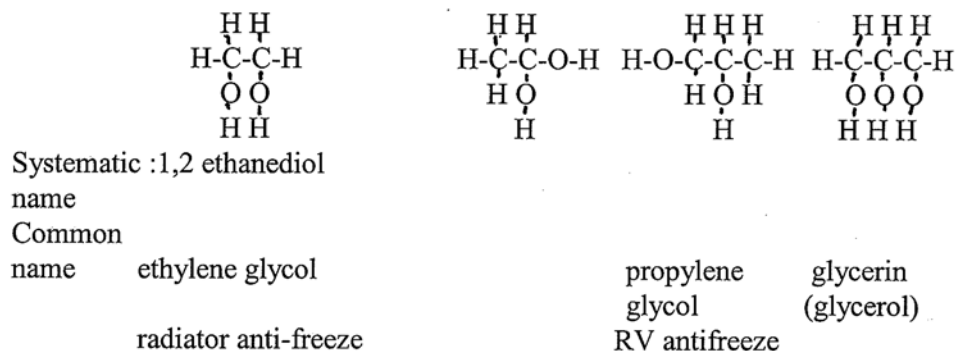
ALCOHOLS

6.1 NAMING OF ALCOHOLS



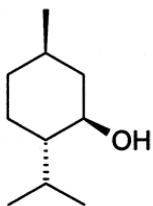
The OH group (alcohol group) is also often referred to as a hydroxy group. Note that this is different from the hydroxide ion, OH^{-1} .

Multiple alcohol groups on a molecule:



Glycerol is commonly used as the solvent for drug syrups. It is non-toxic, viscous (pours slowly, making spills less likely) and sweet (partially covering up the bitter taste of most drugs).

Menthol



Menthol has three chiral centers. Can you label them?

Menthol(2-(2-Propyl)-5-methylcyclohexanol) is a naturally occurring alcohol isolated from peppermint and other members of the mint family. Besides having a pleasant smell and flavor, it provides a mild analgesic effect as well as a cooling sensation (although it doesn't actually lower the temperature). These effects result in its widespread use in cough medicines, creams for relieving muscle cramps and pains (Tiger Balm, Icy Hot), creams for reducing sunburn pain. It has also been added to menthol cigarettes (Kool, Salem) where it provides a pleasant smell, and reduces throat irritation. Menthol cigarettes have been especially popular in the Afro-American population.

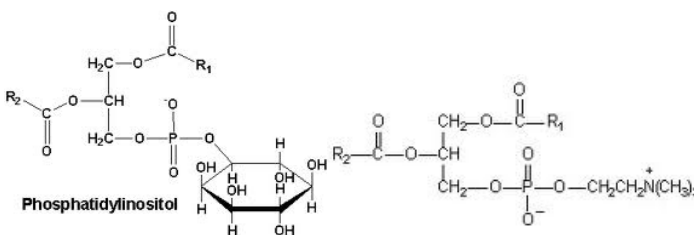
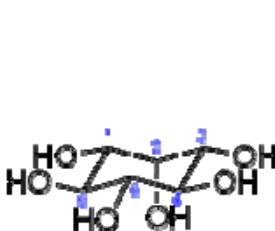


blisstree.com



Eurweb.com

Inositol is a cyclohexane ring with an alcohol functional group on each C of the cyclohexane ring. It is a component of the very important signaling molecule phosphatidylinositol which activates or deactivates portions of cellular metabolism based on the cell's needs

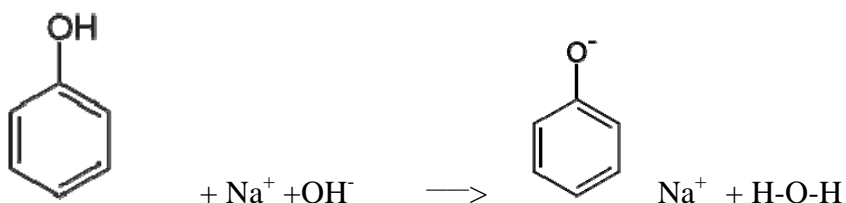


6.2 PHENOL AND ITS ACIDIC PROPERTIES. Phenol is used in Chloroseptic for its bacteriocidal properties and for its local anesthetic effect which reduces the pain of sore throats. It can cause damage to the throat if used routinely for long periods of time and the label recommends that one not use it for a period of more than *one week*. It is also used in facial peels, and embalming fluid. It is an unusual alcohol in that it is acidic. Alcohol groups on aromatic (benzene) rings are acidic, but alcohol groups on alkane chains generally are not. (This is because the extra pair of electrons on the O of the phenolate ion combines with the delocalized pi electrons of the benzene ring, spreading

the cloud of electrons still further, which stabilizes the ionic phenolate or phenoxide ion.)



Phenol can undergo a **neutralization** reaction:



The ionic salt, sodium phenolate (or sodium phenoxide), is more soluble in water than phenol itself and is used in Chloroseptic, probably to increase the concentration (since phenol is not very water soluble) and to reduce the acidity caused by the phenol itself. A variety of molecules containing a phenol group are used for their antiseptic activity. Adding alkyl, phenyl, or halogen groups to a phenol molecule makes the phenol more bacteriocidal.

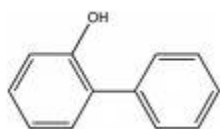


Drugsdepot.com

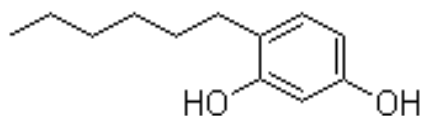
6.3 Phenolic compounds with practical uses

6.3.1 Phenolic compounds used as antiseptics

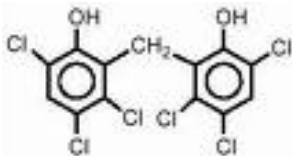
a) **Ortho-phenylphenol** is used on skin of citrus fruit and nuts to prevent mold growth.



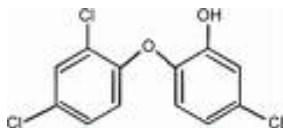
b)Hexyl resorcinol is found in throat lozenges such as Strepsils Extra (most popular sore throat lozenge in England) and some mouthwashes; it produces a local anesthetic effect. It's questionable whether the concentration of hexyl resorcinol released into the saliva is enough to have any clinical effect on bacterial growth(Wilson and Gisvold's Medicinal Chemistry)



e)Hexachlorophene(active ingredient of pHisoHex) is a chlorinated phenolic disinfectant that has been commonly used for scrubbing hands before surgery in hospitals to kill gram positive bacteria (particularly Staph. aureus) on the skin. It is gradually absorbed into the skin and repeated or prolonged scrubbing is needed to build up bacteriocidal activity. Unfortunately it is not active against gram negative bacteria. It used to be used for bathing babies, but in 1972 evidence that it is absorbed through babies' skins was published and that it might cause brain damage. It was taken off the OTC market and is now available only by prescription.



