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Synthesis of 2-Solanesyl-1,4-naphthoquinone, New Member of a Vitamin K_2 Group*,†

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ABSTRACT: 2-Solanesyl-1,4-naphthoquinone and 2-phytyl-1,4-naphthoquinone have been synthesized by the reaction of solanesol and phytol, respectively, with the 1,4-naphthohydroquinone, and have been extensively characterized by spectral and chromatographic data. The 2-solanesyl-1,4-naphthoquinone appears to correspond in ultraviolet absorption characteristics to the described quinone, "SFQ," from *Streptococcus faecalis* 10C1, although the eight-unit isoprenolog is not excluded. The 2-phytyl-1,4-naphthoquinone and "SFQ" appear to be different but related compounds; chromatographic data also support these interpretations. The 3-desmethyl forms of vitamin K_2, which are in nature, are of particular interest in differentiating the biochemical functions of various quinones; the 3-methyl group of the better known methyl homologs is essential to the proposed quinone-methine mechanism of oxidative phosphorylation.

2-Solanesyl-1,4-naphthoquinone (compound I) has been synthesized as a new member of a new group of naphthoquinones which has recently been found to occur naturally and which has been considered as a group of "2-desmethyl vitamin K_2's." A new naphthoquinone from *Streptococcus faecalis* 10C1 has been isolated (Baum and Dolin, 1963b). This quinone, SFQ,[1] was the only one detected in the fermentations of *S. faecalis*. The limited availability of the quinone by isolation did not permit a definitive structural determination of the new quinone. However, it was apparent that the properties of SFQ were consistent with those of a 1,4-naphthoquinone substituted in the 2- position with a 40- to 45-carbon β-alkenyl side chain (compound II); later it was found that synthetic 2-phytyl-1,4-naphthoquinone (having a 20-carbon side chain) is "virtually identical with SFQ" in respect to absorption-peak positions in the ultraviolet spectrum. Through the generosity of Dr. Boyd H. Woodruff of the Merck, Sharp and Dohme Research Laboratories, Rahway, N.J., cells of *S. faecalis* (MB-130) were obtained and extracted. However, the cells of this strain did not yield any such quinone by the isolation techniques which were used, and which were based on those described for *S. faecalis* 10C1 (Baum and Dolin, 1963b).

Three naphthoquinones have more recently been reported (Lester *et al.*, 1964) from *Hemophilus parainfluenzae*. These three compounds were termed "2-desmethyl vitamin K_2's." The principal component appeared to have a C_{30} isoprenoid side chain (compound III) and there were lesser amounts of possibly the C_{25} and C_{35} isoprenologs (compounds IV and V).

A quinone has been isolated from teakwood (*Tectona grandis* L.) which apparently is the cause of marked skin irritation and eczema that results when workers

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† Coenzyme Q. LXI.

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[1] Abbreviations used in this work: SFQ, substance purified from lipid extracts of a strain of *Streptococcus faecalis* (Baum and Dolin, 1963b); NMR, nuclear magnetic resonance.

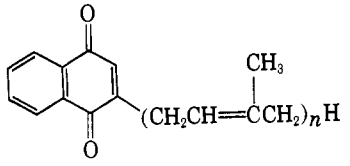
TABLE 1: Ultraviolet Absorption Spectra.[a]

2-Phytyl-1,4-naphthoquinone	Isooctane λ_{max} mμ	238 sh	243	248	254	264	325
	Isooctane $E^{1\%}_{1cm}$		450	460	438	370	72.5
	Ethanol oxidized: λ_{max} mμ			246	251		329
	Ethanol reduced: λ_{max} mμ			246			~328
							~337
2-Solanesyl-1,4-naphthoquinone	Isooctane λ_{max} mμ	239 sh	243	248	254	264	326
	Isooctane $E^{1\%}_{1cm}$		260	268	248	208	42.5
	Ethanol oxidized: λ_{max} mμ			246	251		332
	Ethanol reduced: λ_{max} mμ			246			332
SFQ[b]	Isooctane λ_{max} mμ	238 sh	243	248	254	263	327
	Isooctane $E^{1\%}_{1cm}$		256	264	243	199	36

[a] Ultraviolet spectra were run on a Cary Model 14M spectrophotometer; sh = shoulder. Reduced spectrum obtained by reduction with $NaBH_4$. [b] The data for "SFQ" were abstracted from Baum and Dolin (1963a).

in a veneer factory handle such wood. The constitution of this quinone was established as γ,γ-dimethylallyl-1,4-naphthoquinone (compound VI) (Sandermann and Simatupang, 1962, 1963).

