[CONTRIBUTION FROM THE RESEARCH LABORATORIES, CHEMICAL DIVISION, MERCK & CO., INC.]

The Synthesis of Vitamin K_1[1]

BY RALPH HIRSCHMANN, RICHARD MILLER AND N. L. WENDLER

RECEIVED APRIL 10, 1954

A method has been devised which makes possible the unidirectional condensation of phytol with 2-methyl-1,4-naphthohydroquinone monoacetate to give vitamin K_1 in about 65% yield.

The synthesis of vitamin K_1 was first reported in 1939.[2] During the ensuing period of nearly 15 years little improvement over these original announcements has appeared; consequently the method of Fieser[2a] has, in essence, remained until now the most practical synthetic route to this substance.[3]

The method of Fieser[2a] consists in the oxalic acid-catalyzed condensation of phytol (I) with 2-methyl-1,4-naphthohydroquinone (II) in dioxane solution at 75° for 36 hours. The immediate reaction product, dihydro K_1 (III), is purified as a petroleum ether-insoluble semi-solid and subsequently oxidized with silver oxide to vitamin K_1 (IV) in an over-all yield of 25–30%. By-products isolated from this synthesis include phytadiene (V) (see below) and substantial amounts of the isomeric condensation product 2-methyl-2-phytyl-2,3-dihydro-1,4-naphthoquinone (VI).[4]

The present study was undertaken with the aim of improving the yield in the synthesis of vitamin K_1 by obviating, if possible, the competitive formation of the isomeric by-product VI, which is formed in nearly equal amount with dihydro K_1 (III) in the Fieser synthesis.[4] It had, furthermore, been previously ascertained by us that phytol, contrary to implied literature reports,[5] does not form phytadiene on treatment with oxalic acid at 75° or even at 100° but gives instead phytyl oxalate (VII). The actual formation of phytadiene by this reaction arises from the distillation purification which amounts in effect to a cracking reaction of phytyl oxalate → phytadiene. In view of these observations we were likewise interested in investigating the action of acid catalysts which would be less prone to esterify with phytol.[6]

Phytylation at position 2 of 2-methyl-1,4-naphthohydroquinone to form the isomeric by-product (VI)[4] was found to be blocked effectively by converting the hydroquinone to its 1-monoacetate derivative IIa.[7] The latter derivative when allowed to react with phytol in dioxane solution at 76° in the presence of potassium acid sulfate was found to undergo condensation at a rate far exceeding that of the oxalic acid-catalyzed condensation of phytol with 2-methyl-1,4-naphthohydroquinone (II). The greater rate of reaction in this case can be attributed to the change of catalyst and not to the alteration of the aromatic component. This was demonstrated by observing that phytylation of the monoacetate derivative IIa according to the method of Fieser, employing *oxalic acid* at 76° for 36 hours, gave the desired product in only small yield. Despite the reduction in reaction time from 36 hours to 80 minutes by the use of potassium acid sulfate, the expected condensation to give vitamin K_1 occurred in over 50% yield.[8] The isolation of vitamin K_1 from this synthetic preparation consisted in the initial precipitation of unchanged monoacetate IIa with petroleum ether and subsequent extraction of the dihydro vitamin K_1 monoacetate with Claisen alkali. The precipitation of unreacted monoacetate IIa with petroleum ether was made possible by the fact that dihydro K_1 monoacetate (IIIa), unlike dihydro K_1,[2a] is soluble in this solvent. Last traces of IIa were removed with 2% aqueous potassium hydroxide. Since dihydro K_1 monoacetate is more resistant to air-oxidation than is dihydro K_1 itself, no reduction step (see ref. 2a) is necessary prior to extraction with Claisen alkali. The latter operation not only accomplishes separation of the dihydro vitamin from neutral impurities but also effects subsequent hydrolysis of the ester function at position 1. The solubility of IIIa in Claisen alkali is noteworthy in view of the insolubility of naphthotocopherol (VIII) in this reagent. The dihydro vitamin K_1, moreover, which is obtained in this way from the Claisen-alkali extraction, is sufficiently pure for direct oxidation to vitamin K_1; consequently the tedious purification procedure of previous practice[2a] involving the centrifugal separation of III can be totally dispensed with.

In view of the low solubility of potassium acid sulfate in dioxane ($\leqq$0.1–0.2 mg./cc.) at 76°, the effective catalysis of this substance in the vitamin K_1 condensation appears to be topochemical. Support for this view was gained from the finding that under conditions whereby only *minor* amounts of potassium acid sulfate remained in equilibrium with the saturated solution, the condensation correspondingly yielded only minor amounts of dihydro K_1 monoacetate (IIIa) and phytadiene.

(1) Presented in part at the Meeting-in-miniature of the North Jersey Section of the American Chemical Society in Newark, N. J., January 25, 1954.

