

axes. In the latter instance the central 1.54  $\mu$  component of the band was practically absent.

It is interesting to observe that this 1.54  $\mu$  component was also absent when a specimen of un-oriented, *mercerized* fibers was studied with unpolarized light. Mercerization of cellulose was accomplished by treating the material for about thirty minutes with 20% sodium hydroxide, washing thoroughly with distilled water, washing with very dilute acetic acid and then repeating the washing process with distilled water. This material was then dried and immersed in a mixture of carbon disulfide and carbon tetrachloride of the proper refractive index. It has been demonstrated by means of the X-ray analysis of this mercerized material<sup>1,2</sup> that a shift in the natural arrangement of the cellulose chains occurs. This movement produces no alteration in the *b* axial dimension but changes both *a* and *c*. This may be interpreted as a shifting of the cellulose chains with respect to one another parallel to the fiber axis with a probable rearrangement in the hydrogen bridging. The observations that the 1.54  $\mu$  band is present when *E* is parallel to the axis but not when it is perpendicular to it and that it disappears upon mercerization indicate that certain OH groups having orientations in the direction of the axis are released from hydrogen bridging upon mercerization. In general, it may be stated that mercerization results in an increase in the absorption representing the least amount of perturbation.

(13) O. L. Sponsler and W. H. Dore, THIS JOURNAL, **60**, 1940 (1928).

In the 2  $\mu$  region of the spectrum of unmercerized Ramie the absence of a sharp band at 2.02  $\mu$  and the presence of a broad one at 2.11  $\mu$  confirm the conclusion that all, or practically all, of the OH groups in the natural condition are involved in hydrogen bridges. The diminution in the magnitude of the average perturbation upon mercerization is shown again by a shift of the 2.11  $\mu$  band to 2.09  $\mu$ .

As an example of naturally occurring cellulose obtained from another source a packet of dried wall material from the large alga, *Valonia*, was studied with unpolarized light. The spectrum obtained in this instance was very similar to that for unoriented ramie fibers.

### Summary

Observations of absorption bands characteristic of hydroxyl groups in the region 1.5 and 2.0  $\mu$  have been made for cellulose. The extreme weakness of the band at 1.44  $\mu$  and the failure to detect a band at 2.02  $\mu$  indicate that in natural cellulose fibers relatively few "unperturbed" hydroxyl groups are present. The shifts toward longer wave lengths in the absorption bands in these two regions indicate the presence of OH vibrators which are perturbed through hydrogen bridging. However, in the natural arrangement of these extremely large molecules it appears that intermediate conditions of perturbation occur, corresponding to hydrogen bridges of variable distances and variable bond angles between the hydroxyl groups of the adjacent cellulose chains.

Los ANGELES, CALIF.

RECEIVED JUNE 21, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HARVARD UNIVERSITY, AND THE RESEARCH LABORATORIES, MERCK AND CO., INC.]

## Extensions of the Vitamin K<sub>1</sub> Synthesis

By LOUIS F. FIESER, MAX TISHLER AND NORMAN L. WENDLER

A preliminary account has been given<sup>1</sup> of the synthetic experiments presented in this paper and of some of the assays for antihemorrhagic activity conducted by W. L. Sampson of the Merck Institute for Therapeutic Research. A full report of the biological experiments will be published elsewhere.

Variations in the synthetic method developed for the preparation of vitamin K<sub>1</sub><sup>2</sup> hitherto have

been concerned chiefly with the use of a series of  $\beta$ -unsaturated alcohols and dienes for condensation with a given type of phenolic component,<sup>2,3</sup> and with the employment of various condensing agents (oxalic,<sup>2</sup> trichloroacetic,<sup>2</sup> phosphoric<sup>4</sup> and acetic<sup>5</sup> acids, heat<sup>6</sup>). Phytol, geraniol, and cinnamyl alcohol react much more readily than allyl or benzyl alcohol and at least as well as 2,3-

(3) Fieser, Campbell, Fry and Gates, *ibid.*, **61**, 3216 (1939).