The availability of the nine-unit isoprenoid alcohol, solanesol, from tobacco permits the synthesis of solanesyl-quinone derivatives. By this approach, plastoquinone (Shunk *et al.*, 1959; Kofler *et al.*, 1959) and the vitamin K_2 analog, or 2-methyl-3-solanesyl-1,4-naphthoquinone, were synthesized (Shunk *et al.*, 1959; Noll *et al.*, 1960).



I, n = 9
II, SFQ; n = 8 or 9
III, n = 6
IV, n = 5
V, n = 7
VI, n = 1

1,4-Naphthohydroquinone and solanesol were allowed to react in dioxane solution in the presence of boron trifluoride etherate. The course of the reaction was followed by thin-layer chromatography. The product was partially purified as the hydroquinone and then oxidized with silver oxide to the quinone. Final purification, by a column of silica gel, gave the new 2-solanesyl-1,4-naphthoquinone (compound I). 2-Phytyl-1,4-naphthoquinone was also obtained by this procedure although it had previously been synthesized under other conditions (Fieser *et al.*, 1940a).

The ultraviolet spectral data of synthetic 2-solanesyl-1,4-naphthoquinone and the reported (Baum and Dolin, 1963b) ultraviolet spectrum of SFQ show close similarities (Figure 1; Table I), e.g., λ_{max} 248 ($E^{1\%}_{1cm}$ 268) for compound I, as compared to λ_{max} 248 ($E^{1\%}_{1cm}$ 264) for SFQ assuming a side chain of nine isoprenoid units. On the other hand, if SFQ had a side chain of eight isoprenoid units, the calculated $E^{1\%}_{1cm}$ is 295, and the $E^{1\%}_{1cm}$ for the quinone with phytyl side chain is 460.

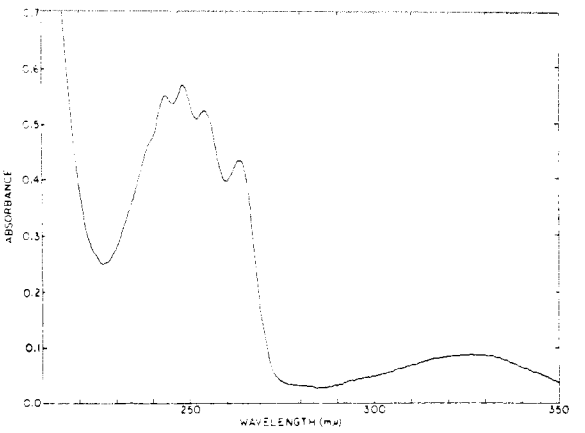


FIGURE 1: Ultraviolet absorption spectrum of 2-solanesyl-1,4-naphthoquinone in isooctane.

These "2-desmethyl" derivatives of vitamin K have greater biochemical interest than just the direct observations of their existence in nature. The ring-methyl group between a carbonyl and an isoprenoid side chain is a structural feature common to vitamin K, vitamin E, and coenzyme Q. This methyl group is necessary for the biochemical mechanisms that have been proposed and that are dependent upon a quinone-methine functionality (Moore *et al.*, 1964; Lederer, 1964). While plastoquinone also lacks a methyl group of this orientation, it does have a 5-methyl group. The "2-desmethyl" derivatives of vitamin K_2 cannot participate in such a quinone-methine mechanism, but they can be fully functional in just electron transfer mechanisms. The dermal toxicity of the lowest isoprenolog (n = 1, compound VI) is provocative in view of the overall biochemistry of isoprenoid quinones.