(2) (a) L. F. Fieser, THIS JOURNAL, **61**, 2559, 3467 (1939); (b) S. B. Binkley, L. C. Cheney, W. F. Holcomb, R. W. McKee, S. A. Thayer, D. W. MacCorquodale and E. A. Doisy, *ibid.*, **61**, 2558 (1939); (c) H. J. Almquist and A. A. Klose, *ibid.*, **61**, 2557 (1939); A. A. Klose and H. J. Almquist, *J. Biol. Chem.*, **132**, 469 (1940); (d) O. Isler, U. S. Patent 2,325,681.

(3) In a recent article O. Isler and K. Doebel (*Helv. Chim. Acta*, **37**, 225 (1954)) describe an improvement in the Fieser synthesis of vitamin K_1 in which a yield increase of about 10% is realized using boron trifluoride instead of oxalic acid as catalyst; see ref. 10.

(4) M. Tishler, L. F. Fieser and N. L. Wendler, THIS JOURNAL, **62**, 1982 (1940).

(5) P. Karrer, H. Simon and E. Zbinden, *Helv. Chim. Acta*, **27**, 317 (1944).

(6) Phytyl oxalate, nonetheless, may serve as a phytylating agent in the Fieser synthesis. Thus we were able to obtain a 24% yield of vitamin K_1 by substituting phytyl oxalate for phytol in the Fieser condensation with 2-methyl-1,4-naphthohydroquinone. Much the same observation appears to have been made by Isler and Doebel with other esters of phytol; see ref. 3.

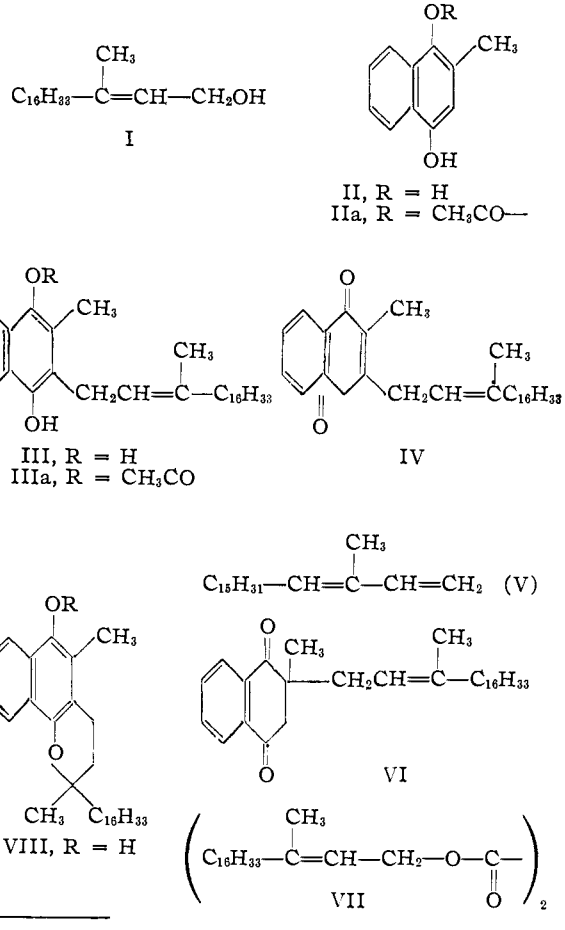
(7) This derivative was first described by B. R. Baker, T. H. Davies, L. McElroy and G. H. Carlson, THIS JOURNAL, **64**, 1096 (1942).

(8) Phytadiene is a by-product in this process.

Furthermore by employing large amounts of the acid exchange resin Duolite C-60[9] as catalyst, the yield of vitamin K_1 from the condensation was again higher than with oxalic acid. The effectiveness of potassium acid sulfate as a catalyst was again evidenced by its role in catalyzing the condensation of the hydroquinone (II) itself with phytol to yield over 40% of vitamin K_1. In the latter instance, however, a significant amount of the isomeric by-product VI also was formed.

The greatly enhanced yields of vitamin K_1 resulting from the employment of 2-methyl-1,4-naphthohydroquinone 1-monoacetate in conjunction with potassium acid sulfate suggested an investigation of the role of various other catalysts. Among those acids tested boron trifluoride proved to be the most efficient; its use in conjunction with the monoacetate IIa resulted in the formation of vitamin K_1 in 66% yield.[10]

Acknowledgment.—The authors are indebted to Mrs. H. Gager, Mrs. A. Bacher and to Messrs. R. Wood and R. Walker for the absorption spectra reported in this paper.



I

II, R = H
IIa, R = CH_3CO—

III, R = H
IIIa, R = CH_3CO

IV

V

VI

VII

VIII, R = H

(9) Obtained from the Chemical Process Co., Redwood City, Calif.

(10) A synthesis of vitamin K_1 involving the reaction of 2-methyl-1,4-naphthohydroquinone (II) and either phytol or isophytol in the presence of boron trifluoride was developed recently by Isler and Doebel (ref. 3); this synthesis was employed by C. C. Lee, F. C. G. Hoskin, L. W. Trevoy, L. B. Jaques and J. W. T. Spinks [*Can. J. Chem.*, **31**, 769 (1953)] for the preparation of C_{14}-labeled vitamin K_1.

