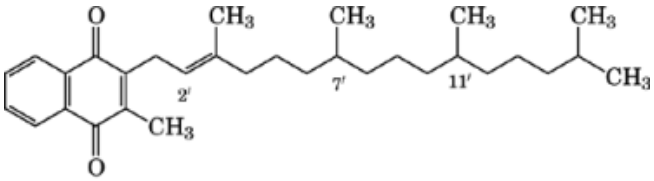
Kirk-Othmer Encyclopedia of Chemical Technology.

VITAMIN K

Vitamin K represents a class of substances which contain the 2-methyl-1,4-naphthoquinone moiety and are characterized by their antihemorraghic properties. Vitamin K was first discovered by Dam in 1929 during experiments with chicks on a lipid-deficient diet (1). Dam coined the term *Koagulations vitamin* to describe this new substance (2, 3). In the late 1930s, several groups identified the causative agent responsible for the antihemorraghic properties of alfalfa (4–7). Structural determination of vitamin K_1 **(1)** was the result of work from several laboratories (8, 9). Stereochemical assignment came much later from Mayer (10). Additional studies isolated and characterized related materials. Vitamin K_2 **(2)** was first found in decaying fish meal (9); it is a crystalline compound and is distinguished by its repeating isoprenyl units. Vitamin K_3 [58-27-5] **(3)** is the simplest form of the vitamin. The chemical name and common names for some important forms of the vitamin follow.

name	vitamin K_1
CAS Registry Number	[84-80-0]
chemical name	1,4-naphthalenedione, 2-methyl-3-(3,7,11,15-tetramethyl-2-hexadecenyl)-, [*R*-[*R**,*R**-(*E*)]]-
common name	phylloquinone, phytomenadione, phytonadione
name	vitamin $K_{2(20)}$
CAS Registry Number	[863-61-6]
chemical name	1,4-naphthalenedione, 2-methyl-3-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-, (*E*,*E*,*E*)-
common name	menaquinone 4, menaquinone K4, MK-4
name	vitamin K_3
CAS Registry Number	[58-27-5]
chemical name	1,4-naphthalenedione, 2-methyl
common name	menadione; menaquinone-0; synkay



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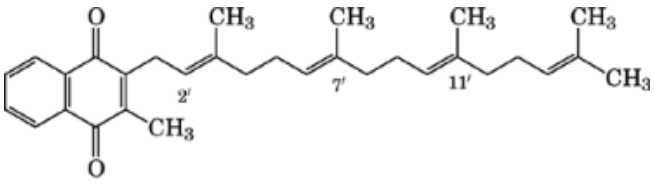

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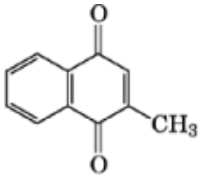

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The K vitamins are named after the original vitamin and the number of carbon atoms in the side chain. Using this convention, vitamin $K_{2(20)}$ is so named because it contains 20 carbon atoms in the chain. In the biological literature, vitamin K_2 is frequently referred to as menaquinone and is further designated by the number of isoprene units in the side chain. For example, vitamin $K_{2(20)}$ is also called menaquinone-4 or MK-4. Vitamin K_3 is also referred to as menadione or MK-0.

Vitamin K is typically found in green, leafy vegetables such as cabbage, broccoli, and spinach at levels of 95–200 μg/100 g of fresh vegetables. Cauliflower at a level of 136 μg/100 g also represents an excellent source of dietary vitamin K. Additionally, animal sources such as liver and eggs provide good sources of vitamin K (11).

1. Chemical/Physical Properties

Vitamin K compounds are yellow solids or viscous liquids. The natural form of vitamin K_1 is a single diastereoisomer with 2′(*E*), 7′(*R*), 11′(*R*) stereochemistry. The predominant commercial form of vitamin K_1 is the racemate and a 2′(*E*)/(*Z*) mixture. Table 1 lists some physical and spectral properties of vitamin K_1.

Table 1. Physical and Spectral Properties of Vitamin K_1[a]

Item	Vitamin K_1	Vitamin $K_{2(30)}$	Vitamin $K_{2(35)}$	Vitamin K_3
color	yellow, viscous oil	yellow crystals	yellow crystals	bright yellow crystals
melting point, °C	−20	50	54	105–107
molecular weight	450.68	580.9	649.02	172.17
molecular formula	$C_{31}H_{46}O_2$	$C_{41}H_{56}O_2$	$C_{46}H_{64}O_2$	$C_{11}H_8O_2$
spectrophotometric data, λ_{max}, nm	242, 248, 260, 269, 325	243, 248, 261, 270, 325	243, 248, 261, 270, 325	244
ϵ, petroleum ether	396, 419, 383, 387, 68	304, 320, 290, 292, 53	278, 195, 266, 267, 48	1150 (hexane)

[a]Ref. 12.

Vitamin K_1 is insoluble in water and is soluble in 70% alcohol, chloroform, petroleum ether, benzene, and hexane. Vitamin K_1 is stable in air but should be protected from light. Although unstable in alkali, the vitamin is stable in acidic medium. Its facile decomposition in basic solution forms the basis of the Dam-Karrer color test.

Early structural determination lends insight into the chemical reactivity of vitamin K_1. Catalytic hydrogenation of vitamin K_1 consumes four moles of hydrogen and affords a colorless compound. Because complete hydrogenation of a 1,4-naphthoquinone structure consumes three molecules of hydrogen, consumption of the fourth mole indicates unsaturation in the side chain. Reductive acetylation of vitamin K_1 affords the diacetate of dihydrovitamin K_1. This behavior further supports the conclusions that vitamin K_1 contains a naphthoquinone group (13).

In addition to its reactivity toward reducing agents, vitamin K_1 is also reactive toward oxidizing agents. Chromic acid oxidation of vitamin K_1 gives rise to two principal products, 2-methyl-1,4-naphthoquinone-3-acetic acid and phthalic acid. By comparison with known compounds, it has been concluded that the benzene ring is unsubstituted and the substitution pattern on the naphthoquinone ring is 2,3-dialkyl (8, 14–16).

2. Analytical Methods

The classical method for the determination of vitamin K is based on the clotting time of a vitamin K-deficient chick. It is relatively easy to produce a hemorraghic state in chicks (17). Vitamin K-deficient rats have also been used for this assay (18). Owing to the development of modern chromatographic techniques, this method of analysis has been supplanted by other methodology.