Experimental

After several exploratory experiments to find a suit-

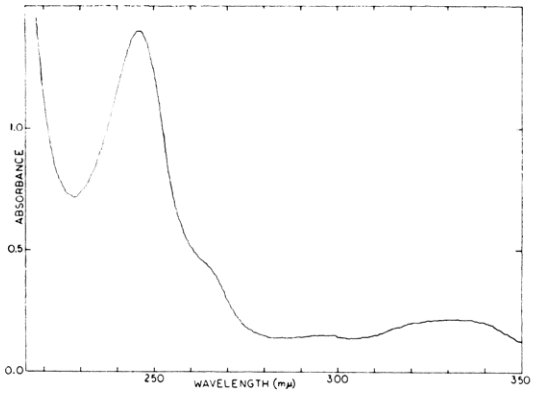


FIGURE 2: Ultraviolet absorption spectrum of 2-solanesyl-1,4-naphthoquinone in absolute ethanol and sodium hydride.

able ratio of solanesol and the hydroquinone as reactants, it was found that about a 2-fold excess of the hydroquinone was effective. Ratios closer to 1:1 yielded the 2,3-disolanesyl-1,4-naphthohydroquinone as evidenced by thin-layer chromatography. In one such experiment, it was found that the NMR spectrum of an eluted thin-layer chromatography spot supported the interpretation of the formation of the disolanesyl derivative.

In other exploratory experiments on the synthesis of the 2-solanesyl derivative, it was found that the products revealed some cyclization of the isoprenoid side chain. It appeared that cyclization of the isoprenoid side chain was minimized or eliminated when very anhydrous solanesol was used, and when acid conditions were avoided during the purification of the 2-solanesyl-1,4-naphthoquinone or its hydroquinone.

2-Solanesyl-1,4-naphthohydroquinone. A solution of 0.8 g (0.005 mmole) of 1,4-naphthohydroquinone, 20 ml of dioxane (freshly distilled from sodium), and 1.26 g of solanesol (0.002 mmole) was stirred at room temperature in a 100-ml, 3-necked flask. After dry nitrogen was passed through the solution, 0.4 ml of freshly distilled BF_3 etherate in 2 ml of dioxane was added over a period of 30 minutes. The reaction mixture was heated at 40–50° for 3 hours. During this time, the reaction was followed by thin-layer chromatography on silica gel G in a solvent of 20% ether in *n*-hexane. At the end of the 3-hour period, no solanesol could be detected on the thin-layer chromatograms by development with 2% aqueous potassium permanganate solution. Development of the plates with the Emmerie-Engel reagent (sensitive to easily oxidizable compounds) showed one major spot with an R_F value of 0.16. The reaction solution was cooled to room temperature, poured into 200 ml of 2% aqueous potassium hydroxide solution containing 10 g of $Na_2S_2O_4$, and then extracted with 2 volumes of diethyl ether. After extraction, the ether layer was separated and washed with 2% potassium hydroxide containing an excess of sodium hydrosulfite and then with distilled water. The ether solution was dried over anhydrous sodium sulfate and then concentrated *in vacuo* to yield a viscous light-yellow oil; yield, 1.5 g. Further purification of the hydroquinone was not undertaken because of the ease of atmospheric oxidation of the hydroquinone to the quinone.