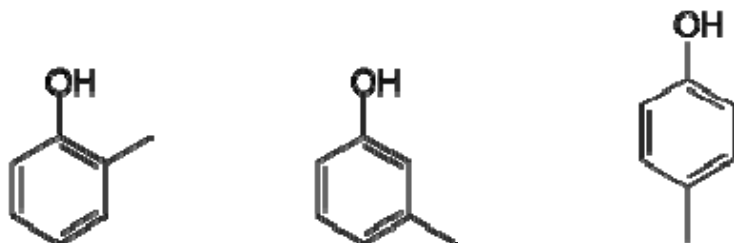
f)Triclosan is still another chlorinated bacteriostatic phenolic compound that is being used in hand soaps, body washes, detergents, dish washing liquids and anti-microbial creams, and lotions. There is evidence that bacteria are becoming resistant to these chlorinated phenolic bacteriocides.





Creative Commons: <http://www.flickr.com/photos/14936293@N03/2389378576/> Jack Black's Stunt Double

g) The original formulation of Lysol contained a mixture of cresols (ortho, meta and para forms of methylphenol) and was used as a feminine hygiene product until the AMA argued against its use, concerned that it could kill off natural flora and leave the vagina more susceptible to pathogenic bacteria. It was heavily marketed from ~1920 to 1960.



Cresols

Love-quiz ... For Married Folks Only



WHY DOES SHE SPEND THE EVENINGS ALONE?

- A. Because she keeps her home immaculate, looks as pretty as she can and really loves her husband, BUT she neglects that one essential . . . personal feminine hygiene.
- Q. Is this really important to married happiness?
- A. Wives often lose the precious air of romance, doctors say, for lack of the intimate daintiness dependent on effective douching. For this, look to reliable "Lysol" brand disinfectant.
- Q. Is "Lysol" safe and gentle as well as extra effective?
- A. Yes, the proved germicidal efficiency of "Lysol" requires only a small quantity in a proper solution to destroy germs and odors, give a fresh, clean, wholesome feeling, restore every woman's confidence in her power to please.
- Q. How about homemade douching solutions, such as salt and soda?
- A. They have no comparison with the scientific formula of "Lysol" which has proved efficiency in contact with organic matter.

ALWAYS USE "LYSOL" in the douche, to help give the assurance that comes with perfect grooming . . . confidence in "romance appeal."



Check these facts with your doctor

Many doctors recommend "Lysol" in the proper solution, for feminine hygiene. Non-caustic, gentle, easy directions for correct douching solution.

"Lysol" is non-harmful to delicate membrane, its clean, antiseptic odor quickly disappears. Highly concentrated, "Lysol" is economical in solution. Follow easy directions for correct douching solution.

For Feminine Hygiene—always use

"Lysol"
Disinfectant



FREE BOOKLETT Learn the truth about intimate hygiene and its important role in married happiness. 16-25 Mr. Lysol in Lysol & Fink, Dept. C-481, 179 Broadway Avenue, New York, N. Y., for booklet informing FREE booklet.

NAME _____
STREET _____
CITY _____ STATE _____

Product of Lysol & Fink



"Read this little book *carefully*, dear. . . . It explains things so much better than I can"

THERE is much misinformation about feminine hygiene—a subject so vital to health and happiness that it behooves every woman to beware of unprofessional advice and to learn the facts.

As a contribution to the proper understanding and practice of scientific bodily care, the makers of "Lysol" Disinfectant offer a booklet which gives the facts—frankly, explicitly and reliably. Its name is "The Scientific Side of Health and Youth" and its author is a woman physician who

has combined sympathetic appreciation of woman's intimate problems with professional knowledge and experience.

The position of "Lysol" Disinfectant itself in the field of feminine hygiene is indicative of the trustworthy nature of this booklet. For 30 years "Lysol" Disinfectant has been the standard personal antiseptic in doctors' offices, hospitals and homes. Its quality never varies. Every drop is potent. And today it has no substitute where complete disinfection is imperative.

Send for the booklet today. It is free. It will reach you in a plain envelope. It will contribute to your peace of mind. Use the coupon below.

In the meantime, play safe in any immediate use of an antiseptic for personal cleansing and protection. Insist on "Lysol" Disinfectant—and "Lysol" Disinfectant alone. It is safe. It is sure. And it cleanses as it kills germs. Buy a bottle today.

Made by Lysol, Incorporated, a division of Lysol & Fink Products Company, 501 Broadway, Lysol & Fink, Inc., New York, N. Y.

Lysol
Disinfectant



Clip the coupon now & free you forget.

LYSOL & FINK, Inc., 501 Broadway, Department 35, New York, New York

Please send me, free, your booklet, "The Scientific Side of Health and Youth."

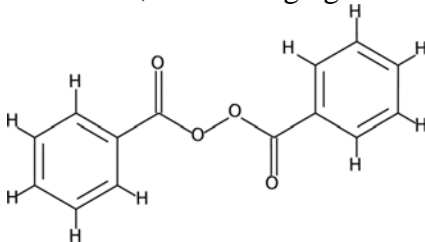
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City _____ State _____

gcaggiano.wordpress.com

mum.org

Other non-phenolic antiseptics and bacteriocides.

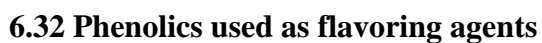
Benzoyl peroxide is used in the treatment of acne. It causes sluffing of the top layer of skins cells, stimulating growth of lower epithelial cells.



Hydrogen peroxide (H_2O_2 as a 3% solution) is used as a common wound disinfectant. It decomposes to form O_2 which is toxic to anaerobic bacteria that can cause serious infections in wounds.

Chlorhexidine.

Chlorhexidine is chlorinated imine that is a common ingredient in mouthwash designed to reduce gingivitis. It is also used in some scrubbing soaps.



- CC(C)c1ccc(O)cc1

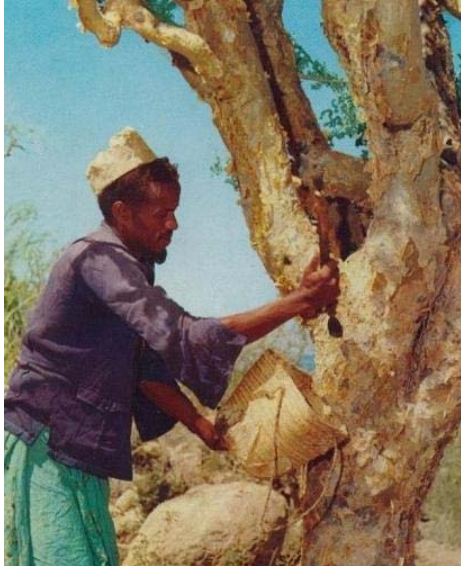
thyme

myrrh

myrrh tree



Creative commons: [Thyme - by Marie Richie.jpg](#)



Creative commons: [Somali man Myrrh tree.jpg](#)
Somalia Ministry of Information and National Guidance



Living clean.com

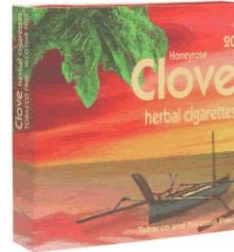
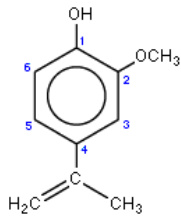


Pagandreams.co.uk

b)Eugenol is a phenolic compound found in cloves as well as nutmeg and cinnamon. It is sometimes added to “natural toothpastes” or mouthwashes. It contributes a clove flavor to the product and also has some antiseptic and local anesthetic effect. It is used in root canal packings.