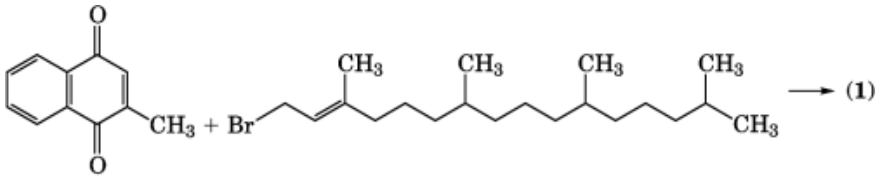
There are several comprehensive reviews of analytical methods for vitamin K (19, 20). Owing to the presence of a naphthoquinone nucleus, the majority of analytical methods use this structural feature as a basis for analysis. Several identity tests such as its reaction with sodium bisulfite or its uv spectrum exploit this characteristic. Although not specific, titrimetric, polarographic, and potentiometric methods have also been used (20).

Chromatographic methods including thin-layer, hplc, and gc methods have been developed. In addition to developments in the types of columns and eluents for hplc applications, a significant amount of work has been done in the kinds of detection methods for the vitamin. These detection methods include direct detection by uv, fluorescence after post-column reduction of the quinone to the hydroquinone, and electrochemical detection. Quantitative gc methods have been developed for the vitamin but have found limited applications. However, gc methods coupled with highly sensitive detection methods such as gc/ms do represent a powerful analytical tool (20).

As described in the USP, phytonadione is a mixture of the cis- and trans-isomers of vitamin K_1. This mixture should not contain more than 103% and not less than 97.0% of total vitamin K content. The amount of the cis-isomer is also specified and is not to exceed 21%. In addition to the pure substance, the USP also describes methods for the analysis of parental as well as tableted forms of the vitamin (21).

3. Synthesis

The first synthesis of vitamin K_1 was reported by several workers in the late 1930s and the synthetic approaches have been reviewed (22). Vitamin K_1 was prepared by the reaction of menadione with phytyl bromide in the presence of zinc (23).



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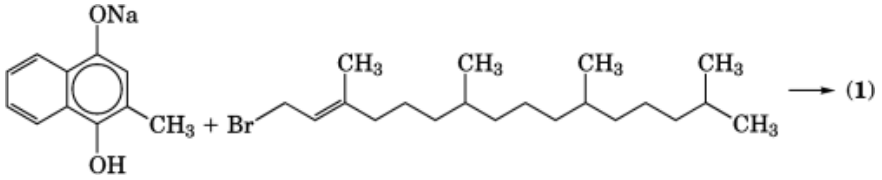
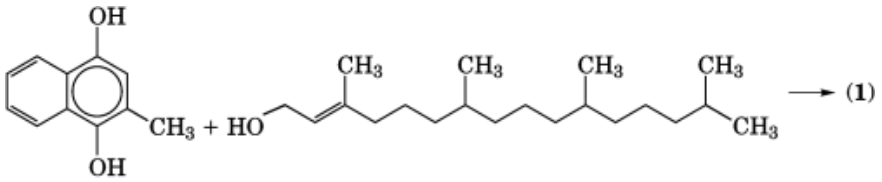
Vitamin K_1 has been synthesized from the condensation of the monosodium salt of menadiol with phytyl bromide (24).



In methodology developed by Fieser, unprotected menadiol **(5)** was condensed with natural phytol using oxalic acid as catalyst (25). Oxidation of the hydroquinone to the naphthoquinone yielded vitamin K_1. A similar approach has been reported (26). The commercial synthesis of vitamin K_1 is largely based on the above with some important improvements from Roche (27) and Merck (28).



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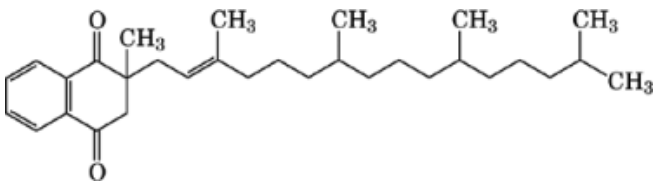
A significant improvement in this technology was the discovery that BF_3-etherate could be substituted as a condensation catalyst in place of oxalic acid (qv). Owing to the fact that oxalate esters of isophytol did not form, this substitution reduced the formation of undesired phytadiene by-products. A second notable advance was the use of 1-acetyl-2-methyl-1,4-naphthoquinone as starting material for the condensation. In addition to phytadiene, a significant by-product is 2-methyl-2-phytyl-2,3-dihydro-1,4-naphthoquinone. The use of the monoprotected compound eliminates the formation of this impurity. Moreover, in the earlier process, the sensitivity of the unprotected compound toward air oxidation necessitated a reduction before purification by base extraction of the crude condensation mixture. The acetylated compound is not labile toward air oxidation. As a result, the reduction step is not warranted and its inherent complications are avoided.



