Kirk-Othmer Encyclopedia of Chemical Technology.

VITAMIN E

Vitamin E was first described in 1922 and the name was originally applied to a material found in vegetable oils. This material was found to be essential for fertility in rats. It was not until the early 1980s that symptoms of vitamin E deficiency in humans were recognized. Early work on the natural distribution, isolation, and identification can be attributed to Evans, Burr, and Emerson (University of California) and Mattill and Olcott (University of Iowa). Subsequently a group of substances (Fig. 1), which fall into either the family of tocopherols or tocotrienols, were found to act like vitamin E (1–4). The structure of α-tocopherol was determined by degradation studies in 1938 (5).

1. Chemical, Biological, and Physical Properties

The structures (see Fig. 1) of all vitamin E compounds are characterized by a 6-chromanol ring with a C_{16} side chain. As a result of three asymmetric carbons, there are eight possible optical isomers. However, it is the configuration around the 2-position on the ring which determines, to the largest extent, biological activity (6). Natural vitamin E is characterized by all R stereochemistry. The tocopherols are distinguished by a saturated phytol side chain and the tocotrienols are characterized by an unsaturated side chain. The isomers within the two families differ by the extent and position of the methylation on the ring. Although tocopherols and tocotrienols are chemically related, they have varying degrees of vitamin E activity depending on their structure and stereochemistry (Table 1).

The biological activity of various vitamin E forms was established by the fetal resorption assay in rats and is assumed to be applicable to humans. The results of some human studies may indicate that the ratio of 1.36 underestimates the biological activity of the *RRR* form relative to the *all-rac* form of α-tocopheryl acetate (10–12).

α-Tocopherol and α-tocopheryl acetate are viscous oils. The fat solubility of α-tocopherol and α-tocopheryl acetate is characteristic of the family of compounds. Both are readily soluble in ethanol, chloroform, and acetone but are insoluble in water. Other physical properties of α-tocopherols and their acetate esters are given in Table 2.

Although they are generally stable to heat and alkali, and acids in the absence of oxygen, free tocopherols and tocotrienols can be oxidized by atmospheric oxygen in the presence of light, unsaturated fatty acids, heat, or metal ions. The reported oxidation products of α-tocopherol are shown in Figure 2. These products can be readily synthesized by oxidizing α-tocopherol with such reagents as nitric acid, silver nitrate, ferric chloride, or benzoyl peroxide. As a result of the ease of oxidation, significant amounts of vitamin E (tocopherols) may be lost during food processing (qv). The severity of the processing, ie, cooking, canning, and baking, determines the amount of tocopherol remaining in foods and edible oils. Storage conditions can also impact the losses of vitamin E in foods and animal feeds (see Feeds and feed additives). The stability of α-tocopherol is significantly enhanced by esterification. Although the acetate ester does not have any inherent antioxidant activity, it is bioactive and is the commercially important form because of its greater stability.

Table 1. Relative Activity of Vitamin E Forms[a]

Substance	Vitamin E activity
all-rac-α-tocopheryl acetate	1.00
RRR-α-tocopheryl acetate	1.36
all-rac-α-tocopheryl acid succinate	0.89
RRR-α-tocopheryl acid succinate	1.21
all-rac-α-tocopherol	1.10
RRR-α-tocopherol	1.49
β-tocopherol	0.50
γ-tocopherol	0.35
α-tocotrienol	0.30
γ-tocotrienol	0.10

[a]Refs. (7–9).