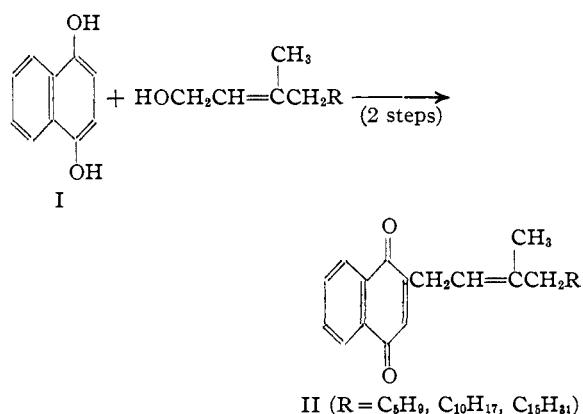
(4) Fieser, *J. Biol. Chem.*, **133**, 391 (1940).

(5) Tishler, Fieser and Wendler, THIS JOURNAL, **62**, 1982 (1940).

(1) Fieser, Tishler and Sampson, THIS JOURNAL, **62**, 996 (1940).  
(2) Fieser, *ibid.*, **61**, 3467 (1939).

dimethylbutadiene, the most reactive of the hydrocarbons tried. Farnesol likewise can be employed satisfactorily, and 2-methyl-3-farnesyl-1,4-naphthoquinone has now been added to the series of compounds of the vitamin K type. The only phenolic components previously studied are the 2-methyl, 2-ethyl, and 2,6-dimethyl derivatives of 1,4-naphthohydroquinone. With the object of exploring the limits of the reaction and of gaining further information on the relationship of vitamin K activity and structure, we have now extended the study to other types.

In the presence of dioxane and oxalic acid 1,4-naphthohydroquinone (I) condenses with phytol, farnesol, or geraniol more readily than does the 2-methyl derivative, for the reactions can be conducted at a somewhat lower temperature.

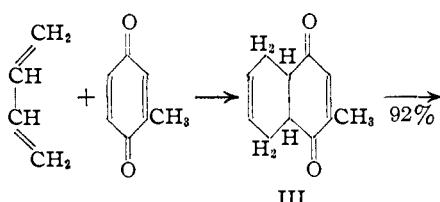


The yields are also better, that of 2-phytyl-1,4-naphthoquinone being 45% (based on phytol), and that of the 2-geranyl compound being 49% (based on 1,4-naphthohydroquinone), as compared with 29% for vitamin K<sub>1</sub>.<sup>2</sup> The reaction mixture from the condensation of naphthohydroquinone with phytol was examined carefully for the presence of a ketonic by-product comparable with that obtained from methylnaphthohydroquinone<sup>5</sup> but no such substance was found. As already noted,<sup>5</sup> the absence of a by-product and the consequently higher yield accords with the interpretation that the side reaction in the vitamin K<sub>1</sub> synthesis involves attachment of the phytol group at an already substituted position. Such a reaction apparently occurred in an attempt to introduce a second phytol group by heating phytolnaphthohydroquinone with a large excess of phytol for thirty-nine hours at 80°. When the mixture was processed by a method whereby any 2,3-diphytyl-1,4-naphthoquinone present

should have been recovered along with unchanged starting material in the quinone form, the sole product was the pure monophytol compound. The material recovered was only about one-third that used, and since cyclization does not occur to an appreciable extent under the conditions used<sup>5</sup> it is likely that the remainder was largely converted to a ketonic by-product. The failure of the 2-phytyl compound to undergo substitution at the 3-position doubtless is attributable to the steric factor and is in line with the observation that the yields in the condensations using 2-ethyl-1,4-naphthohydroquinone are only about half those obtained with the 2-methyl derivative.<sup>2,3</sup>

The mono-substituted naphthoquinones having a β-unsaturated isoprenoid chain of ten, fifteen or twenty carbon atoms are yellow oils closely resembling vitamin K<sub>1</sub>. It is interesting to note that the corresponding *n*-hexadecyl- and *n*-octadecynaphthoquinones are crystalline solids, m. p. 81 and 85°.<sup>6</sup> As expected, our β-alkenyl compounds give an intense and unusually persistent purple-blue color with alcoholic alkali (Dam-Karrer test)<sup>7</sup> and give the usual Craven test<sup>8</sup> with cyanoacetic ester and ammonia. Karrer and co-workers<sup>9</sup> have reported the synthesis of 2-phytyl-1,4-naphthoquinone by an entirely different method. They note that their substance, which corresponds to ours in chemical and physical properties, probably is not homogeneous with respect to the position of the double bond.