Clove cigarettes(kretek) are a mixture of ground clove and tobacco (typically about a 40:60 mix) that were first created in Indonesia in the 1880's and became very popular fad in the US in the 1980's. Besides the pleasant clove smell, the eugenol would provide some anesthetic effect. Unfortunately the eugenol also probably reduces smooth muscle motility, making it more difficult for the lungs to remove some of the tar that has been inhaled. Clove cigarettes typically provide nicotine and tar at twice the levels of typical American brand of cigarettes. They received bad publicity when several smokers of clove cigarettes came down with severe pulmonary problems and their popularity has dropped since their peak in the 1980's. Several states have made the sale of clove cigarettes illegal, and similar bills have been introduced in the US senate in 2004, presumably with the blessing of the US tobacco manufacturers. In 2005 Phillip Morris

bought control of one Indonesian clove cigarette company. (If you can't beat them, buy them out!)

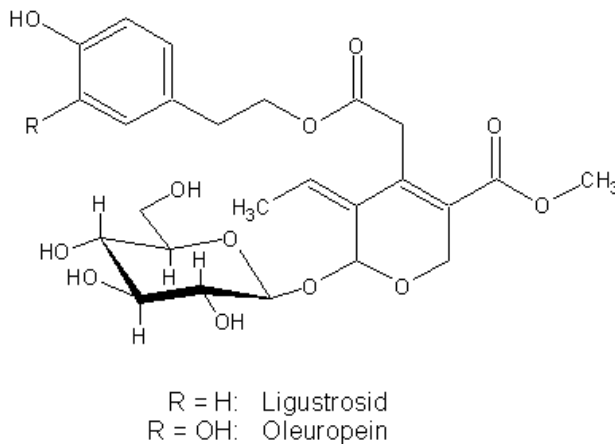


Wikipedia: clove cigarettes

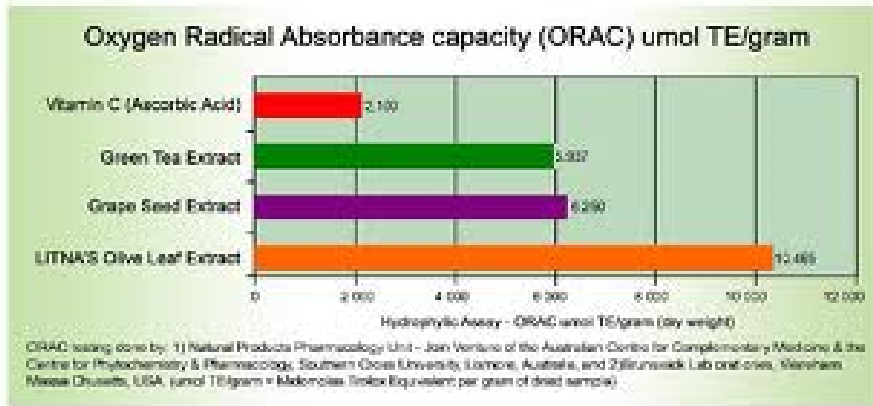
Eugenol

c) Oleuropein

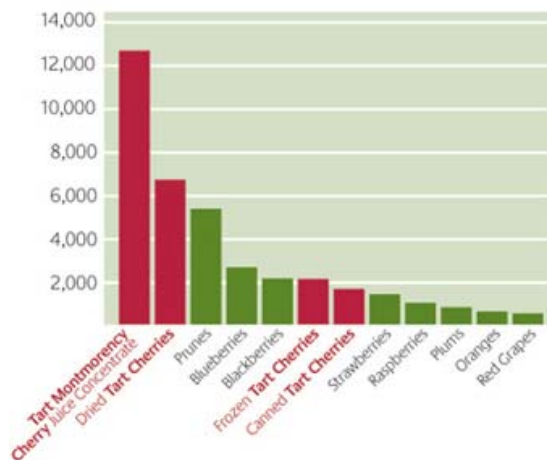
Oleuropein is a phenolic compound in olives that has a very bitter taste. Small amounts in virgin olive oil give a slight bitterness. It is removed from olives by long soaking in an alkaline brine. The alkali converts the phenolic groups into phenolate ions which increases the water solubility of the oleuropein and increases the amount that leaches out of the olives.



Wikipedia: olive

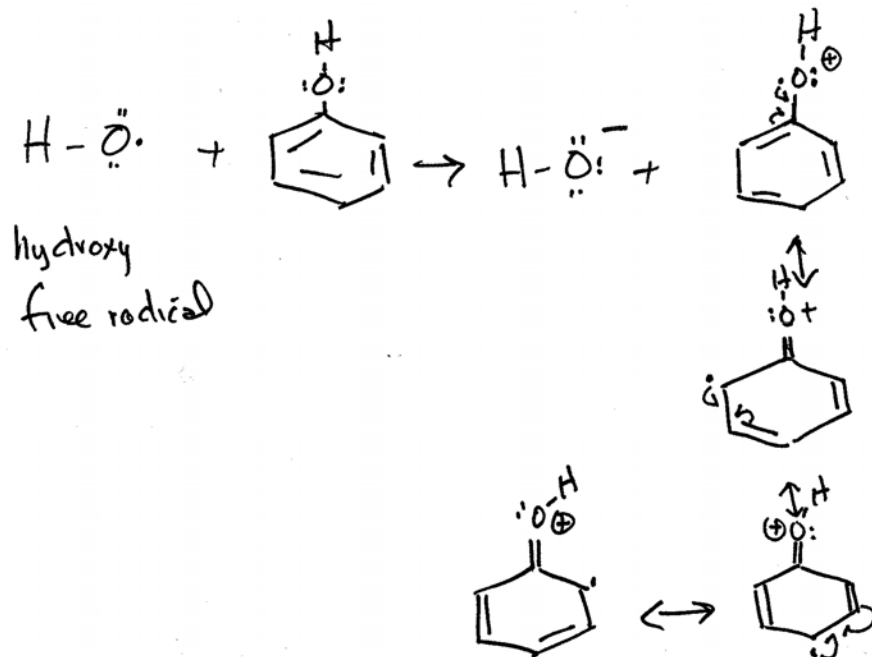


Cherries



6.33 Phenol compounds with electron transfer and antioxidant roles

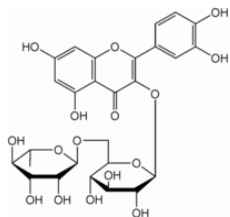
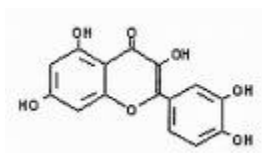
A variety of naturally occurring molecules with multiple phenol groups (**polyphenols** or **polyphenolics**) have been promoted as antioxidants in the popular press. The term antioxidant is not clearly defined. The name implies that antioxidants prevent oxidation reactions. Many antioxidants react with free radicals that are formed during oxidation reactions and reduce the damage that may occur to other molecules. In the process, they often become a free radical. However the unpaired electron can be delocalized over the whole benzene ring, in a manner analogous the pi electrons of benzene, and this stabilizes the unpaired electron and frequently allows the further metabolism of the phenol free radical in a less destructive manner.