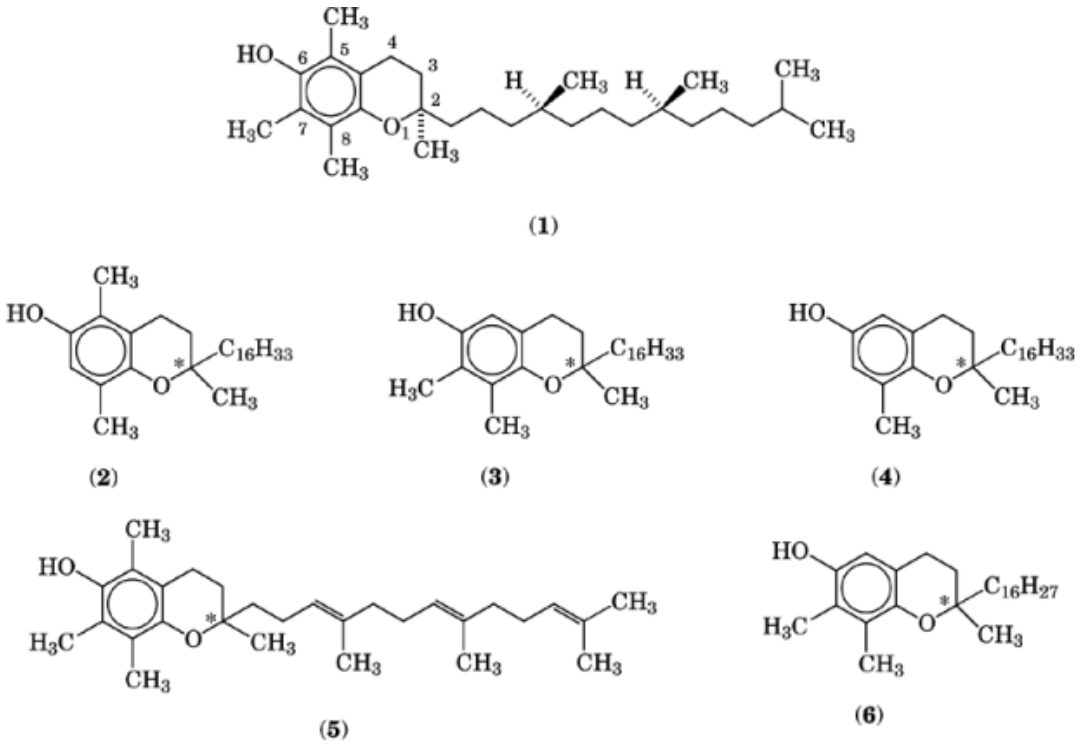


Fig. 1. The four naturally occurring tocopherols (α-tocopherol, *RRR* [59-02-9]/*all-rac* [2074-53-5] (**1**); β-tocopherol [148-03-8] (**2**); γ-tocopherol [54-28-4] (**3**); δ-tocopherol [119-13-1] (**4**)), α-tocotrienol [1721-51-3] (**5**), and β-tocotrienol [14101-61-2] (**6**) where asterisks denote asymmetric centers and the absolute configuration of *RRR*-α-tocopherol is shown.

2. Natural Occurrences and Sources

Unesterified tocopherols are found in a variety of foods; however, concentration and isomer distribution of tocopherols vary greatly with source. Typically, meat, fish, and dairy contain <40 mg/100 g of total tocopherols. Almost all ($>75\%$) of this is α-tocopherol for most sources in this group. The variation in the content of meat and dairy products can be related to the content of the food ingested by the animal. A strong seasonal variation

Table 2. Physical Properties of Tocopherols

Property	*all-rac*-α-Tocopherol	*RRR*-α-Tocopherol	*all-rac*-α-Tocopheryl Acetate	*RRR*-α-Tocopheryl-Acetate
CAS Registry Number	[2074-53-5]	[59-02-9]	[7695-91-2]	[58-95-7]
color	← colorless to pale yellow →			
form	← viscous oil →			
bp, °C	200–220 (0.1 mm)		224 (0.3 mm)	
sp $gr^{25}{}_{25}$,	0.947–0.958	0.950–0.964	0.950–0.964	
$n^{20}{}_{D}$	1.5030–1.5070	1.4940–1.4985	1.4940–1.4985	
mol wt	430.69	430.69	472.73	472.73
uv absorption				
maxima, nm	292–294	292–294	285.5	285.5
$E^{1\%}_{1\,cm}$ (ethanol)	71–76	71–76	40–44	40–44

Table 3. Vitamin E Content of Common Oils, mg/100 g[a]