As a further variation, the synthetic condensation reaction has been applied to two hydroquinones having a single aromatic nucleus. One starting material of this nature was obtained from the product of the addition of butadiene to toluquinone,<sup>10</sup> III.



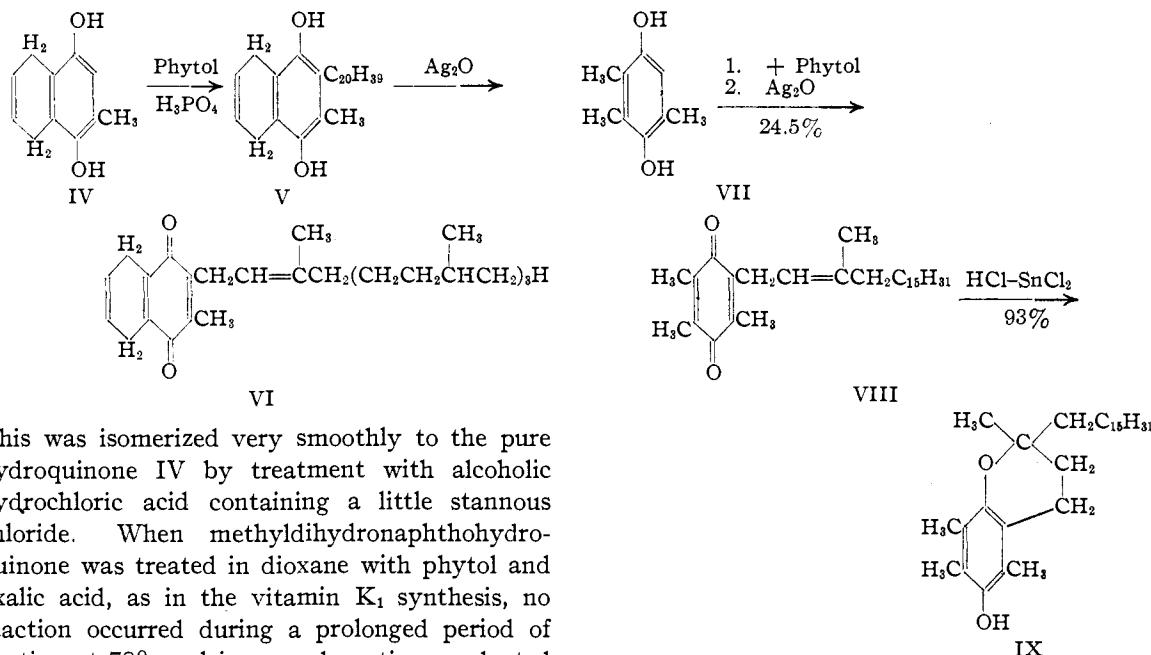
(6) Fernholz, Ansbacher and MacPhillamy, *This Journal*, **62**, 430 (1940).

(7) Dam, Geiger, Glavind, P. Karrer, W. Karrer, Rothschild and Salomon, *Helv. Chim. Acta*, **22**, 310 (1939).

(8) Craven, *J. Chem. Soc.*, 1605 (1931).

(9) Karrer, Geiger, Ruegger and Salomon, *Helv. Chim. Acta*, **22**, 1513 (1939); Karrer, Geiger, Ruegger and Schwab, *ibid.*, **23**, 585 (1940).

(10) I. G. Farbenindustrie, English Patent 324,661 (1930); Chuang and Han, *Ber.*, **68**, 676 (1935).



This was isomerized very smoothly to the pure hydroquinone IV by treatment with alcoholic hydrochloric acid containing a little stannous chloride. When methyldihydronaphthohydroquinone was treated in dioxane with phytol and oxalic acid, as in the vitamin K<sub>1</sub> synthesis, no reaction occurred during a prolonged period of heating at 78°, and in a condensation conducted at the reflux temperature (thirteen hours) the yield of product isolated as the quinone was only 9%. The best yield, obtained using phosphoric acid as the condensing agent and at the reflux temperature (twenty-two hours), was 20%, and it is evident that the dihydride IV is definitely less reactive than the corresponding naphthalenoid component. The substituted hydroquinone V was isolated easily as a pure white solid by centrifugation from petroleum ether, and on oxidation this afforded the quinone VI as a yellow oil. This substance, which may be described as 5,8-dihydrovitamin K<sub>1</sub>, closely resembles the vitamin in all properties except the color test with alcoholic alkali. In an oxygen-free solution the dihydride gives an orange-red color and the transient blue phase characteristic of the vitamin first appears on shaking the solution with air. Very probably the vitamin is formed in the course of the test by a process of enolization and oxidation.