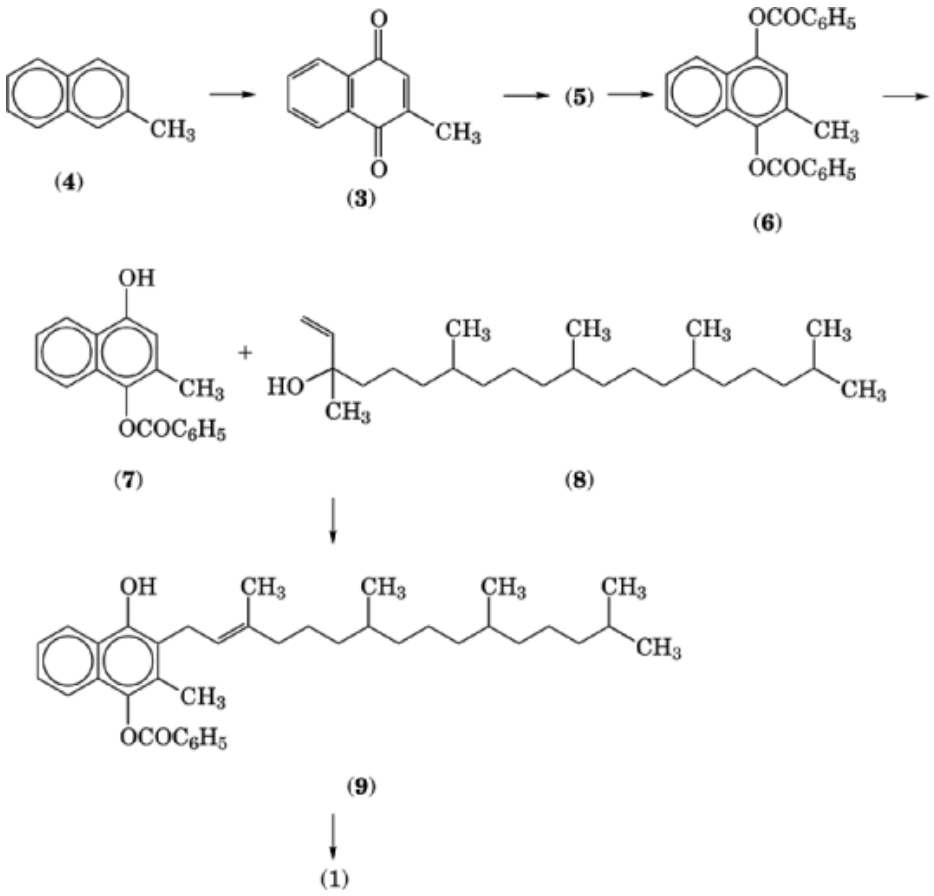


Fig. 1. Synthesis of vitamin K_1.

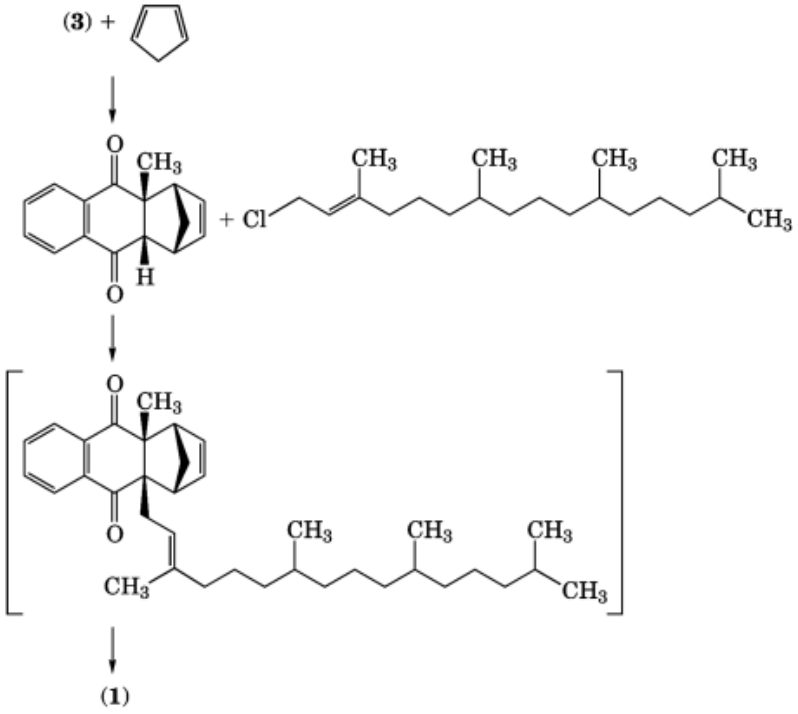
As practiced by Hoffmann-La Roche, the commercial synthesis of vitamin K_1 is outlined in Figure 1. Oxidation of 2-methylnaphthalene 1 yields menadione **(3)**. Catalytic reduction to the naphthohydroquinone **(5)** is followed by reaction with a benzoating reagent to yield the bis-benzoate 1. Selective deprotection yields the less hindered benzoate 1. Condensation of isophytol 1 (see Vitamins, vitamin E) with 1 under acid-catalyzed conditions yields the coupled product 1. Saponification followed by an air oxidation yields vitamin K_1 **(1)** (29).

Although the industrial synthesis of vitamin K_1 remains largely unchanged from its early beginnings, significant effort has been devoted to improvements in the condensation step, the oxidation of dihydrovitamin to vitamin K_1, and in economical approaches to vitamin K_3 (*vide infra*). Also, several chemical and biochemical alternatives to vitamin K_1 have been developed.

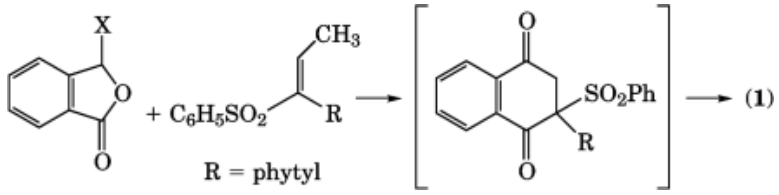
A Japanese patent has claimed improvements in the direct condensation of menadione with phytyl chloride in the presence of a reducing metal such as zinc or iron powder (30). Tin chloride has been reported to be a useful catalyst for this condensation (31, 32).

In a patent assigned to Mitsubishi, air oxidation is carried out in the presence of copper salts to avoid the formation of complicating impurities in the oxidation of dihydrovitamin K_1 to vitamin K_1 (33). In other work, high yields of vitamin K_1 were obtained by performing the oxidation in an alkali medium (34). High purity vitamin K_1 can also be obtained by an oxidation in dimethyl sulfoxide (35).

In a novel approach to vitamin K_1, Hoffmann-La Roche has exploited the potential acidity at C-3 as a means to attach the side chain of vitamin K_1 (36). Menadione was reacted with cyclopentadiene to yield the Diels-Alder adduct. The adduct is treated with base and alkylated at C-3 with phytyl chloride. A retro Diels-Alder reaction yields vitamin K_1. Process improvements in this basic methodology have been claimed by Japanese workers (37).



Although not of industrial importance, many organometallic approaches have been developed (38). A one-pot synthesis of vitamin K_1 has been described and is based on the anionic $[4 + 2]$ cycloaddition of three-substituted isobenzofuranones to 1-phytyl-1-(phenylsulfonyl)propene. Owing to the rather mild chemical conditions, the (*E*)-stereochemistry is retained (39).



Although the predominant commercial form of vitamin K_1 is the racemate, natural (2′(*E*), 7′(*R*), 11′(*R*))–vitamin K_1 is accessible either from a natural source or from condensation with natural phytol. In the curative blood clotting test, these compounds have been shown to have nearly equivalent biopotencies. The synthesis and spectral properties of all four stereoisomers of (*E*)-vitamin K_1 has been described and their biopotencies determined. Using natural vitamin K_1 as a standard, the relative activities were found to be 1.0, 0.93, 1.19, and 0.99 for 2′(*E*), 7′(*R*), 11′(*R*); 2′(*E*), 7′(*R*), 11(*S*′); 2′(*E*), 7′(*S*), 11′(*S*); and 2′(*E*), 7′(*S*), 11′(*R*), respectively. These

differences were not considered significant and it was concluded that these compounds have identical activities (40).