Oil source	Total tocopherols	α-Tocopherol	γ-Tocopherol	β-Tocopherol	δ-Tocopherol
soybean	14	8–10	59		26
corn	24	10–16	60	5	2
safflower	41	40	17		1
canola	23	19	43		
cottonseed	48	39–44	39		
sunflower	49	49	5		0.8
coconut	1	0.5–1			0.6
palm	29	20–26	32		7
olive	10	5–10			
peanut		13	22		2
rapeseed		18	17		1
wheatgerm		133	26	71	27

[a]Refs. 13 and 14.

can also be observed. Vegetable oils contain significant levels of γ-, β-, and δ-tocopherol, along with α-tocopherol (Table 3).

Vegetable oils, typically soybean, are important feedstocks for the commercial production of the *RRR* forms of vitamin E.

3. Synthesis

Although all four tocopherols have been synthesized as their *all-rac* forms, the commercially significant form of tocopherol is *all-rac*-α-tocopheryl acetate. The commercial processes in use are based on the work reported by several groups in 1938 (15–17). These processes utilize a Friedel-Crafts-type condensation of 2,3,5-trimethylhydroquinone with either phytol (16), a phytyl halide (7, 16, 17), or phytadiene (7). The principal synthesis (Fig. 3) in current commercial use involves condensation of 2,3,5-trimethylhydroquinone 3 with synthetic isophytol 3 in an inert solvent, such as benzene or hexane, with an acid catalyst, such as zinc chloride, boron trifluoride, or orthoboric acid/oxalic acid (7, 8, 18) to give the *all-rac*-α-tocopherol 3. Free tocopherol is protected as its acetate ester 3 by reaction with acetic anhydride. Purification of tocopheryl acetate is readily accomplished by high vacuum molecular distillation and rectification (<1 mm Hg) to achieve the required USP standard.