An example of the application of the condensation reaction in the benzohydroquinone series is in the case of 2,3,5-trimethylhydroquinone (VII). This substance, which is structurally analogous to the above dihydride IV, likewise entered into the condensation with phytol somewhat less readily than does methylnaphthohydroquinone. Oxidation of the intermediate hydroquinone, which is a crystalline substance melting at 92°, gave 2,3,5-trimethyl-6-phytyl-1,4-benzoquinone

(VIII) as a pure yellow oil. The quinone showed no blue phase in the Dam-Karrer test and yielded a crystalline hydroquinone diacetate.

Since the trimethylphytylquinone can be purified easily and effectively via the petroleum ether-insoluble hydroquinone, it was of interest to attempt the preparation of α-tocopherol (IX) from this intermediate. As in the naphthoquinone series,<sup>5</sup> treatment of VIII with stannous chloride and hydrochloric acid in acetic acid effects reduction and cyclization very smoothly. The product was identified as α-tocopherol by characteristic tests and through the crystalline allophanate and *p*-nitrophenylurethan.<sup>11</sup>

### Experimental Part<sup>12</sup>

**2-Methyl-3-farnesyl-1,4-naphthoquinone.\***—A small quantity of farnesol supplied by the Paragon Testing Laboratories on two distillations afforded a satisfactory fraction, b. p. 143–146° at 3.7 mm. A solution of 2.84 g. each of the alcohol and 2-methyl-1,4-naphthohydroquinone and 1 g. of anhydrous oxalic acid in 10 cc. of dioxane was heated for thirty-one hours at 78° (ethanol boiler). On working up the mixture in the usual way<sup>2</sup> the substituted hydroquinone was obtained as a colorless solid after three

(11) Subsequent experiments have indicated that the reduction procedure recorded below can be modified to advantage by the use of dioxane as the solvent. The physical and biological properties of the α-tocopherol prepared by the new method, as well as of α-tocoquinone and other derived members of the series, will be reported later.—M. T.

(12) The experiments indicated by the symbol \* were carried out at Harvard (L. F. F.), with microanalyses by Lyon Southworth; those designated † were conducted at the Merck Research Laboratories (M. T. and N. L. W.), with microanalyses by D. Hayman, W. Reiss and H. C. Clark.

washings with petroleum ether and afforded 0.81 g. of the quinone on oxidation. After treatment of the residual oil with alcohol-hydrosulfite and extraction from petroleum ether with Claisen's alkali,<sup>13</sup> a further quantity of white solid was obtained giving 0.21 g. of the quinone (total yield 21%, based on farnesol).

The quinone is a yellow oil resembling vitamin K<sub>1</sub> and with alcoholic alkali in the cold it gives an intense indigo solution fading to dull red (Dam-Karrer test<sup>7</sup>).

*Anal.* Calcd. for C<sub>26</sub>H<sub>32</sub>O<sub>2</sub>: C, 82.94; H, 8.57. Found: C, 82.97; H, 8.98.

**2-Phytol-1,4-naphthoquinone.\***—1,4-Naphthohydroquinone was conveniently prepared starting with the crude α-naphthoquinone obtained by a published procedure.<sup>14</sup> A solution of 10 g. of this material in 300 cc. of ether was clarified with Norit, concentrated to the point of crystallization, and shaken with 15 g. of sodium hydrosulfite in 50 cc. of water. The pale yellow ethereal solution was washed with saturated sodium chloride solution containing a little hydrosulfite, filtered through a layer of magnesium sulfate, evaporated to a paste, and the product was stirred with petroleum ether and collected as a light cream colored powder (7.5 g.).