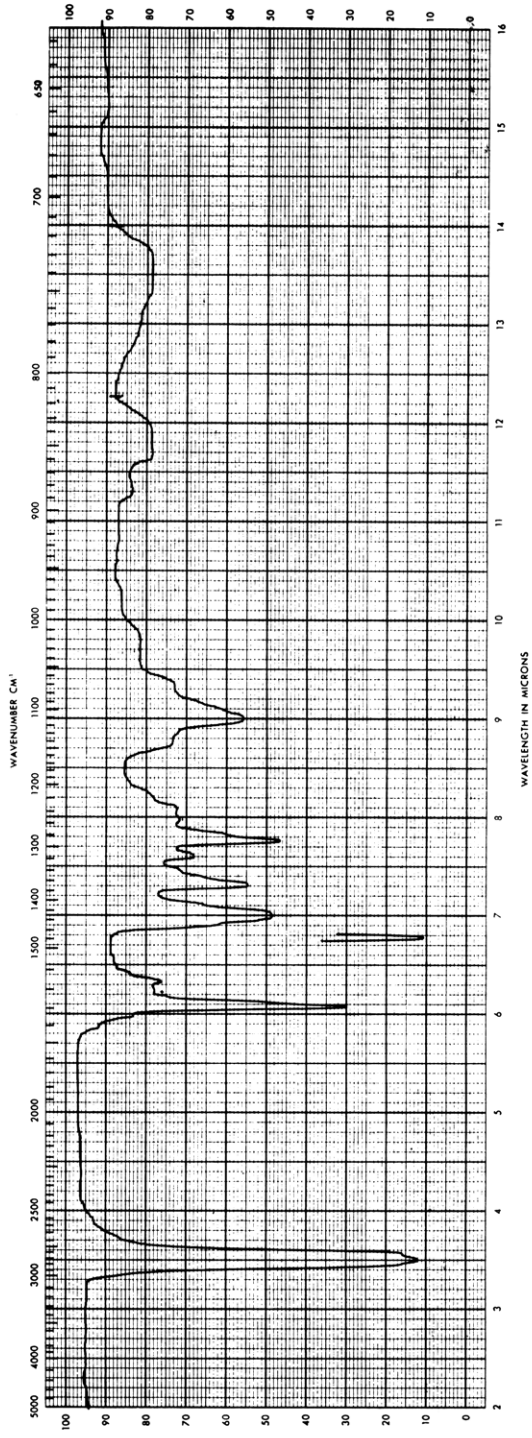


FIGURE 3: Infrared absorption spectrum of 2-solanesyl-1,4-naphthoquinone in carbon tetrachloride.

2-Solanesyl-1,4-naphthoquinone. The hydroquinone (1.50 g) was dissolved in 100 ml of diethyl ether. Silver oxide (2 g) was added and the suspenslon was stirred at room temperature for 1 hour. Thin-layer chromatog-

raphy on silica gel G (5% ether in *n*-hexane) showed that the oxidation was complete. The chromatogram showed the disappearance of the spot corresponding to the hydroquinone (R_F = 0.1) and the appearance of a yellow spot with R_F = 0.25 corresponding to the quinone. The reaction mixture was filtered and concentrated *in vacuo* to yield a viscous yellow oil (1.500 g). The crude product (0.600 g) was dissolved in freshly distilled hexane and chromatographed through a column of silica gel (2 × 25 cm). The column was first developed with *n*-hexane (250 ml) to elute a yellow-brown oil containing no quinone. The major product was eluted with 3% ether in *n*-hexane. The fractions containing the quinone were concentrated *in vacuo* to yield 2-solanesyl-1,4-naphthoquinone as a yellow oil (0.420 g, 65% yield, based upon solanesol) which crystallized after one day at 0°. An analytical sample was prepared by crystallization from absolute ethanol: yellow crystals, mp 42–44°. The spectral (NMR, infrared, and ultraviolet) and chromatographic data are reported in Tables I, II, III, IV, and V, and Figures 1, 2, and 3.

TABLE II: Infrared Spectra.[a]

2-Phytyl-1,4-naphthoquinone	2959 (s); 1664 (s); 1626; 1600; 1471; 1379; 1333; 1307; 1271; 1250; 1149–1105; 950–920
2-Solanesyl-1,4-naphthoquinone	2950 (s); 1664 (s); 1627; 1608; 1449; 1387; 1332; 1271; 1248; 1124; 890; 865–840

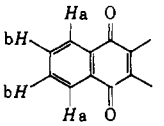
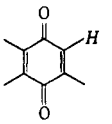
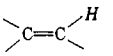
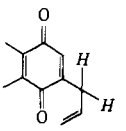
[a] Infrared spectra were run in CCl_4 solutions on a Beckman Infrared 5A spectrophotometer. s = strong band.

Anal. Calcd for $C_{55}H_{78}O_2$: C, 85.64; H, 10.17. Found: C, 85.37; H, 10.19.