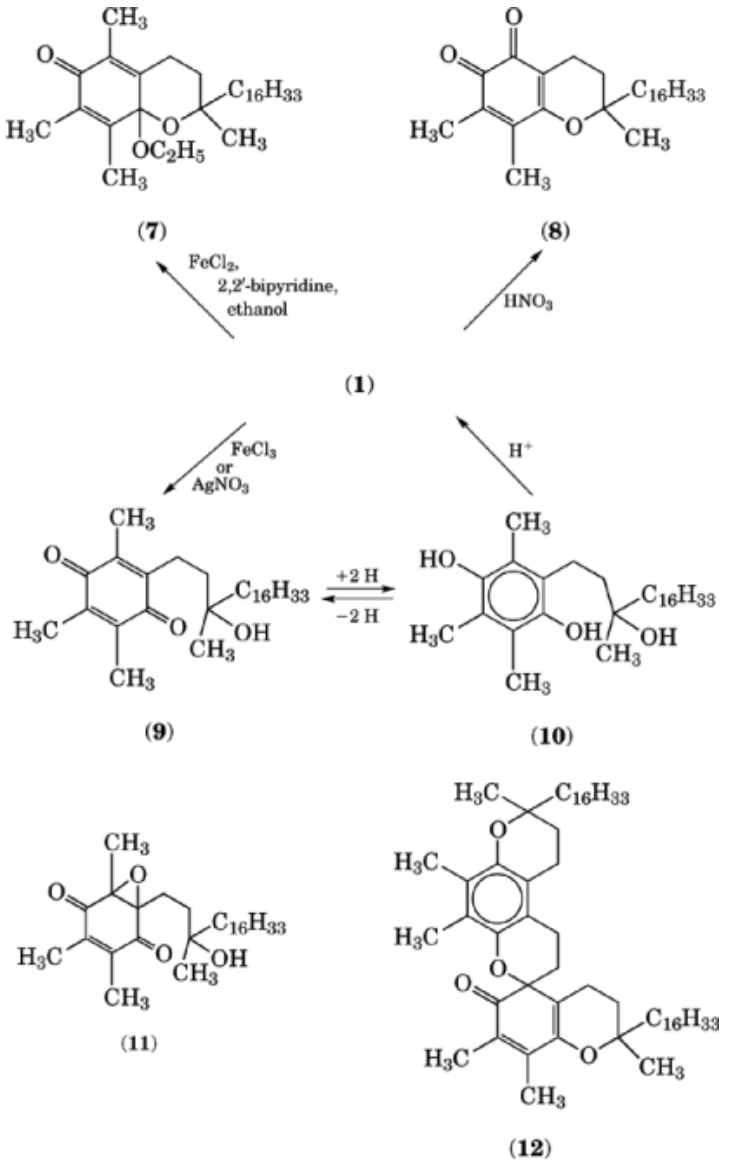


Fig. 2. Oxidation products of α-tocopherol: tocopherethoxide [511-72-8] (**7**), tocored [17111-16-9] (**8**), α-tocoquinone [7559-04-8] (**9**), α-tocohydroquinone [14745-36-9] (**10**), α-tocoquinone-2,3-oxide [35499-91-3] (**11**), and α-tocopherol dimer [1604-73-5] (**12**).

Trimethylhydroquinone can be synthesized from various isomeric trimethylphenols such as 2,4,6- or 2,3,6-trimethylphenol (Fig. 4). When starting with 2,3,6-trimethylphenol 4, this can be accomplished by catalytic oxidation using oxygen and cupric halide catalysts in a solvent such as water–alcohol, 2-methoxyethanol, acetone, or *N,N*-dimethylformamide (19, 20). The resulting benzoquinone 4 can then be hydrogenated catalytically using Pd or Pt in an inert solvent, such as methanol, isobutanol, or toluene (21) to yield 2,3,5-trimethylhydroquinone 3. When 2,4,6-trimethylphenol 4 is used, 4-hydroxy-2,4,6-trimethyl-2,5-cyclohexadien-1-one 4 is obtained by oxidation with sodium hypochlorite (22) or oxygen and base (23). This compound can then

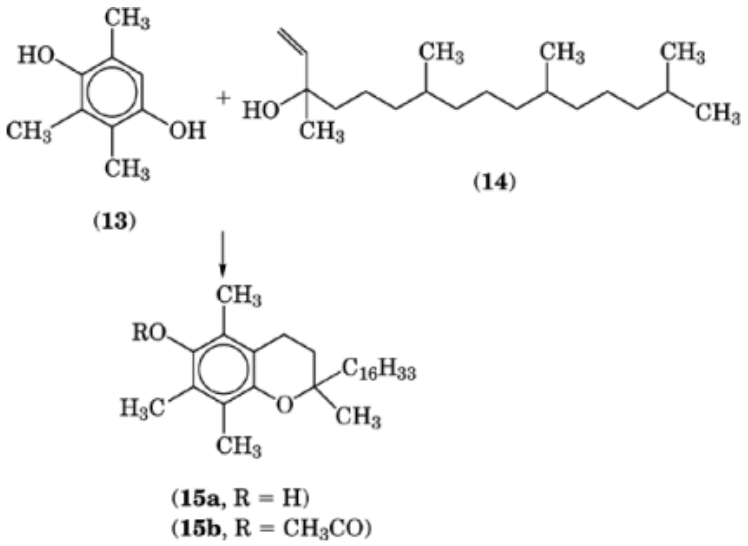


Fig. 3. Synthesis via trimethylhydroquinone [700-13-0] (TMHQ) (**13**) and isophytol [505-32-8] (**14**) of α-tocopherol (**15a**) and α-tocopherol acetate (**15b**).