Aside from chemical methods, several patents have appeared on the biochemical production of natural vitamin K_1 from callus tissue cultures (41). In addition, a patent has appeared which describes the concentration and purification of natural vitamin K_1 from deodorizer distillates (42). The biosynthesis of vitamin K_1 and vitamin K_2 has been reviewed (43).

4. Vitamin K_2

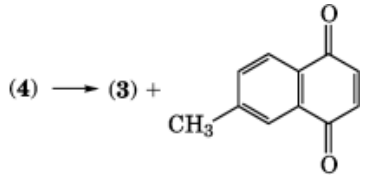
As compared to vitamin K_1, vitamin K_2 is relatively unimportant industrially with only a few producers, such as Teikoku Kagaku Sangyo and Eisai, and is dominated by the manufacture of vitamin $K_{2(20)}$. The industrial synthesis parallels that of vitamin K_1 and involves as a key step alkylation of monosubstituted menadione with an appropriate (all-*E*) reagent (44, 45). Several academic syntheses have been described (46–49).

In contrast to vitamin K_1, there has been considerably more activity on fermentative approaches to vitamin K_2 (50). The biosynthetic pathway to vitamin K_2 is analogous to that of vitamin K_1 except that poly(prenylpyrophosphates) are the reactive alkylating agent (51, 52). Menaquinones of varying chain lengths from C_5 to C_{65} have been isolated from bacteria. The most common forms are vitamin $K_{2(35)}$, $K_{2(40)}$, and $K_{2(45)}$. A significant amount of $K_{2(20)}$ was observed in a *Flavobacterium* fermentation and was increased by the use of a mutant resistant to usnic acid (53). In other work, production of vitamin K_2 was enhanced by the use of 1-hydroxy-2-naphthoate (54). Many Japanese patents have appeared that describe production of menaquinones from bacteria (55).

5. Vitamin K_3

Industrially, vitamin K_3 is prepared from the chromic acid oxidation of 2-methylnaphthalene (56). Although the yields are low, the process is economical owing to the low cost and availability of the starting material and the oxidizing agent. However, the process is complicated by the formation of isomeric 6-methyl-1,4-naphthoquinone. As a result, efforts have been directed to develop process technology to facilitate the separation of the isomeric naphthoquinone and to improve selectivity of the oxidation.

A process has been disclosed in which the mixture of naphthoquinones is reacted with a diene such as butadiene. Owing to the fact that the undesired product is an unsubstituted naphthoquinone, this dieneophile readily reacts to form a Diels-Alder adduct. By appropriate control of reaction parameters, little reaction is observed with the substituted naphthoquinone. Differential solubility of the adduct and vitamin K_3 allows for a facile separation (57, 58).

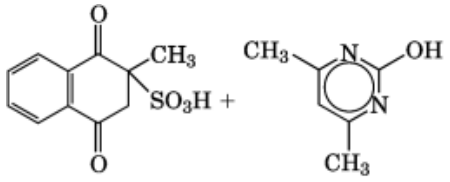


In an alternative approach, the desired 2-methyl-1,4-naphthoquinone is derivatized to form a water-soluble and commercially important sodium bisulfite adduct. Extraction of the organic phase with water separates the isomeric quinones (59).

In order to circumvent this problem, there has been significant activity directed toward the search for a less environmentally toxic and more selective oxidizing agent than chromium. For example, Hoechst has patented a process which uses organorhenium compounds. At a 75% conversion, a mixture of 86% of 2-methyl-1,4-naphthoquinone and 14% 6-methyl-1,4-naphthoquinone was obtained (60). Ceric sulfate (61) and electrochemistry (62, 63) have also been used.

In a biotechnology-based approach, Japanese workers have reported on the microbial conversion of 2-methylnaphthalene to both 2-methyl-1-naphthol and menadione by *Rhodococcus* (64). The intermediate 2-methyl-1-naphthol can readily be converted to menadione by a variety of oxidizing agents such as heteropoly acids (65) and copper chloride (66). A review of reagents for oxidizing 2-methylnaphthalene and naphthol is available (67).

In addition to its industrial importance as an intermediate in the synthesis of vitamin K_1, menadione, or more specifically, salts of its bisulfite adduct, are important commodities in the feed industry and are used as stabilized forms in this application. Commercially significant forms are menadione dimethyl pyrimidinol (MPB) **(10)** and menadione sodium bisulfite (MSB) **(11)**. MSB is sold primarily as its sodium bisulfite complex. The influence of feed processing, ie, pelleting, on the stability of these forms has been investigated (68). The biological availabilities and stability of these commercial sources has been determined (69, 70).



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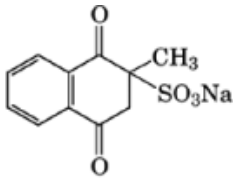
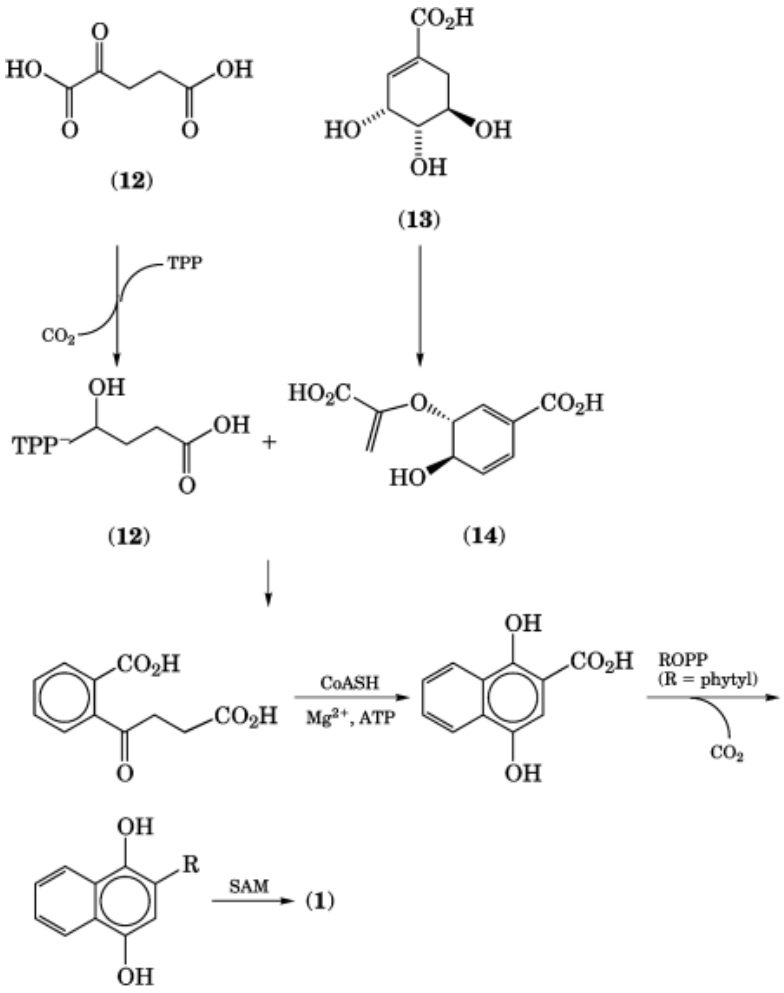