The best yield in the condensation was obtained using 1.48 g. of phytol, 5 g. of the hydroquinone, 1 g. of oxalic acid, and 15 cc. of dioxane, heated at 60–65° for seventeen hours. Unchanged naphthohydroquinone was removed by extraction of the washed ethereal solution with 2% potassium hydroxide containing hydrosulfite. The phytol-naphthohydroquinone is not extracted from ether even with 10% aqueous alkali; it is considerably more soluble in petroleum ether than vitamin K<sub>1</sub> hydroquinone, but by limiting the amount of solvent and cooling in ice-salt before centrifugation the bulk of the product was separated as a good white solid and this afforded 0.84 g. of quinone on oxidation. Recovery from the mother liquor was not conducted by the most satisfactory procedure but gave 0.15 g. more pure quinone, indicating a yield of at least 45%. It was noted that, on diluting the yellow Claisen's alkali extract of the phytolnaphthohydroquinone under petroleum ether with four volumes of water, the product largely remained in the alkaline layer. To liberate the material it was necessary to neutralize the solution partially with acetic acid, added along with pieces of ice. During these operations it was evident that the 2-phytol compound is more sensitive to oxidation than the 2-methyl-3-phytol derivative.

The quinone was obtained as a yellow oil. In the Dam-Karrer test in the cold the substance gives an intense purple color persisting for about one-half hour before fading to red. The Craven test<sup>8</sup> is positive.

*Anal.* Calcd. for C<sub>26</sub>H<sub>44</sub>O<sub>2</sub>: C, 82.51; H, 10.16. Found: C, 82.48; H, 10.47.

On heating 1.12 g. of 2-phytol-1,4-naphthohydroquinone with 4 g. of phytol and 1 g. of oxalic acid in 15 cc. of dioxane for thirty-nine hours at 80° there was obtained 4.80 g. of light tan oil giving no solid with petroleum ether. After

(13) In this series of experiments (\*) the alkali was made from 25 g. of potassium hydroxide in 25 cc. of water, diluted to 100 cc. with methanol.

(14) Fieser and Fieser, THIS JOURNAL, 57, 491 (1935); Fieser, "Organic Syntheses," Vol. 17, 1937, p. 68.

extraction with Claisen's alkali a white solid was obtained and on oxidation gave 0.38 g. of pure 2-phytol-1,4-naphthoquinone (found: C, 82.82; H, 10.31).

In a test experiment† to determine whether a neutral by-product is formed in the condensation, 13.5 g. of phytol was heated with 27 g. of α-naphthohydroquinone, 8.2 g. of oxalic acid and 120 cc. of dioxane for thirty-four hours at 75°. The initial crop of 2-phytol-1,4-naphthoquinone, isolated as above, amounted to 5 g., and 2 g. more was collected after extraction of the reduced material from petroleum ether with Claisen's alkali, dilution of the extract with twelve volumes of 2% sodium hydrosulfite solution in the presence of petroleum ether, and oxidation of the solid deposited from this solvent. The neutral solution remaining after extraction with Claisen's alkali was washed, dried and concentrated. On distillation at 10<sup>-4</sup> mm. practically all of the residue came over below 90° (inside temperature) as a mobile liquid (4 cc.) of refractive index indicating a mixture of phytadiene containing a little phytol. The residue (about 0.7 cc.) darkened considerably when heated further and did not distil up to 150°. Evidently no substance comparable with the vitamin K<sub>1</sub> by-product was present.

**2-Geranyl-1,4-naphthoquinone\*** was prepared best in a condensation conducted as above for forty-one hours at 66° (methanol boiler) but using an excess of geraniol (4 g. for 2.77 g. of α-naphthohydroquinone). After removal of the starting hydroquinone with 2% alkali the substituted hydroquinone can be extracted with 10% alkali, but a large volume is required. In the experiment cited the bulk of the product (1.78 g., as quinone) was collected by treatment with petroleum ether at –13° (very voluminous white precipitate) and the remainder was obtained after treatment with aqueous hydrosulfite-alkali by extraction with Claisen's alkali. The quinone was obtained as a mobile yellow oil giving an intense and persistent Dam-Karrer test; the total yield was 2.48 g. (49% based on the hydroquinone).

*Anal.* Calcd. for C<sub>26</sub>H<sub>32</sub>O<sub>2</sub>: C, 81.59; H, 7.53. Found: C, 81.60; H, 7.88.