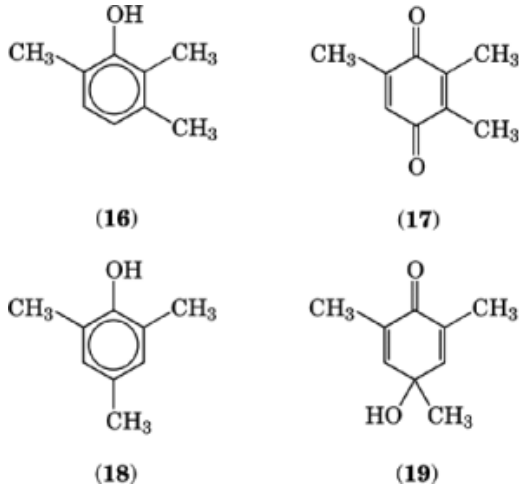


Fig. 4. Starting materials and intermediates in the TMHQ syntheses: 2,3,6-trimethylphenol [2416-94-6] (**16**), 2,3,5-trimethylquinone [935-92-2] (**17**), 2,4,6-trimethylphenol [527-60-6] (**18**), and 4-hydroxy-2,4,6-trimethyl-2,5-cyclohexadien-1-one [2875052-9] (**19**).

be rearranged by base to trimethylhydroquinone (22, 23). The trimethylphenols can be obtained by methylation of phenol.

The isophytol side chain can be synthesized from pseudoionone (Fig. 5) using chemistry similar to that used in the vitamin A synthesis (9). Hydrogenation of pseudoionone 5 yields hexahydropseudoionone 5 which can be reacted with a metal acetylide to give the acetylenic alcohol 5. Rearrangement of the adduct of 5 with isopropenylmethyl ether yields, initially, the allenic ketone 5 which is further transformed to the C_{18}-ketone

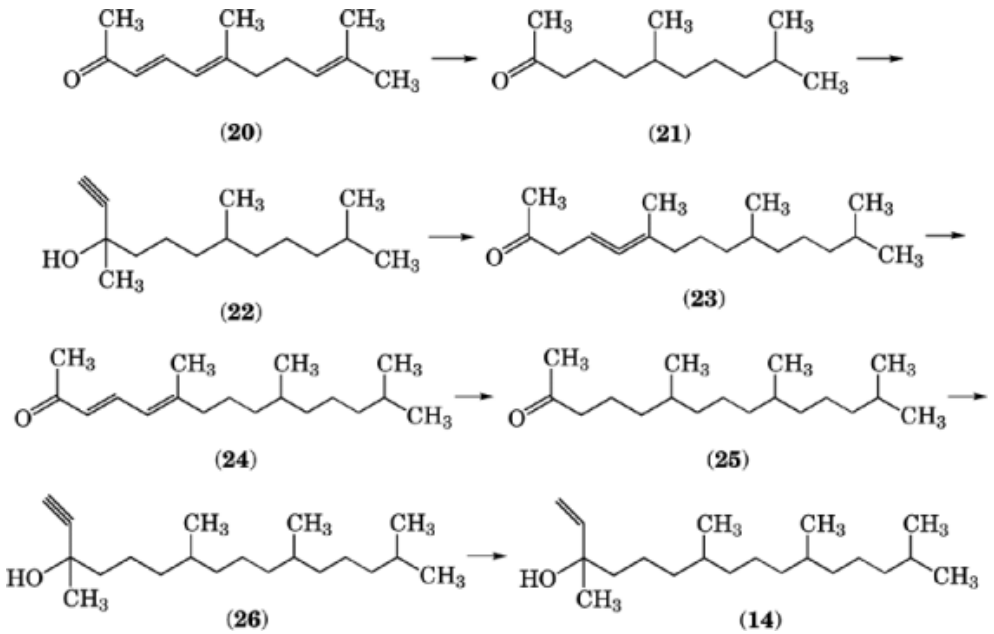


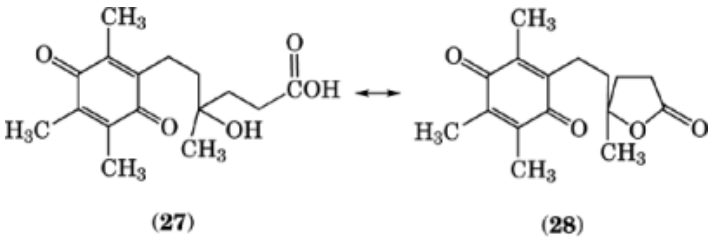
Fig. 5. Synthesis of isophytol 3: pseudoionone [141-10-6] (**20**), hexahydropseudoionone [1604-34-8] (**21**), C_{15}-acetylenic alcohol [1604-35-9] (**22**), C_{18}-allenic ketone [16647-10-2] (**23**), C_{18}-diene ketone [1604-32-6] (**24**), C_{18}-saturated ketone [16825-16-4] (**25**), and C_{20}-acetylenic alcohol [29171-23-1] (**26**).