A variety of phenolic plant molecules called **flavonoids** contribute to the color of many fruits (red grapes, apples, colored vegetables) and have been found to be antioxidants in test tube (in vitro) studies. Epidemiological data suggests that people who eat large amounts of fruits and vegetables are at lower risk of cancer and cardiovascular disease and the result has been that many dietary supplements containing these compounds have been promoted as antioxidants which would reduce the risk of cancer and cardiovascular disease. It needs to be pointed out (and the dietary supplement marketers don't do this) that there is virtually no direct data showing that taking these supplements actually improves health in a carefully done randomized controlled study.

Flavonoids are found in fruits and leafy green vegetables. They are usually found covalently bonded with sugars which are hydrolyzed off in the process of absorption and metabolism. Absorption of flavonoids from the GI tract into the bloodstream is typically less than 5% and metabolism in the liver appears to be rapid with excretion in the urine. This makes it difficult to argue that their presence in the blood stream is high enough and long enough for them to be physiologically important antioxidants. Recent research suggests that some other factor besides the antioxidant activity of the flavonoids themselves may be responsible for the improved health of individuals eating lots of fruits and vegetables.

a)Quercetin. Quercetin is one of the most studied flavonoids. It is found in tea, onions, and a variety of fruits combined with a sugar to produce a **quercetin glycoside** called rutin.



(upside down)

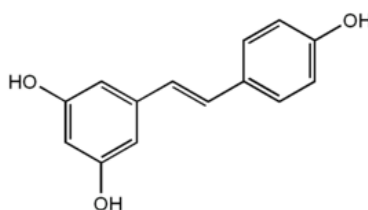
b) Resveratrol is a polyphenolic that is found in the skins of red grape, red wine, and other fruits. It appears to inhibit the growth of fungi and molds. It received a lot of media attention in 2003 when Harvard Professor David Sinclair published a paper showing that feeding yeast high concentrations of resveratrol extended their lives. His research has worked its way up the family tree, showing similar results in nematodes (a microscopic worm), fruit flies, fish and most recently on mice fed a high fat diet. It was heralded as the molecule responsible for the “French paradox” (the relatively long life span of the French whose traditional diet has been high in saturated fats). However, the amount of resveratrol needed to produce these results far exceeds the amount found in grapes and other fruits (by a factor of ~ 1000) and would require supplements to attain the same blood levels in humans. There is no data yet available in humans to show that resveratrol reduces disease or increases life span of humans, but this has not prevented resveratrol from becoming a very popular dietary supplement.



Resveratrol

Wikimedia Commons: [San Diego Bay Wine & Food Festival](#)

Chocolate (particularly dark chocolate) contains a variety of phenolic flavonols.



(What type of geometric isomer is the C=C between the two benzene rings?)

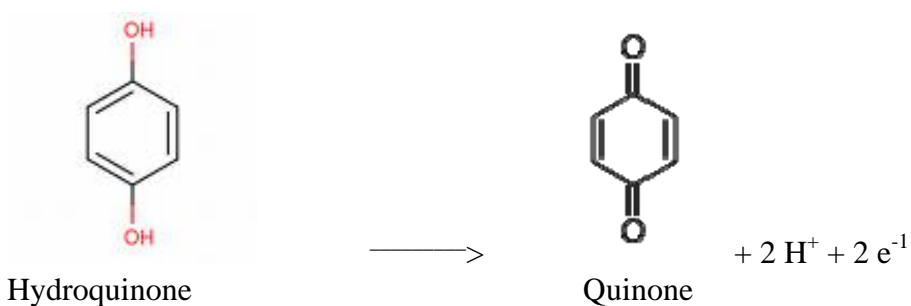
c) Curcumin is a primary ingredient in turmeric spice which is often a component of curry. A large variety of claims have been made for it (anti-inflammatory, anticancer, treatment of psoriasis) based on limited data. It does have two phenolic rings which may provide some anti-oxidation properties.



A large stainless steel pot filled with a thick, orange-red chicken curry. The curry contains numerous pieces of chicken and is garnished with fresh green herbs. A wooden spoon is resting in the center of the pot.

CC(C)CCCC[C@H]1C[C@@H](C)[C@H](OC2=C(C)C(=C(C)C)C(=O)O2)C1

e) **Hydroquinone** is a common structure found in larger biological molecules which undergoes oxidation and reduction. A hydroquinone is the active center of the coenzyme Q10; it helps transfer H atoms from the metabolism of sugar and fats in a multi-step process to the final H acceptor, molecular oxygen, O₂. In the process it is converted into **quinone**.

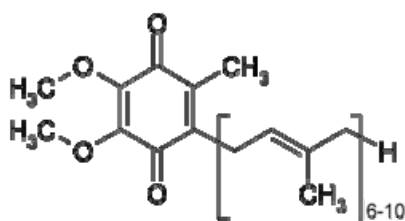


<http://www.flickr.com/photos/superskinlightener/4927625326/sizes/l/in/photostream/>

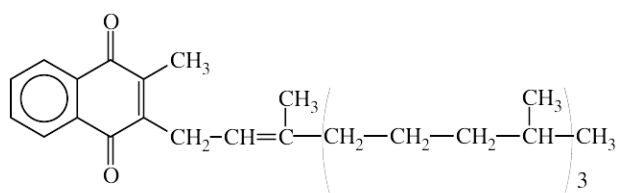


Wikipedia: Michael Jackson

Hydroquinone/quinone structures are also found in vitamin K. Hydroquinone is used as an OTC and prescription skin whitener.