(11)

6. Biosynthesis

Animals cannot synthesize the naphthoquinone ring of vitamin K, but necessary quantities are obtained by ingestion and from manufacture by intestinal flora. In plants and bacteria, the desired naphthoquinone ring is synthesized from 2-oxoglutaric acid **(12)** and shikimic acid **(13)** (71, 72). Chorismic acid **(14)** reacts with a putative succinic semialdehyde TPP anion to form *o*-succinyl benzoic acid (73, 74). In a second step, *ortho*-succinyl benzoic acid is converted to the key intermediate, 1,4-dihydroxy-2-naphthoic acid. Prenylation with phytyl pyrophosphate is followed by decarboxylation and methylation to complete the biosynthesis (75).



7. Economic Aspects

The total market for vitamin K_1 is relatively small and the principal producer of vitamin K_1 is Hoffmann-La Roche. Nisshin Flour Milling Company is the predominant manufacturer for the optically active form of vitamin K_1. Total world market for vitamin K_3 is 1500 t with Vanetta Company as the dominant manufacturer. The list price for vitamin K USP grade is \$3.75–\$4.05/g. For the 1% spray dried formulated product, the price ranges from \$76–\$79/kg. The majority of vitamin K_1 is sold to the pharmaceutical industry, whereas vitamin K_3 is consumed primarily by the feed industry (see Pharmaceuticals).

8. Requirements

Owing to the ubiquitous natural occurrence of vitamin K and its production by intestinal bacteria, vitamin K deficiencies are rare. However, they can be caused by certain antibiotics (qv) coupled with a reduced dietary

intake. Newborn infants who do not possess the necessary intestinal bacterial population are at danger for vitamin K deficiency. As a result, vitamin K injections are routinely given to the newborn.

Table 2 lists the Recommended Dietary Allowances (RDA) for vitamin K. Although manufacture by intestinal bacteria represents a significant source of plasma menaquinone concentrations, reliance on this source alone is not sufficient to maintain healthy concentrations of menaquinone. Consequently, dietary supplementation is necessary (76).

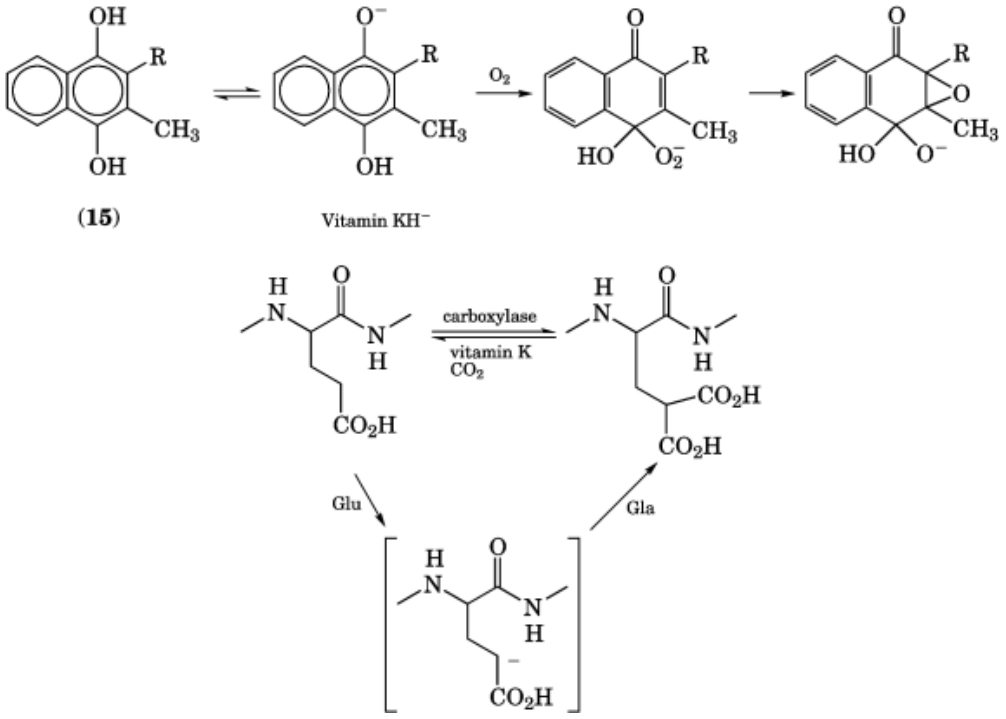
Table 2. RDA Requirements for Vitamin K

Category	Age	Vitamin K, μg
infants	0.0–0.5	5
	0.5–1.0	10
children	1–3	15
	4–6	20
	7–10	30
males	11–14	45
	15–18	65
	19–24	70
	25–50	80
	$>$ 51	80
females	11–14	45
	15–18	55
	19–24	60
	25–50	60
	$>$ 51	60
U.S. RDA	none established	

9. Biochemistry

As a result of empirical findings that alfalfa and other plants can alleviate a hemorrhagic situation in chicks, work was initiated to identify and isolate the causative agent. Concurrent to these activities was the observation that prothrombin levels in chicks given certain leafy green vegetables were enhanced. Studies on the role of vitamin K in blood clotting and more specifically, in the conversion of fibrinogen to fibrin, have led to the conclusion that the important function of vitamin K in the clotting mechanism is to act as a cofactor in the biosynthesis of the active form of prothrombin (11).