5. After reduction of 5, the saturated ketone 5 is treated with a second mole of metal acetylide. The acetylenic alcohol 5 formed is then partially hydrogenated to give isophytol 3.

Although the eight stereoisomers of α-tocopherol have been synthesized (24), these preparations are at present only of academic interest. However, *RRR*-α-tocopherol and the other natural forms of vitamin E can be isolated from deodorizer distillates produced as by-products of vegetable oil processing. This requires a series of steps built around key molecular distillations which are required to increase the purity of the *RRR*-α-tocopherol and mixed tocopherol fractions for use in commercial preparations. A typical process would involve a distillation of alkali-treated soybean oil at high vacuum ($<$1 mm Hg) in a continuous molecular still. This minimizes thermal degradation. The distillate, which contains α-, γ-, and δ-tocopherols, is then cooled to low temperature ($\sim -10\ ^\circ$C) in a solvent to remove impurities such as sterols. The other impurities, such as fatty acids, can be removed by saponification. Further molecular distillation is required to produce a fraction containing high levels ($\geq$60%) of tocopherols. The sterols and fatty acids can be sold.

The yield of the more active *RRR*-α-tocopherol can be improved by selective methylation of the other tocopherol isomers or by hydrogenation of α-tocotrienol (25, 26). Methylation can be accomplished by several processes, such as simultaneous haloalkylation and reduction with an aldehyde and a hydrogen halide in the presence of stannous chloride (27), aminoalkylation with ammonia or amines and an aldehyde such as paraformaldehyde followed by catalytic reduction (28), or via formylation with formaldehyde followed by catalytic reduction (29).

The *all-rac* forms of β-, γ-, and δ-tocopherols can be synthesized using the same condensation reaction as used for *all-rac*-α-tocopherol. To synthesize *all-rac*-β-tocopherol, 2,5-dimethylhydroquinone instead of trimethylhydroquinone is condensed with isophytol. For *all-rac*-γ- and δ-tocopherol, 2,3-dimethylhydroquinone and methylhydroquinone are used, respectively.



(27) (28)

Fig. 6. α-Tocopheronic acid [1948-76-1] (**27**) and its lactone, α-tocopheronolactone [3121-68-4] (**28**).

Although apparently not commercially important, fermentation (qv) processes have been reported for the production of tocopherols. *Aspergillus niger* (30), *Lactobacter* (31), *Euglena gracilis Z.* (32, 33), and *Mycobacterium* (34) have been shown to produce (*RRR*)-α-tocopherol. In the case of *Euglena*, titers of 140–180 mg/L have been reported.

4. Physiological Effects and Requirements

The symptoms of vitamin E deficiency in animals are numerous and vary from species to species (13). Although the deficiency of the vitamin can affect different tissue types such as reproductive, gastrointestinal, vascular, neural, hepatic, and optic in a variety of species such as pigs, rats, mice, dogs, cats, chickens, turkeys, monkeys, and sheep, it is generally found that necrotizing myopathy is relatively common to most species. In humans, vitamin E deficiency can result from poor fat absorption in adults and children. Infants, especially those with low birth weights, typically have a vitamin E deficiency which can easily be corrected by supplements. This deficiency can lead to symptoms such as hemolytic anemia, reduction in red blood cell lifetimes, retinopathy, and neuromuscular disorders.