**2-Farnesyl-1,4-naphthoquinone.\***—From 6 g. each of 1,4-naphthohydroquinone and farnesol, 4.8 g. of oxalic acid and 30 cc. of dioxane, heated for thirty-one hours at 66°, there was obtained after a reduction operation, extraction with Claisen's alkali from petroleum ether, and centrifugation from a very small volume of this solvent cooled to –15°, 1.26 g. (13%) of colorless farnesylnaphthohydroquinone as a waxy solid. The mother liquor gave a strong Dam-Karrer test, indicating the presence of more material, but this was not recovered. Oxidation afforded a yellow oil resembling the phytol compound in properties.

*Anal.* Calcd. for C<sub>26</sub>H<sub>30</sub>O<sub>2</sub>: C, 82.83; H, 8.34. Found: C, 82.40; H, 8.61.

**2-Methyl-3-phytol-5,8-dihydro-1,4-naphthoquinone.\***—The starting material was prepared by heating 15 g. of toluquinone with 10 g. of butadiene and 15 cc. of benzene at 70° for six hours, taking up the product in ether, clarifying and concentrating the solution, and adding ligroin. On cooling, butadiene-toluquinone<sup>10</sup> crystallized in the form of faintly yellow needles, m. p. 80–81°; yield 14.7 g. (68%, the mother liquor contained toluquinone). For isomerization to 2-methyl-5,8-dihydro-1,4-

naphthohydroquinone 13 g. of the addition product was dissolved in 50 cc. of alcohol and the yellow solution treated with a solution of 0.5 g. of stannous chloride and 3 cc. of concentrated hydrochloric acid in 10 cc. of water and heated on the steam-bath for about twenty minutes, when the solution had become completely colorless. Water was added to the point of saturation and on cooling the product separated as a pure white microcrystalline powder, m. p. 173–174° with darkening at 170°; yield 11.9 g. (92%). The substance gives a positive Craven's test on shaking the solution with air; the diene addition product gives the same coloration more slowly, while toluquinone instantly gives an intense blue solution.

In trial experiments 1.48 g. of phytol was heated with 2 g. of 2-methyl-5,8-dihydro-1,4-naphthohydroquinone or of butadiene-toluquinone in the presence of various condensing agents and solvents. Using oxalic acid (1 g.) and dioxane (10 cc.) no reaction was observed after forty-two hours at 78°, but after refluxing such a mixture for thirteen hours the pure phytol-substituted quinone (5,8-dihydrovitamin K<sub>1</sub>) was obtained in 9% yield. On replacing the oxalic acid by 1 cc. of 85% phosphoric acid and refluxing for twenty-two hours the yield was 20% (0.45 g.). When concentrated hydrochloric acid (1 cc.) was added to a solution of the components in dioxane (10 cc.) the mixture separated into two layers. In trials conducted at 66° the yield was 15% after heating for thirty-six hours without stirring and 17% after stirring for fifty hours. A homogeneous solution resulted on using 1 cc. of concentrated hydrochloric acid, 10 cc. of acetic acid, and 3 cc. of dioxane but in this case after heating at 91° for four hours only a trace of the substituted hydroquinone was formed, although nearly the theoretical amount of starting hydroquinone was consumed.

The working up of the reaction mixtures was conducted in the usual way.<sup>2</sup> Unused methyldihydronaphthohydroquinone was recovered in good yield and purity from either starting material and the substituted hydroquinone was obtained easily as a pure white solid from petroleum ether. 5,8-Dihydrovitamin K<sub>1</sub> was obtained on oxidation as a pure yellow oil closely resembling the vitamin but giving a somewhat more intensely yellow solution in ether.

*Anal.* Calcd. for C<sub>31</sub>H<sub>46</sub>O<sub>2</sub>: C, 82.24; H, 10.69. Found: C, 82.27; H, 10.86.

When an oxygen-free alcoholic solution of the quinone is treated in the cold with an equal volume of 10% alcoholic potassium hydroxide the solution soon acquires an orange-red color (no blue), and on shaking with air this changes at once to a deep indigo blue soon fading to dull red.

**2,3,5-Trimethyl-6-phytyl-1,4-benzoquinone.**†—A solution of 15 g. of 2,3,5-trimethylhydroquinone, 4.5 g. of phytol and 3.5 g. of anhydrous oxalic acid in 45 cc. of dioxane was heated at 75° for thirty-four hours and the reaction mixture was processed as in the vitamin K<sub>1</sub> synthesis. The trimethylphytylhydroquinone is a colorless crystalline substance melting at 92°. The yield of pure quinone, obtained as a rather mobile, pure yellow oil, was 1.6 g. (24.5%).