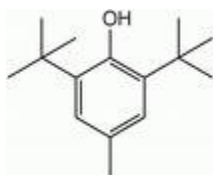
Coenzyme Q-10



PHYLLOQUINONE (K1)

Vitamin K

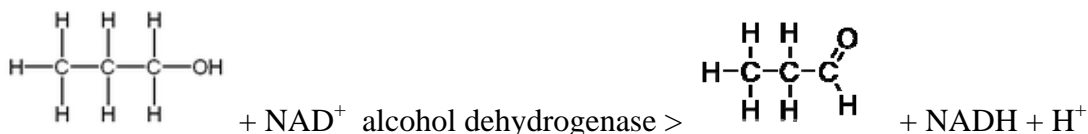
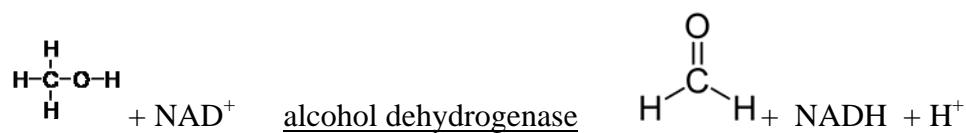
f) **Butylated hydroxytoluene (BHT)** is an antioxidant added to food and food packaging material to scavenge oxygen free radicals and to slow down the rate at which food goes rancid. There are numerous contradictory claims in the literature about its health effects.



6.4 METABOLIC REACTIONS OF ALCOHOLS

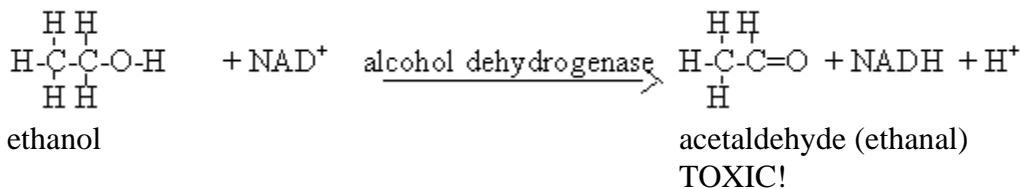
6.41 Dehydrogenation

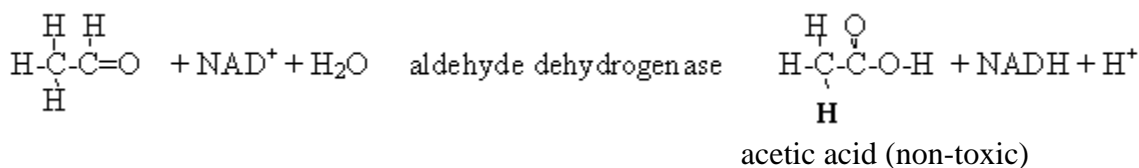
Dehydrogenation is the opposite of the hydrogenation reaction we saw with alkenes. We will not show a full reaction pathway, but simply show the product formed. In the chemical laboratory dichromate is used as an oxidizing agent. In the body (especially in the liver) an enzyme alcohol dehydrogenase acts as a catalyst for the reaction; a H^{-1} hydride ion is transferred to an acceptor molecule called NAD^{+} (nicotinamide adenine dinucleotide) and a H^{+} ion is released into solution.



6.42 Dehydrogenation of ethanol.

The metabolism of ethanol is of obvious physiological importance and we will look at it in some detail.





Acetic acid is then converted into Acetyl-CoA and metabolized in the Krebs cycle into carbon dioxide and water.

When one drinks small amounts of alcohol, acetaldehyde levels do not build up to very high levels and adverse effects are not experienced by most people. Higher levels of alcohol result in a build-up of acetaldehyde because the aldehyde dehydrogenase can only slowly metabolize acetaldehyde. Acetaldehyde is a toxic molecule, contributing to the the nausea and vomiting experienced by those who have over-indulged. There is substantial variation in the levels of these two enzymes among individuals. Individuals with low levels of alcohol dehydrogenase will have alcohol circulate for longer periods of time and with greater CNS effect. (These are the “cheap drunks!”) On the other hand individuals with low levels of aldehyde dehydrogenase will not be able to metabolize the acetaldehyde quickly. They are susceptible to flushing, increased heart rate, and nausea when consuming alcohol. Asians have a particularly high incidence(~50%) of this condition due to a mutation in their aldehyde dehydrogenase enzyme that causes it to have substantially lower ability to bind NAD, the H acceptor in the dehydrogenation of the acetaldehyde. This is sometimes referred to as the “Asian flush” although it is by no means limited to Asians. Acetaldehyde is a known carcinogen and the higher levels of acetaldehyde exposure may also increase these individuals’ risk of esophageal cancer.



cureasianflush.yolasite.com



tamayou.com



There are claims that Asian flush can be reduced by taking drugs such as Pepcid, Axid and Tagamet which inhibit acid secretion in the stomach.

Alcoholics who are trying to maintain their sobriety (and their driver's license) are sometimes prescribed a drug called Antabuse. Antabuse acts as an inhibitor of the enzyme aldehyde dehydrogenase. As a result, acetaldehyde levels build up, and toxic symptoms appear after even a small amount of alcohol consumption. Patients given Antabuse should be thoroughly informed of the adverse effects that will occur should they drink. They should also be aware that some mouthwashes, cold medications, and after-shave lotions contain sufficient alcohol to cause nausea and vomiting if used by someone on Antabuse.

This knowledge is supposed to help motivate the alcoholic to stay sober, although it has not proven successful in large numbers of cases. There is also a liability problem in that a patient on Antabuse who drinks large quantities of alcohol may die. Quoting from the informational insert for Antabuse, the Antabuse-alcohol reaction in small amounts "produces flushing, throbbing in head and neck, throbbing headache, respiratory difficulty, nausea, copious vomiting, sweating, thirst, chest pain, palpitations, dyspnea, hyperventilation, tachycardia, hypotension, syncope, weakness, vertigo, blurred vision and confusion. In severe reactions there may be respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions and death."

Studies (NEJM 322,95-99, 1990) have shown that for the same amount of alcohol ingestion and weight females have higher levels of blood alcohol than males. This appears to be due to the presence of alcohol dehydrogenase in the stomachs of males, but not females, resulting in significant conversion of ethanol into acetate before the ethanol is absorbed into the blood stream. There are also substantial variations in the level of aldehyde dehydrogenase. In general there is a higher incidence of low levels of aldehyde dehydrogenase in Asian ethnic groups. Some individuals have very low levels of alcohol dehydrogenase and these people do not tolerate alcohol consumption. On the bright side, people with low levels of aldehyde dehydrogenase have much less tendency to become alcoholics because any significant consumption of alcohol makes them sick!

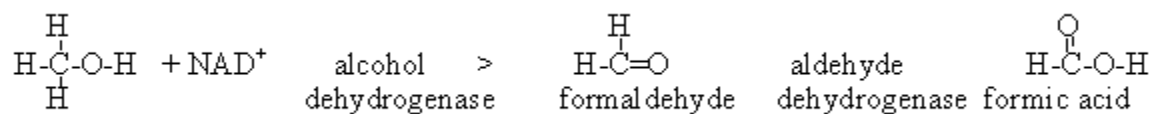
Although **chronic** alcoholism can cause cirrhosis of the liver and eventual death, **acute** poisoning by ethanol is not too common because most people will vomit if they drink large quantities of ethanol in a short period of time, thus limiting the amount of

acetaldehyde that builds up in their body at any given time. Fatal acute ethanol poisoning does occur occasionally.