Vitamin E can also act as an antioxidant (qv) in animals and humans alone or in combination with vitamin C (qv). Both are good free-radical scavengers with the vitamin C acting to preserve the levels of vitamin E (35). Vitamin E in turn can preserve the levels of vitamin A in animals (13). It has been shown that vitamin E reduces the incidence of cardiovascular disease (36–39). This most likely results from the antioxidant property of the vitamin which inhibits the oxidation of low density lipoproteins (LDLs) (40–42). The formation of the oxidized LDLs is considered important in decreasing the incidence of cardiovascular disease (43).

The recommended daily allowance for vitamin E ranges from 10 international units ($1_{\text{IU}=1\text{ mg}}$ *all-rac-*α-tocopheryl acetate) for children under 4 years of age to 30 IU for adults and children over 4 years of age. This should be adequate to prevent vitamin E deficiency in humans. High levels enhance immune responses in both animals and humans. Requirements for animals vary from 3 USP units/kg diet for hamsters to 70 IU/kg diet for cats (13). The complete metabolism of vitamin E in animals or humans is not known. The primary excreted breakdown products of α-tocopherol in the body are gluconurides of tocopheronic acid 6 (Fig. 6). These are derived from the primary metabolite α-tocopheryl quinone 2 (see Fig. 2) (44, 45).

Vitamin E is considered nontoxic at levels up to 3200 mg/day. It has not been found to be teratogenic, mutagenic, or carcinogenic at doses below 1 g/kg of body weight. Vitamin E can heighten the effect of vitamin K deficiency (coagulation defect) or anticoagulation therapy. A recent study, however, indicates that it may be the oxidation product α-tocoquinone that causes the effect (46).

Table 4. Bulk Prices of Pharmaceutical-Grade α-Tocopheryl Acetate, $/kg[a]

Product	1948	1951	1954	1960	1970	1982	1991	1994	1995
(*RRR*)-form	250	250	185	122	68	68	57	59	59
all rac-form	750	350	136	90	50	27	23	34	34

[a] Refs. (48–51).

5. Economic Aspects

World production in the late 1990s of both natural and synthetic forms of vitamin E is estimated at 22,000 metric tons and growth is expected to keep pace with increasing need. The 1993 U.S. production was 14,096 metric tons (47) with an additional 1080 metric tons from imports. The principal U.S. producers of the natural form are Eastman Chemical Company, Archer Daniels Midland Company, and Henkel, and of synthetic vitamin E, Hoffmann-La Roche and BASF. International producers include Hoffmann-La Roche, BASF, Eisai, and Rhône-Poulenc.

The price of synthetic vitamin E decreased steadily until about 1990 when prices began to increase. The price of the natural form, although higher than the synthetic form, has approximately paralleled the synthetic form (Table 4).

6. Analytical Methods and Specifications

Specifications and standards for various vitamin E forms and preparations for use in pharmaceutical applications are given in the *United States Pharmacopeia* (52). All products should contain not less than 96.0% or more than 102.0% of the appropriate form. The products must be labeled to indicate both the chemical and stereochemical forms contained in the product.

Label claims for tocopherol levels in preparations can be based on milligrams or International Units. Only the *RRR* or *all-rac*-α-tocopherol and its esters can be claimed. No vitamin E activity can be claimed for the tocotrienols and the non-α-tocopherols. International Units are also used in some reference books and compendia, eg, *Food Chemicals Codex* (40, 53), which is of particular importance for specifications for food fortification.

All formulations of vitamin E must show low acidity, and contain not more than 0.004% heavy metals (reported as Pb) and not more than 10 ppm Pb. Formulations that contain *RRR*-α-tocopherol must have a specific rotation of $+24^\circ$ for the oxidation product with alkaline potassium ferricyanide.