*Anal.* Calcd. for C<sub>32</sub>H<sub>48</sub>O<sub>2</sub>: C, 81.24; H, 11.22. Found: C, 81.04; H, 11.00.

The substance gives no purple-blue color in the Dam-Karrer test with alcoholic alkali (brownish solution). In a

trial reaction conducted as above but at the reflux temperature for three hours no product was obtained.

The hydroquinone diacetate, prepared by reductive acetylation using pyridine, formed small colorless needles, m. p. 56°.

*Anal.* Calcd. for C<sub>33</sub>H<sub>56</sub>O<sub>4</sub>: C, 77.04; H, 10.51. Found: C, 76.95; H, 10.37.

**α-Tocopherol.**†—A mixture of 7 g. of the above quinone, 14 g. of stannous chloride, 7 cc. of concentrated hydrochloric acid and 70 cc. of acetic acid was refluxed for six hours and the resulting faintly yellow solution was poured onto ice water. The product was extracted with petroleum ether and the solution was washed repeatedly with water and with sodium bicarbonate solution, dried and evaporated. Distillation from a pot still at 10<sup>-5</sup> mm. and a liquid temperature of 145° gave 6.5 g. of a colorless, viscous liquid.

*Anal.* Calcd. for C<sub>29</sub>H<sub>50</sub>O<sub>2</sub>: C, 80.89; H, 11.73. Found: C, 80.72, 80.73; H, 11.66, 11.85.

The substance reduced alcoholic silver nitrate solution in the cold, gave a positive Furter-Meyer test, and yielded an allophanate, m. p. 175–176°, and a *p*-nitrophenylurethan derivative, m. p. 130°. For these derivatives Karrer, et al.,<sup>16</sup> report the m. p. 172° and 131°, respectively. A mixture of the former substance with an authentic sample of the allophanate of synthetic α-tocopherol<sup>16</sup> showed no depression in m. p.

**2,3,5 - Trimethyl - 6 - dihydrophytyl - 1,4 - benzoquinone.**†—On shaking 1 g. of the unsaturated quinone in 10 cc. of methanol with 0.1 g. of palladium chloride, the calculated amount of hydrogen (2 moles) was absorbed in about one and one-half hours. The solution was filtered, diluted with water, and extracted with petroleum ether (15 cc.). A waxy solid appeared in the organic layer and, after chilling, this was collected and washed by centrifugation. Oxidation in dry ether with silver oxide in the presence of magnesium sulfate gave 0.88 g. of a golden yellow oil.

*Anal.* Calcd. for C<sub>28</sub>H<sub>48</sub>O<sub>2</sub>: C, 80.93; H, 11.63. Found: C, 80.92; H, 11.39.

The hydroquinone diacetate formed fluffy needles from alcohol which melted at 54–55°.

*Anal.* Calcd. for C<sub>33</sub>H<sub>56</sub>O<sub>4</sub>: C, 76.69; H, 10.93. Found: C, 76.69; H, 11.28.

### Summary

α-Naphthohydroquinone reacts readily with phytol, farnesol or geraniol in the presence of a mild acid catalyst with the formation in good yield of the monoalkenylnaphthohydroquinone. This can be isolated as a solid and converted into the corresponding 2-β-alkenyl-1,4-naphthoquinone. The synthetic reaction, however, is not applicable to the introduction of large isoprenoid groups at both the 2 and the 3 positions.

The condensation can be realized with phenolic

(15) Karrer, Fritzsche, Ringier and Salomon, *Helv. Chim. Acta*, **21**, 520 (1938).

(16) Smith, Ugnade, Stevens and Christman, *THIS JOURNAL*, **61**, 2615 (1939).

components containing a benzohydroquinone nucleus, although such substances are less reactive than the compounds of the naphthalene series and the yields are lower. 5,8-Dihydrovitamin K<sub>1</sub> and 2,3,5-trimethyl-6-phytyl-1,4-benzoquinone

have been prepared by the standard synthesis and the latter substance has been utilized in a new synthesis of  $\alpha$ -tocopherol.