Work in the mid-1970s demonstrated that the vitamin K-dependent step in prothrombin synthesis was the conversion of glutamyl residues to γ-carboxyglutamyl residues. Subsequent studies more clearly defined the role of vitamin K in this conversion and have led to the current theory that the vitamin K-dependent carboxylation reaction is essentially a two-step process which first involves generation of a carbanion at the γ-position of the glutamyl (Gla) residue. This event is coupled with the epoxidation of the reduced form of vitamin K and in a subsequent step, the carbanion is carboxylated (77–80). Studies have provided thermochemical confirmation for the mechanism of vitamin K and have shown the oxidation of vitamin KH_2 **(15)** can produce a base of sufficient strength to deprotonate the γ-position of the glutamate (81–83).



Although the role of vitamin K in blood clotting has clearly been demonstrated and involves carboxylation of multiple proteins in addition to prothrombin and includes factor VII, factor IX, and factor X, proteins containing Gla residues have been found in other tissues. For example, in 1975, Hauschka isolated an EDTA-soluble protein fraction of chick bones and identified the presence of Gla (84). Additional work sequenced the protein, which was called bone Gla protein or osteocalcin (85). The properties of the protein and its function in bone mineralization have been extensively studied (86, 87). However, its specific function is not completely understood. In addition, vitamin K-dependent carboxylase activity has been observed in cell cultures. For example, a vitamin K-dependent protein has been identified in a screen for growth arrest specific gene products. This protein, Gas6, has been identified as a ligand for tyrosine kinase (88). This observation has suggested that vitamin K may have a more general metabolic role (89–94).

10. Conclusions

Despite the fact that commercial synthesis in the 1990s of vitamin K has largely remained unchanged from its early roots, there has been significant activity in the area of process improvements to the basic approach. Also, several biotechnological systems have been described and this may be a future research area. A thorough understanding of the role of vitamin K in biological systems will continue as an active research area.

BIBLIOGRAPHY

"Vitamins (Vitamin K)" in *ECT* 2nd ed., Vol. 14, pp. 858–874, by R. F. Hirschmann.

Cited Publications

1. H. Dam, *Biochem. Z.* **215**, 475 (1929).
2. H. Dam, *Biochem. J.* **29**, 1273 (1935).
3. H. Dam, *Nature*, **135**, 652 (1935).
4. H. J. Almquist, *J. Biol. Chem.* **114**, 241 (1936).
5. H. J. Almquist, *J. Biol. Chem.* **115**, 587 (1936).
6. H. Dam and F. Schonheyder, *Biochem. J.* **30**, 897 (1936).
7. S. A. Thayer, D. W. MacCorquodale, S. B. Binkley, and E. A. Doisy, *Science*, **88**, 243 (1938).
8. D. W. MacCorquodale, L. C. Cheney, S. B. Binkley, W. F. Holcomb, R. W. McKee, S. A. Thayer, and E. A. Doisy, *J. Biol. Chem.* **131**, 357 (1939).
9. D. W. MacCorquodale, S. B. Binkley, R. W. McKee, S. A. Thayer, and E. A. Doisy, *Proc. Soc. Exptl. Biol. Med.* **40**, 482 (1939).
10. H. Mayer, U. Gloor, O. Isler, R. Ruegg, and O. Wiss, *Helv. Chim. Acta*, **47**, 221 (1964).
11. J. W. Suttie, in L. J. Machlin, ed., *The Handbook of Vitamins*, Marcel Dekker, Inc., New York, 1991, 145–169.
12. *Merck Index*, 11th ed., Merck & Co., Rahway, N.J., 1989, 1580–1581.
13. R. W. McKee, S. B. Binkley, D. W. MacCorquodale, S. A. Thayer, and E. A. Doisy, *J. Am. Chem. Soc.* **61**, 1295 (1939).
14. S. B. Binkley, D. W. MacCorquodale, L. C. Cheney, S. A. Thayer, R. W. McKee, and E. A. Doisy, *J. Am. Chem. Soc.* **61**, 1612 (1939).
15. D. W. MacCorquodale, S. B. Binkley, S. A. Thayer, and E. A. Doisy, *J. Am. Chem. Soc.* **61**, 1928 (1939).
16. S. B. Binkley, L. C. Cheney, W. F. Holcomb, R. W. McKee, S. A. Thayer, D. W. MacCorquodale, and E. A. Doisy, *J. Am. Chem. Soc.* **61**, 2558 (1939).
17. H. Dam and E. Sondegarrd, in P. György and W. N. Pearson, eds., *The Vitamins*, 2nd ed., Vol. **VI**, Academic Press, Inc., New York, 1967, 245–260.
18. J. T. Matshirer and W. V. Taggart, *J. Nutr.* **94**, 52 (1968).
19. M. M. A. Hussan, J. S. Mossa, and A. H. U. K. Taragan, *Anal. Profiles Drug Subst.* **17**, 449–531 (1988).
20. W. E. Lambert and A. P. De Leenheer, in A. P. De Leenheer, W. F. Lambert, and H. J. Nelis, eds., *Modern Chromatographic Analysis of the Vitamins*, Marcel Dekker, New York, 1992, 197–233.
21. *The United States Pharmacopeia XXII* (USP XXII-NF XVII), United States Pharmacopeial Convention, Inc., Rockville, Md., 1990, 1081–1082.
22. A. Ruettimann, *Chimia*, **40**, 290 (1986); S. Yamada, T. Takeshita, and J. Tanaka, *Yuki Gosei Kagaku Kyokai Shi*, **40**, 268 (1982).
23. H. J. Almquist and A. A. Klose, *J. Am. Chem. Soc.* **61**, 2557 (1939); H. J. Almquist and A. A. Klose, *J. Biol. Chem.* **132**, 469 (1940).
24. S. B. Binkley, L. C. Cheney, W. F. Holocomb, M. W. McKee, S. A. Thayer, D. W. MacCorquodale, and E. A. Doisy, *J. Am. Chem. Soc.* **61**, 2553 (1939).
25. L. F. Fieser, *J. Am. Chem. Soc.* **61**, 3467 (1939).
26. P. Karrer, H. Simon, and E. Zbinden, *Helv. Chem. Acta*, **27**, 317 (1944).
27. O. Isler and K. Doebel, *Helv. Chim. Acta*, **37**, 225 (1954).
28. R. Hirschmann, R. Miller, and N. L. Wendler, *J. Am. Chem. Soc.* **76**, 4592 (1954).
29. D. Bhatia, ed., in *Encyclopedia of Food Science and Technology*, John Wiley & Sons, Inc., New York, 1991, 2727–2732.
30. Rus. Pat. 76-154299 (1979), Y. Tachibana (to Nisshin Flour Milling Co.).
31. Rus. Pat. 661212 (1971), S. Kitamura, S. Matsuyama, and M. Morioka (to Teikoku Chemical Industry).
32. Rus. Pat. 670414 (1970), S. Kitamura, Y. Fujita, and M. Morioka (to Teikoku Chemical Industry).
33. Rus. Pat. 95-218011 (1989), A. Shinno, I. Teraro, T. Matsuda, and I. Tadashi (to Mitsubishi Gas Chemical Co., Inc.).
34. Rus. Pat. 77-69415 (1979), S. Himoto, K. Miyahara, and Y. Yoshino (to Nisshin Flour Milling Co., Ltd.).
35. Rus. Pat. 680309 (1971), S. Kitamura, Y. Fujita, and M. Morioka (to Teikoku Chemical Industry, Inc.).
36. Eur. Pat. 84-108332 (1985), A. Ruettimann and G. Buechi (to Hoffmann-La Roche Inc.).
37. Eur. Pat. 94-102979 (1994), K. Hamamura, T. IIwana, C. Seki, and M. Konishi (to Eisai Chemical Co., Ltd.).