The alcohol dehydrogenase and aldehyde dehydrogenase enzymes are not specific for ethanol. They carry out similar reactions on other alcohols such as methanol (found in windshield wiper fluid), ethylene glycol(antifreeze), propylene glycol(RV antifreeze), and rubbing alcohol) that are sometimes imbibed on purpose or accidentally. Generally, these products are even more toxic than acetaldehyde. Poison control center data base shows 842 inquiries about methanol ingestion and 5022 inquiries about ethylene glycol poisoning.

6.43 Dehydrogenation of methanol.

Methanol is a solvent used in windshield wiper fluid, some paint strippers, and other industrial solvents. Small amounts are also found in alcoholic beverages. Occasionally some of it is “diverted” to human consumption. The metabolism is as follows:

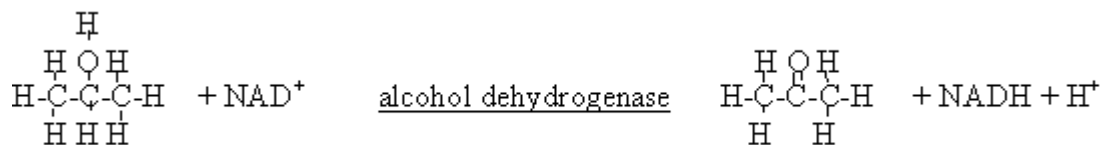


Formaldehyde reacts with and inactivates proteins; it is used to preserve cadavers. The production of large amounts of formic acid can produce metabolic acidosis. Formic acid is accumulated in neural cells, particularly the optic nerve. In small quantities it can cause blindness. Large quantities cause paralysis and death.

Small amounts of methanol or benzene have been added to ethanol that is sold for “industrial” purposes. (e.g. paint solvent and Sterno).(think Andromeda Strain) Industrial ethanol is not subject to the “sin tax” of alcoholic beverages but the federal government wants to make sure that it is not diverted for drinking. As a result, federal laws require addition of a **denaturing agent**, a toxic agent such as methanol or benzene, to industrial grade ethanol to discourage consumption.

6.44 Dehydrogenation of 2-propanol (rubbing alcohol)

2-propanol (rubbing alcohol) is readily available from any drug store. It is occasionally consumed by people who don’t know any better. The metabolism is as shown

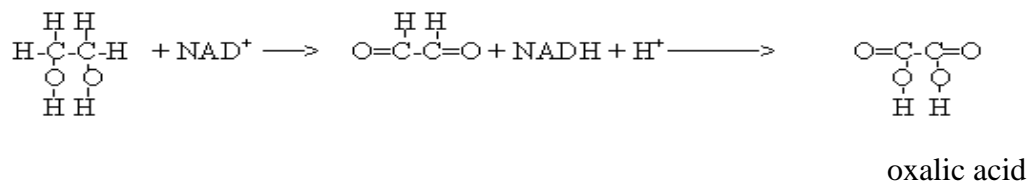


acetone is toxic

Similarly to ethanol, vomiting usually prevents buildup of acetone to lethal levels, but deaths due to rubbing alcohol consumption have occurred.

6.45 Dehydrogenation of 1,2 ethanediol (ethylene glycol). As already mentioned, ethylene glycol is used for radiator anti-freeze. Containers and open pans of anti-freeze often get left around and are the source of poisoning of cats, dogs and occasionally babies and small children. A Missouri radio talk show host poisoned his wife in 2004 by adding ethylene glycol (which tastes sweet) to her Gatorade.

The usual cause of death is metabolic acidosis and irreversible kidney damage. Ethylene glycol is sweet and so an unknowing baby or child may drink significant amounts. The metabolism is similar to other alcohols and is shown below:



Name the enzymes that will catalyze each of the above reactions.

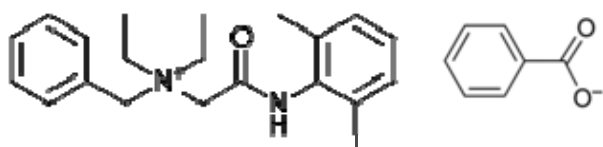
Most of these metabolic products are toxic in some way. The aldehyde groups can react with proteins as does formaldehyde; the carboxylic acids tend to produce metabolic acidosis; at high concentrations, oxalic acid reacts with Ca^{+2} ions in the kidney to form needle-like crystals which permanently damage to kidney nephrons. Dogs and cats which drink antifreeze frequently die of irreversible kidney damage. There is some disagreement about whether the cause of kidney damage is acidosis or damage from crystal formed in the kidney glomeruli.

Ethylene glycol (and propylene glycol, see below) also is used as a deicing compound for plane wings prior to takeoff in icy conditions. In the past the ethylene glycol was allowed to run off and went into adjacent soil or streams. The ethylene glycol provides a nutrient source for bacteria in surface water which unfortunately use up oxygen in the process of metabolizing it, thus killing off other organisms (such as fish) which are deprived of oxygen. Requirements to prevent this runoff of deicing compounds are increasingly stringent.

There is a treatment protocol for poisoning with ethylene glycol as well as the less common cases of poisoning due to methanol and rubbing alcohol. Gastric lavage with activated charcoal can be done if ingestion has occurred within 1 hour. This is followed by saturation of the alcohol metabolizing enzymes with ethanol (either sterile IV or by oral consumption). This keeps the enzymes “busy” metabolizing ethanol, and ethylene glycol is excreted unchanged. Ethylene glycol is very soluble in water and does not need any metabolism to be excreted in the urine. The major adverse effect of this treatment is one hell of a hangover! Blood dialysis to remove the ethylene glycol and its metabolic products can also be done, if equipment is available.

Ethylene glycol has sometimes been added in small quantities to cheap wines because it improves the flavor and takes some of the “edge” off of the cheaper wines. Luckily, clinically significant poisoning is unlikely by this route, because the antidote (ethanol) is being consumed at the same time!

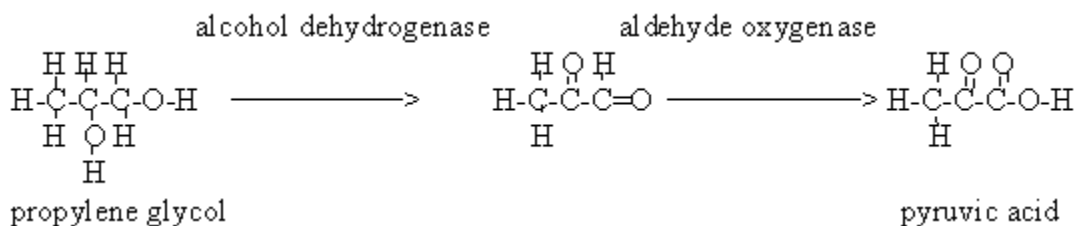
Since 1995 the state of Oregon has required the addition of very small amounts of denatonium benzoate, the bitterest compound known, to antifreeze. This counteracts the pleasant sweet taste of the ethylene glycol itself and will cause the antifreeze to be spat out, avoiding the potential for poisoning. Like the addition of methanol or benzene to industrial ethanol, denatonium acts as a denaturing agent and in fact that is what the “denat” in the name stands for! It is also used in products to inhibit nail biting and in animal repellants.