Analysis of vitamin E can be done by a variety of methods, depending on the form and level present and the preparation in which the form is found (54). For pure or highly concentrated forms, this is accomplished by reaction with Emmerie-Engel reagent (2,2′-bipyridine (α,α'-dipyridyl) and ferric chloride) to give a red color. This color results from the combination of bipyridine with ferrous ions formed from the reduction of the ferric ions by the tocopherol and is directly proportional to the amount of tocopherol present. Analysis of α-tocopherol in forms which contain low levels, such as vegetable oils, foods, or feeds, is difficult because the colorimetric method is nonspecific and significant sample preparation is involved to remove interferences such as other tocopherols, tocotrienols, and β-carotene. The AOAC Official Methods of Analysis describes a packed column gas chromatographic method for the analysis of tocopherol isomers in mixed concentrates (41). This method separates α- and δ-tocopherols as discrete peaks, but β- and γ-tocopherols elute as a combined peak.

Numerous high pressure liquid chromatographic techniques have been reported for specific sample forms: vegetable oils (55, 56), animal feeds (57, 58), sera (59, 60), plasma (61, 62), foods (63, 64), and tissues (63). Some of the methods require a saponification step to remove fats, to release tocopherols from cells, and/or to

free tocopherols from their esters. All require an extraction step to remove the tocopherols from the sample matrix. The methods include both normal and reverse-phase hplc with either uv absorbance or fluorescence detection. Application of supercritical fluid (qv) chromatography has been reported for analysis of tocopherols in marine oils (65).

6.1. Bioassay Method

A modification of the Evans resorption–gestation method can be used to determine α-tocopherol activity in supplements. Although the method is time-consuming, when carefully performed, it can produce reasonably accurate results. The method requires raising female rats on a vitamin E-free diet and mating them with normal males. Unless a vitamin E supplement containing more than 0.3–1.0 mg (depends on methodology) of α-tocopherol is administered in the first 10–12 days of pregnancy, the embryos die and are reabsorbed without apparent harm to the mother. If the test supplement contains greater than the threshold dose of α-tocopherol, the pregnancy proceeds normally.

7. Applications and Product Forms

Both α-tocopherol and its esters are constituents of multivitamin and single-dose nutrient capsules or liquid dietary supplements. Supplements for human use range from a few milligrams in multivitamin preparations to 500–1000 mg in single-dose supplements. Specialty items, such as ointments, creams, salves, and suppositories containing vitamin E provide other outlets for α-tocopherol. Tocopherols have significant application in cosmetics (qv) and dermatology. Tocopherols can be used in topical cream or oil forms to treat chronic skin diseases (66), reduce scarring in wound healing (67), reduce inflammation (68), and protect against uv radiation (69). Tocopherols are also incorporated into cosmetic formulations to reduce nitrosamine and nitrosamide formation from amines and amides also present in the formulation (70).

Animal feeds consume approximately 40% of the commercial production of α-tocopherol acetate. Although tocopherol is normally found in feed, the poultry, beef and dairy cattle, lamb, and swine industries use vitamin E in supplements and concentrates to replace tocopherol lost during feed processing and storage. The acetate ester is added to the feeds as either a dry, granular, free-flowing, nondusting powder containing 44,000–276,000 units per kilogram (20,000–125,000 units per pound) or as a high potency oil concentrate (23–100%α-tocopheryl acetate).

Foods are not typically fortified with vitamin E because of the lack of signs of deficiency in the general population. Fortification does occur for infant formulas as a supplement and cereals to replace processing losses. Tocopherols are finding additional applications as antioxidants in foods as the less expensive butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) used are being prohibited in more and more countries. Foods such as lards and citrus oils which do not contain appreciable levels of natural tocopherols can be protected with α-tocopherol at 0.02% levels (weight based on lipid phase) (9). The meat from turkeys and chickens is less prone to rancidity when refrigerated or frozen if the animal's diet contains vitamin E. The meat from pigs fed vitamin E supplements also has better storage (71) and color (72) stability than meat from pigs with normal diets. It has also been reported that veal has better storage stability (73) and beef has better color stability (74) when vitamin E supplements are used in the animal feeds. Tocopherol can be used in bacon and similar foods to prevent the formation of nitrosamines. The traditional antioxidants, such as BHT and phosphites, used in high density polyethylene (HDPE) and polypropylene (PP), can be replaced by *all-rac*-α-tocopherol (75–77).

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