38. S. Araki, T. Sato, H. Miyagawa, and Y. Bukugan, *Bull. Chem. Soc. Jpn.* **57**, 3523 (1984); Y. Naruta, *J. Org. Chem.* **45**, 4097 (1980); B. L. Chenard, M. J. Manning, P. W. Reynolds, and J. W. Swenton, *J. Org. Chem.* **45**, 378 (1980); K. H. Doetz and I. Pruskil, *J. Organomet. Chem.* **209**, C4 (1981); Ger. Pat. 2909091 (1980), K. H. Doetz (to Hoffmann-La Roche); Y. Tachibana, *Chem. Lett.*, 901 (1977); P. W. Raynolds, M. J. Manning, and J. S. Swenton, *J. Chem. Soc. Chem. Comm.*, 499 (1977); C. D. Synder and H. Rapport, *J. Am. Chem. Soc.* **96**, 8046 (1974).
39. H. Tso and Y. J. Chen, *J. Chem. Res.* (*S*), **3**, 104 (1995).
40. R. Schmid, S. Antoulus, A. Rüttimann, M. Schmid, M. Vecchi, and H. Weiser, *Helv. Chim. Acta*, **73**, 1276 (1990).
41. Rus. Pat. 87-287021 (1990), T. Fujita and S. Takato (to Snow Brand Milk Products Co., Ltd.); Rus. Pat. 87-287022 (1990), T. Fujita, H. Hatamoto, and S. Takato (to Snow Brand Milk Products Co., Ltd.).
42. Rus. Pat. 85-90577 (1987), K. Kuihara and Y. Takagi (to Nisshin Oil Mills, Ltd.).
43. E. Leistner, *Recent Adv. Phytochem.* **20**, 243 (1986).
44. Rus. Pat. 67-67366 (1973), S. Kitamura, M. Morioka, H. Tono, and Y. Fujita (to Teikoku Chemical Industry Co., Ltd.).
45. Rus. Pat. 86-308171 (1989), T. Ichino, K. Nakano, T. Udagawa, Y. Kusaba, T. Muramatsu, and A. Katayama (to Eisai Chemical Co., Ltd.).
46. B. Liu, L. Gu, and J. Zhang, *Recl. Trav. Chim. Pays-Bas*, **110**(4), 99 (1991).
47. M. Inoue, T. Uragaki, and S. Enomoto, *Chem. Lett.* **12**, 2075 (1986).
48. Y. Naruta, *J. Am. Chem. Soc.* **102**, 3774 (1980).
49. K. Sato, S. Inoue, and K. Saito, *J. Chem. Soc., Perkin Trans. I*, **20**, 2289 (1973).
50. D. H. L. Bishop and H. H. King, *Biochem. J.* **85**, 550 (1962); D. H. L. Bishop, K. P. Pandya, and H. K. King, *Biochem. J.* **83**, 606 (1962); D. R. Threfall, *Vitam. Horm.* (*NY*), **29**, 155 (1971).
51. H. Taber, "Vitamin K Metab.–Vitamin K-Dependent Proteins," in J. W. Suttie, ed., *Proc. Steenbock Symp. 8th*, University Park Press, Baltimore, Md., 1980, for a review of function of Vitamin K_2.
52. H. Taguchi and Y. Tani, *Microb. Util. Renewable Res.* **8**, 350 (1993).
53. Y. Tani, S. Asahi, and H. Yamada, *J. Nutr. Sci. Vitaminol.* **32**, 137 (1986).
54. Y. Tani, S. Asahi, and H. Yamada, *J. Ferment. Technol.* **62**, 321 (1984).
55. Rus. Pat. 87-29722 (1988), Y. Tani (to Mitsubishi Gas Chemical Co., Inc.); Rus. Pat. 86-237128 (1988), S. Uragami, Y. Tani, and Y. Tokunaga (to Mitsubishi Gas Chemical Co., Inc.); Rus. Pat. 86-41840 (1988), Y. Tani (to Mitsubishi Gas Chemical Co., Inc.); Rus. Pat. 85-55458 (1987), Y. Tani (to Mitsubishi Gas Chemical Co., Inc.).
56. Rus. Pat. 92-72044 (1995), S. Nakoyooji (to wa Kasei KK).
57. U.S. Pat. 5,329,026 (July 12, 1994), N. Sugishiwa, N. Ikeda, and Y. Fujii (to Nippon Shokubui Kajaka Kogyo Co., Ltd.).
58. Eur. Pat. 490-122643 (1991), N. Sugishiwa, N. Ikeda, Y. Fujii, R. Aoki, and Y. Hatta (to Nippon Shokuba).
59. Rus. Pat. 85-252445 (1986), T. Komatsui and T. Sumino (to Kawasaki Kasei Kogyo).
60. Eur. Pat. 665209 A1 950802 (1995), W. A. Hermann, J. D. Galamba Correia, R. W. Fischer, W. Adam, J. Lin, R. C. Saha-Moeller, and M. Shimizu (to Hoechst AG).
61. World Pat. 91-EP1958, H. M. Becher (1992) (to Shell International Research).
62. World Pat. 91-US3623 (1991), J. E. Toomey (to lly Industries, Inc.).
63. S. Ito, Y. Karob, M. Iwata, K. Susuki, and A. Okika, *J. Appl. Electrochem.* **23**, 671 (1993).
64. Rus. Pat. 92-178171 (1994), S. Tanyoshi (to asaki Steel Co.).
65. K. I. Matveev, E. G. Zhizhina, and V. F. Odyakov, *React. Kinet. Catal. Lett.* **55**, 47 (1995); R. Neumann and M. de la Vega, *J. Mol. Catal.* **84**, 93 (1993); K. I. Matveev, E. G. Zhizhina, V. F. Odyakov, and V. N. Parmon, *Izv. Akad. Nauk. Ser. Khim.* **7**, 1208 (1994).
66. Rus. Pat. 92-352595 (1994), K. Nakao and H. Tamui (Kurary Co.); Rus. Pat. 87-247363 (1989), N. Hirose and S. Kijima (Eisai Co., Ltd.).
67. U. M. Azizov and L. I. Leonteva, *Zhim. Farm. Zh.* **23**, 1488 (1989).
68. I. Nir, I. Kafri, and R. Cohen, *Poultry Sci.* **57**, 206 (1978).
69. P. W. Waldroup, W. D. Bussel, A. B. Burke, and Z. B. Johnson, *Arkansas Farm Res.* **26**, 11 (1977).
70. P. W. Waldroup, W. D. Bussell, A. B. Burke, and Z. B. Johnson, *Animal Feed Sci. Technol.* **3**, 329 (1978).
71. R. Bentley, *Pure Appl. Chem.* **41**, 47 (1975).
72. R. Bentley and R. Megananthan, *Microbial. Rev.* **46**, 241 (1978).
73. I. M. Campbell, *Tetrahedron Lett.* **10**, 4777 (1969).
74. J. Soll and G. Schultz, *Biochem. Biophys. Res. Comm.* **99**, 907 (1981).
75. O. Samuel and R. Azerad, *FEBS Lett.* **2**, 336 (1969).