CAMBRIDGE, MASSACHUSETTS  
RAHWAY, NEW JERSEY

RECEIVED AUGUST 10, 1940

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK AND CO., INC., AND THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

## Hydro, Oxido and Other Derivatives of Vitamin K<sub>1</sub> and Related Compounds

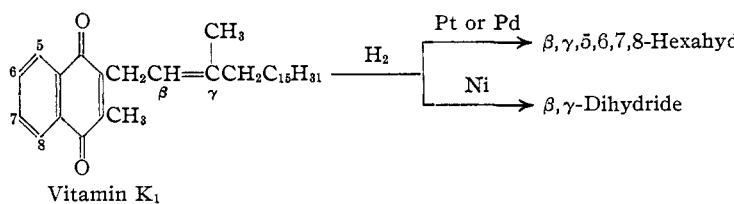
By MAX TISHLER, LOUIS F. FIESER AND NORMAN L. WENDLER

This paper presents the details of preparative work which has been reported briefly in part in recent Communications.<sup>1</sup> The more significant findings concerning the biological activities of the compounds have been indicated in these preliminary reports and the complete assay data will be presented later.

One series of experiments was concerned with the preparation of various hydro derivatives. Doisy and co-workers<sup>2</sup> found that on hydrogenation of vitamin K<sub>1</sub> in a mixture of acetic acid and *n*-butyl ether in the presence of platinum catalyst the reaction proceeds readily to the stage of absorption of four moles of hydrogen. In the present work trial hydrogenations were conducted in various solvents with platinum and palladium catalysts in the search for conditions under which the reaction would stop after reduction of the quinone to the hydroquinone and the saturation of the double bond in the side chain, but the absorption of gas proceeded without noticeable break to the four-mole stage. The hydroquinone produced as the end-product of the reaction was separated, as in the vitamin K<sub>1</sub> synthesis, by virtue of its sparing solubility in petroleum ether

talline hydroquinone diacetate. The preparation of the quinone by a similar method has been described also by Fernholz, MacPhillamy and Ansbacher.<sup>3</sup> When Raney nickel was used as catalyst in combination with methanol as solvent there was a sharp drop in the rate of hydrogenation after the absorption of two moles of gas. Purification was again accomplished through the solid hydroquinone produced, and after oxidation with silver oxide there was obtained a yellow oil which appears to be pure  $\beta,\gamma$ -dihydrovitamin K<sub>1</sub>, or 2-methyl-3-dihydrophytyl-1,4-naphthoquinone. In contrast to the isomeric 5,8-dihydrovitamin K<sub>1</sub>,<sup>4</sup> the quinone gives no blue color with alcoholic alkali in the presence of air. The preparation of the  $\beta,\gamma$ -dihydride by a longer synthesis has been reported by Karrer and Epprecht,<sup>5</sup> who isolated the material from a reaction mixture by chromatographic adsorption. The method of hydrogenation in the presence of Raney nickel and purification of the product in the hydroquinone form has been applied also to the conversion of 2-phytyl-1,4-naphthoquinone into the 2-dihydrophytyl compound. In the case of 2-methyl-3-cinnamyl-1,4-naphthoquinone hydrogenation in the presence of nickel failed to proceed beyond saturation of the quinone grouping, but the  $\beta,\gamma$ -dihydride was obtained satisfactorily using palladium chloride.

The biologically interesting oxido derivatives of several naphthoquinones possessing antihemorrhagic activity were prepared easily in almost quantitative yield by treatment of the quinone in alcohol or dioxane



and oxidized to  $\beta,\gamma,5,6,7,8$ -hexahydro-vitamin K<sub>1</sub>, which was obtained as a yellow oil giving a negative Dam-Karrer color test and affording a crys-

(1) Fieser, Tishler and Sampson, THIS JOURNAL, **62**, 996, 1628 (1940); Tishler, Fieser and Sampson, *ibid.*, **62**, 1881 (1940).

(2) Binkley, MacCorquodale, Thayer and Doisy, *J. Biol. Chem.*, **130**, 219 (1939).

(3) Fernholz, MacPhillamy and Ansbacher, THIS JOURNAL, **62**, 1619 (1940).

(4) Fieser, Tishler and Wendler, *ibid.*, **62**, 2861 (1940).

(5) Karrer and Epprecht, *Helv. Chim. Acta*, **23**, 272 (1940).