2-Phytyl-1,4-naphthohydroquinone. This substance was prepared differently from the known procedure (Fieser *et al.*, 1940a,b). 1,4-Naphthohydroquinone, 7.1 g (0.044 mole), and 9.8 g (0.033 mole) of phytol were dissolved in 60 ml of dioxane (freshly distilled from sodium) and placed in a flask under nitrogen. BF_3 etherate (7 ml; freshly distilled) in 10 ml of dioxane was added dropwise over a 1-hour period. The mixture was heated at 45° for 3 hours and then stirred overnight at room temperature. The reaction mixture was poured into a separatory funnel and 2 volumes of ether were added. The ether solution was first washed with water, then with 2% potassium hydroxide containing an excess of sodium hydrosulfite (the 2-phytyl-1,4-naphthohydroquinone is not extracted from the ether solution even with 10% aqueous alkali). The ether layer was then washed with water, dried over anhydrous sodium sulfate, and finally concentrated *in vacuo*. The crude hydroquinone obtained was a yellow oil (15 g), very easily oxidized by air.

2-Phytyl-1,4-naphthoquinone. The crude hydroquinone (15 g) was oxidized to the quinone with silver oxide (20 g) in ether by stirring at room temperature for 1 hour. Thin-layer chromatography on silica gel G (5% ether in *n*-hexane) showed that the oxidation was complete. The chromatogram showed the disappearance of the spot corresponding to the hydroquinone (R_F = 0.1) and the appearance of a yellow spot at R_F = 0.24 corresponding to the quinone. The reaction mixture was filtered and concentrated *in vacuo* to yield a viscous dark-brown oil (15 g). The crude quinone (0.1 g) was purified by preparative thin-layer chromatography (silica gel G plates using 5% ether in *n*-hexane as de-

TABLE III: NMR Spectra.[a]

	2-Phytyl-1,4-naphthoquinone	2-Solanesyl-1,4-naphthoquinone
	(a) 2.00 m (2) (b) 2.30 m (2)	(a) 2.05 m (2) (b) 2.36 m (2)
	3.36 t (1)	3.40 t (1)
	4.80 t (1)	4.95 b (9)
	6.72 d (2)	6.73 d (2)
CH_3 | $—CH—$	8.05 m (3)	
$=C—CH_2—CH_2—C=$		8.03 (32)
CH_3 |		8.30 8.40 (30)
$=C—$	8.38 s (3)	
Saturated $—CH_2—$	8.85	
Saturated $—CH_3—$	9.20 (30)	

[a] NMR spectra were run on CCl_4 solutions with tetramethylsilane as internal reference using a Varian Associates HR-60 spectrometer. s = singlet, d = doublet, t = triplet, m = multiplet, b = broad. The number in ( ) is the number of protons. Chemical shifts in τ.

TABLE IV: R_F Values on Thin-Layer Chromatography.[a]

	Benzene	1% Methanol in Benzene	30% Ether in Isooctane	Chloroform	50% Benzene in Chloroform
2-Phytyl-1,4-naphthoquinone	0.47	0.57	0.51	0.46	0.40
2-Solanesyl-1,4-naphthoquinone	0.52	0.63	0.52	0.47	0.43
Vitamin K_1	0.46	0.56	0.50	0.45	0.39
Plastoquinone 45	0.55	0.62	0.61	0.48	0.44
Coenzyme Q_{10}	0.17	0.49	0.34	0.18	0.14

[a] Chromatography carried out on 0.3-mm silica gel G plates.

TABLE V: R_F Values on Paper Chromatography.[a]

	20% Water in 1-Propanol	95% Methanol, 5% Water, 0.1% Acetic Acid
2-Phytyl-1,4-naphthoquinone	0.71	0.12
2-Solanesyl-1,4-naphthoquinone	0.31	0.01
Vitamin K_1	0.68	0.10
2,3,6-Trimethyl-5-solanesyl-1,4-benzoquinone	0.28	0.01
Plastoquinone 45	0.29	0.01
Coenzyme Q_{10}	0.33	0.01

[a] Reverse-phase chromatography carried out on 5% silicon-impregnated paper (Lester and Ramasarma, 1959).

veloping solvent) to yield pure 2-phytyl-1,4-naphthoquinone (0.065 g, 65% yield, based upon phytol) as a yellow oil. Spectral (NMR, infrared, and ultraviolet) and chromatographic data are reported in Tables I, II, III, IV, and V.

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