What functional groups are in denatonium benzoate?

6.46 Propylene glycol

Propylene glycol is also used as antifreeze, particularly for the potable water systems in RV vehicles. It is metabolized as shown below:



Luckily, pyruvic acid has no clinically significant solubility problems. It is an essential component of intermediary metabolism. Thus propylene glycol is non-toxic to humans



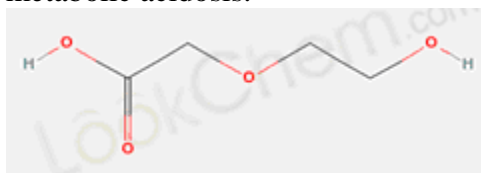
6.47 Diethylene glycol



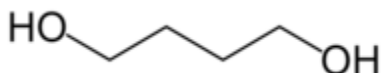
In 1937 the Massengill pharmaceutical company used diethylene glycol (structure shown above) as a solvent for the sulfanilamide (one of the first modern antibiotics) in their Elixir Sulfanilamide. It was used because, like glycerol, it is very sweet, which helps to partially cover the bitter taste of the drug, and because it is a very viscous liquid (easier to pour onto a spoon with less spilling) and (last but not least) it was cheaper than glycerol. It caused a rash of poisoning, mostly children, including 105 fatalities. This incident resulted in the passage of the 1938 Federal Food Drug and Cosmetic Act which for the first time required safety tests for drugs and approval by the FDA before a drug went on the market. (It may come as a surprise to the reader that until this law was passed, there was no legal requirement that a drug be safe, let alone that it actually be **efficacious** (that it actually works better than placebo)!). Requiring a drug to show efficacy would have to wait until the Kefauver Harris amendment in 1962

The Massengill company was given a small fine for mislabeling their syrup as an elixir, which technically means that it contains ethanol, when in fact it contained diethylene glycol).

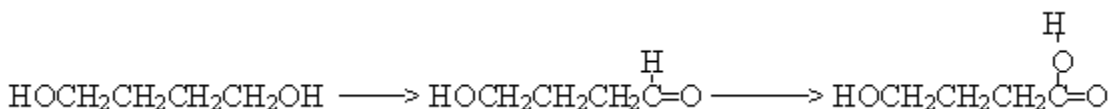
Diethylene glycol appeared in the media again in 2006 and 2007 in Panama, the US, and several other countries in products such as toothpaste and expectorant. Most if not all of this diethylene glycol has been traced to manufacture in China. Diethylene glycol is sweet and viscous, like glycerol, and it is cheaper than glycerol, which appears to be a major motivating factor for the substitution. Unfortunately it is also toxic.). Diethylene glycol apparently is metabolized into 2-hydroxyethoxyacetic acid, which produces metabolic acidosis.



6.48 1,4 butanediol



1,4 butanediol received media attention in November 2007 when it was discovered to have replaced 1,5 pentanediol coating the surface of children's beads marketed as Aqua Dots, helping the beads to stick together when they are wetted. One alcohol group of the 1,4 butanediol is metabolized by the alcohol dehydrogenase and aldehyde dehydrogenase enzymes into an aldehyde and then a carboxylic acid group, producing 4-hydroxy butanoic acid, better known as **gamma hydroxy butyric acid or GHB**.



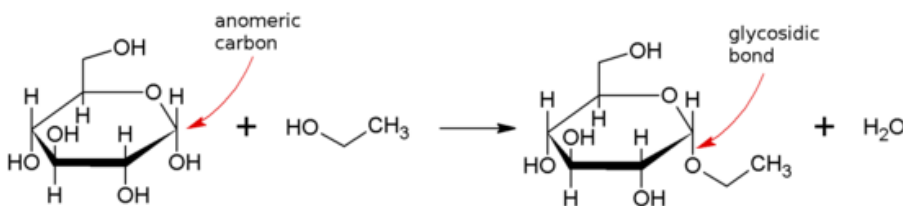


As discussed in the carboxylic acid chapter, GHB is used as an illegal recreational drug for producing feelings of euphoria and sociability. At higher concentrations it can also cause unconsciousness and amnesia, leading to its use as a “date rape” drug. It can also cause respiratory depression which may lead to death.

6.3 Alternative metabolic routes of Alcohols

Although the dehydrogenation of ethanol is the primary route of ethanol metabolism, small amounts of ethanol undergo alternative routes.

Ethanol can be covalently bonded to a molecule of glucuronic acid and then slowly excreted in the urine.

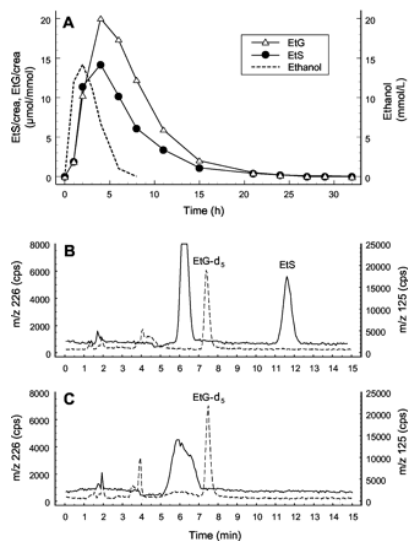


Glucuronic acid

This reaction is analogous to the addition of glucuronic acid to bilirubin, which was discussed in Alkene chapter.

Although this reaction occurs on less than 1% of the ethanol ingested, it is excreted in the urine and can be detected for several days, in contrast to the dehydrogenation reactions which usually metabolize the ethanol in a few hours. This test thus allows determination of whether an individual has been drinking in the last several days as opposed to the direct breath and blood tests which will give positive results for 5-10 hours after drinking.

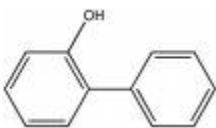
This method is very sensitive and one has to be careful of false positives which can result from using cough medicines, some mouth washes, and after shave lotions.



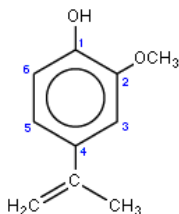
It is used primarily on individuals who have an alcohol abuse problem and have agreed to abstain from alcohol completely in return for not being jailed or having their license revoked. It is not a cheap or routine test and has most commonly been used on doctors and other health professionals who have an alcohol abuse problem which is endangering their patients.

Alcohol Study Guide

1. Draw the structure of a) cis 1,2 cyclopentanediol b) trans 1,2 cyclopentanediol c) 2,3-dimethyl-2,3- butanediol d) 1,2,3- propanetriol e) phenol
2. What reaction occurs between phenol and sodium hydroxide? Write the chemical equation. Would this reaction occur with ethanol? Why or why not?
3. Would you expect ortho phenyl phenol and eugenol (structures shown below) to be acidic? If so, write the equation that produces the hydrogen ion.