76. Committee on Dietary Allowances, Food and Nutrition Board, *Recommended Dietary Allowances*, 10th ed., National Academy Press, Washington, D.C., 1989.
77. J. Stenfo, *J. Biol. Chem.* **249**, 5527 (1974).
78. J. Stenflo, P. Fernlund, W. Egan, and P. Roepstorff, *Proc. Natl. Acad. Sci. USA* **71**, 2730 (1974).
79. G. L. Nelsestuen, T. H. Zytkovicz, and J. B. Howard, *J. Biol. Chem.* **249**, 6347 (1974).
80. S. Magnusson, L. Sottrup-Jensen, T. E. Petersen, H. R. Morris, and A. Dell, *FEBS Lett.* **44**, 189 (1974).
81. P. Dowd, S. W. Ham, and S. J. Geib, *J. Am. Chem. Soc.* **113**, 7734 (1991).
82. R. A. Flowers, II., S. Naganmathan, P. Dowd, E. M. Arnett, and S. W. Ham, *J. Am. Chem. Soc.* **115**, 9409 (1993).
83. E. A. Arnett, P. Dowd, R. A. Flowers, II., S. W. Ham, and S. Naganmathan, *J. Am. Chem. Soc.* **114**, 9209 (1992).
84. P. V. Hauscka, J. B. Lian, and P. M. Gallop, *Proc. Natl. Acad. Sci. USA*, **72**, 3925 (1975).
85. P. A. Price, A. S. Ofsuka, J. W. Poser, J. Kiristaposis, and N. Raman, *Proc. Natl. Acad. Sci. USA*, **73**, 1447 (1976).
86. P. A. Price, J. W. Poser, and N. Raman, *Proc. Natl. Acad. Sci. USA* **73**, 3374 (1976).
87. J. B. Lian, P. V. Hauschksa, and P. M. Gallop, *Fed. Proc.* **37**, 2615 (1978).
88. T. N. Stitt and co-workers, *Cell* **80**, 661 (1995).
89. J. B. Lianm, R. J. Levy, J. T. Levy, and P. A. Friedmann, in F. L. Siegel, E. Carafoli, R. H. Kretsinger, D. H. MacLennan, and R. H. Wassermann, eds., *Calcium-Binding Proteins: Structure and Function*, Elsevier North-Holland, New York, 1980, p. 449.
90. R. J. Lecvy, C. Gundberg, and R. Scheinmann, *Artheroscelerosis* **46**, 49 (1983).
91. J. A. Helpern, S. J. McGee, and J. M. Riddle, *Henry Ford Hosp. Med. J.* **30**, 152 (1982).
92. J. W. Suttie, in A. T. Diplock, ed., *The Fat Soluble Vitamins*, William Heienemann, Ltd., London, 1985, p. 225.
93. C. Vermeer, *Haemostatsis*, **16**, 239 (1986).
94. M. C. Roncaglioni, A. P. B. Dalessandro, B. Casali, C. Vermeer, and M. B. Donati, *Haemostatis*, **16**, 295 (1986).

General References

95. D. Bhatia, ed., *Encyclopedia of Food Science and Technology*, John Wiley & Sons, Inc., New York, 1991, 2727–2732.
96. O. Isler and G. Brubacher, *Vitamine I*, Georg Thieme Verlag, New York, 1982, 152–176.
97. W. E. Lambert and A. P. De Leenheer, in A. P. De Leenheer, W. F. Lambert, and H. J. Nelis, eds., *Modern Chromatographic Analysis of the Vitamins*, Marcel Dekker, New York, 1992, 197–233.
98. S. Patai, ed., *The Chemistry of Quinonoid Compounds*, Parts 1 and 2, John Wiley & Sons, Inc., New York, 1974.
99. S. Patai and Z. Rappoport, eds., *The Chemistry of Quinonoid Compounds*, Vol. **2**, Parts 1 and 2, John Wiley and Sons, Ltd., Chichester, U.K., 1988.
100. J. W. Suttie, in L. J. Machlin, ed., *The Handbook of Vitamins*, Marcel Dekker, Inc., New York, 1991.

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