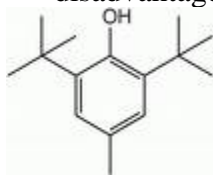
ortho phenyl phenol



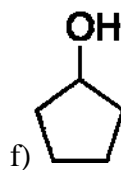
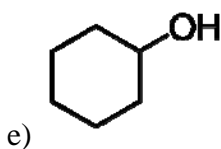
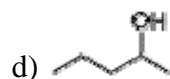
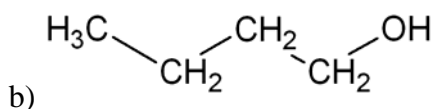
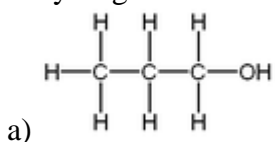
eugenol

4. What are the problems with using phenol as an antiseptic? What problems can result from the routine use of Chloroseptic as a throat antiseptic? What other commercial uses does phenol have? Name several chlorinated phenolic compounds and describe their uses. What effect does chlorination have on their activity?

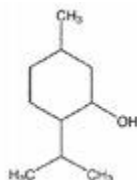
- What health claims have been made for dietary polyphenolics? Name some foods that are particularly rich in polyphenolics.
- Give the name of one of the most thoroughly studied flavonoids.
- Give several reasons why one might be skeptical about the importance of flavonoids being important antioxidants in the body.
- What are some good sources of resveratrol? What health claims have been made for resveratrol? What geometric isomer of resveratrol is shown in the text? Promoters have claimed that resveratrol may be the reason for the French paradox. Explain what the French paradox is and why this claim is unlikely to be true.
- Will BHT be soluble in water? How could you increase the water solubility without adding new functional groups to the molecule? BHT and BHA are sometimes added to the waxy coating of sealed food packaging. Think about advantages or disadvantages of putting the BHT in the packaging rather than the food itself.



- In each of the examples below, write the structure of the product resulting from the dehydrogenation reaction.



Menthol (structure shown below) can be dehydrogenated into menthone. Show the structure of the product.



11. Write the two successive reactions involved in the dehydrogenation and oxidation of alcohol (ethanol) in your body. Indicate which product(s) are toxic. Indicate the molecular mechanism and clinical effect of Antabuse.

12. Write the product of the dehydrogenation of methanol (methyl alcohol, wood alcohol). Indicate why methanol is regarded as a potent poison, even though the methanol itself is not terribly toxic. What is the treatment for methanol poisoning?

What common commercial product contains methanol?

13. Write the metabolic products for ethylene glycol. What are the medical problems that arise from ethylene glycol poisoning? What is the treatment? What common commercial products contain ethylene glycol? Why is the presence of small amounts of ethylene glycol in cheap wines NOT a problem?

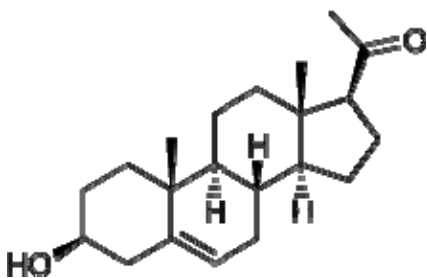
14. What is meant by the term “denatured” alcohol. Why is alcohol denatured?

15. Why is it difficult (but not impossible) for a person to drink so much ethanol at one sitting as to kill himself.

16. What is the alcohol in RV antifreeze? What molecule is it metabolized into? What part of intermediary metabolism is this used in?

17. Explain what tests can be used to determine whether an individual has had any alcohol in the last several days. What are some of the limitations on this method?

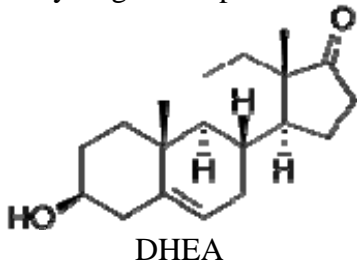
18. Cholesterol is metabolized in multiple steps into a molecule of pregnenolone which then undergoes a dehydrogenation of its alcohol group on C #3 of the A ring (ring on the lower left side) into a ketone group. Show the structure of the resulting ketone when pregnenolone is dehydrogenated.



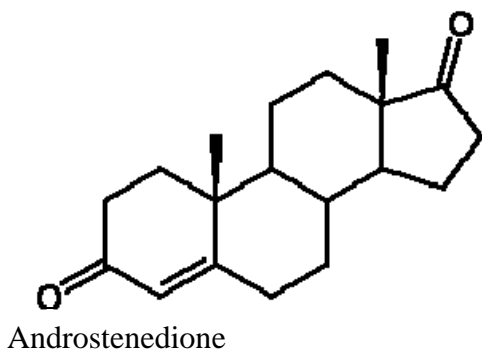
The resulting ketone is isomerized into progesterone, a potent female hormone

19. Dehydroepiandrosterone (DHEA) is a commonly used “dietary supplement” which is promoted as increasing muscle mass and virility. It is dehydrogenated into androstenedione in a reaction analogous to the conversion of pregnenolone into

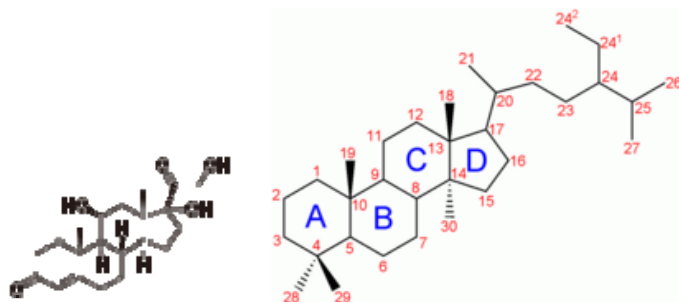
progesterone. Given the structure of DHEA shown below, show the structure of the dehydrogenated product.



20. Androstenedione can be enzymatically converted into testosterone by **hydrogenation (addition of 2 H atoms)** of the ketone group on the 5 membered ring in androstenedione. Show the product of this hydrogenation reaction.



21. Cortisol is metabolized to cortisone by a dehydrogenation of cortisone of the alcohol group on ring C. Draw the structure of cortisone.

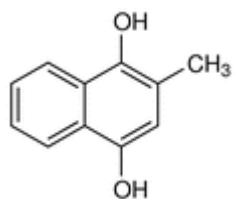


Skip

Digging deeper.

2-methyl 1,4 hydroquinone is oxidized by hydrogen peroxidase in a very exothermic reaction to produce superheated water that the bombardier beetle can spray at potential predators. See W. Agosta, Bombardier Beetles and Fever Trees.

Menadiol, a synthetic form of vitamin K, is converted into menadione, by dehydrogenation of the two alcohol groups. Show the structure of menadione.



Draw the structure of inositol (you don't have to worry about exact stereochemistry). What is the biological importance of inositol?