Experimental[11]

Vitamin K_1 (IV) from 2-Methyl-1,4-naphthohydroquinone 1-Monoacetate (IIa) and Phytol. (A) Potassium Acid Sulfate as Catalyst.—A mixture of 1.481 g. of phytol, 12.06 g. of the 2-methyl-1,4-naphthohydroquinone 1-monoacetate,[7] 3.02 g. of potassium acid sulfate and 15 cc. of dioxane was heated at 76° for one and one-third hours. The reaction mixture was cooled and the bulk of the catalyst was removed by filtration. After washing with ether the combined filtrates were concentrated *in vacuo* to remove most of the solvents and the residue was triturated with petroleum ether, b.p. 30–60°. The unchanged monoacetate IIa which separated on chilling was removed by filtration and washed with petroleum ether and then with water to afford 10.48 g. of good starting material, m.p. 125–127°; the reported[7] m.p. is 124.5–125.8°.

The mother liquor from the isolation of IIa was extracted with a dilute aqueous potassium hydroxide[12] solution and then with 27 cc. of Claisen alkali[13] containing 3 cc. of a freshly prepared solution of sodium hydrosulfite. The alkaline extract was washed with 20 cc. of petroleum ether in a second separatory funnel. The washed yellow liquor was run into a third separatory funnel containing a previously shaken mixture of 100 cc. of ether and 150 cc. of a 3% aqueous hydrosulfite solution. The dihydrovitamin thus liberated was extracted into the ether layer. The aqueous layer was re-extracted with ether and the combined extract was washed with a saturated salt solution, dried over magnesium sulfate and concentrated to a small volume. The residual ethereal solution of dihydrovitamin K_1 was shaken with magnesium sulfate and with silver oxide for 40 minutes, filtered and concentrated to dryness to give 1.285 g. of vitamin K_1. A 1.220-g. aliquot was dissolved in 8 cc. of a solution of petroleum ether–benzene (19:1), adsorbed on 6.1 g. of Florisil and eluted with the same solvent pair to give 1.081 g. (51%) of a mobile yellow oil,[11,14] $\lambda\lambda_{max}$ 244 mμ (log ϵ 4.27), 248 (4.27), 263 (4.20), 270 (4.22), 328 (3.50), in good agreement with the reported[2,3,14,15] values.

The Claisen alkali-insoluble fraction consisted largely of phytadiene and contained no isomeric by-product (VI) (see below), as indicated by the *infrared* spectrum and by a single absorption maximum in the ultraviolet at 228 mμ (CH_3OH) characteristic of the diene.

(B) Oxalic Acid as Catalyst.—When 1.482 g. of phytol was treated with 6.03 g. of the monoacetate IIa and 1 g. of oxalic acid in 16 cc. of dioxane for 80 minutes essentially as described under (A), the Claisen alkali-soluble fraction after oxidation with silver oxide amounted to less than 0.05 g. of impure vitamin K_1. The unchanged starting material IIa, isolated as described above, weighed 5.67 g., m.p. 125–127°.

(C) Duolite C-60 Cation Exchange Resin as Catalyst.—To a stirred mixture of 10.9 g. of the monoacetate IIa, 3.0 g. of the exchange resin Duolite C-60[9] (on the acid cycle) and 16 cc. of dioxane maintained at 76–78° was added a solution of 1.583 g. of phytol in 4.0 cc. of dioxane over a one-

(11) All m.p.'s were taken on a micro hot-stage and are corrected. All experiments reported were carried out under nitrogen. Ultraviolet absorption spectra of vitamin K_1 were determined by dissolving a *ca.* 0.020-g. sample in 1 cc. of chloroform and diluting this solution 100-fold with methanol. The spectra were measured by a Cary recording spectrophotometer.

(12) In one experiment this solution was acidified with acetic acid and extracted with ether. After drying and evaporating the solvent 2-methyl-1,4-naphthohydroquinone (II) was obtained.

(13) Prepared from 35 g. of potassium hydroxide in 25 cc. of water, diluted to 100 cc. with methanol.

(14) The spectra of vitamin K_1 were determined in alcoholic solution to allow comparison with constants recorded in the earlier literature. Determination of the ultraviolet spectrum in hydrocarbon solvents, however, gave far better resolution and higher extinction values. The spectrum determined with the Cary spectrophotometer revealed a point of inflection at 240 mμ (isoöctane) but not a maximum as reported by Ewing, Tomkins and Kamm.[15] The solvent effect is exemplified by the following data obtained with a representative specimen: (a) in chloroform–methanol (1:100): $\lambda\lambda_{max}$ 245 mμ (log ϵ 4.25), 248 (4.26), 264 (4.19), 271 (4.20), 329 (3.48). (b) The same material in isoöctane solution exhibited $\lambda\lambda_{max}$. 243 mμ (log ϵ 4.25), 248 (4.28), 261 (4.24), 269 (4.24), 325 (3.50), infl. 240 (4.21.)

(15) D. T. Ewing, F. S. Tomkins and O. Kamm, *J. Biol. Chem.*, **147**, 233 (1943).

hour interval. Heating was continued for an additional 20 minutes after the addition was complete. The condensation was worked up essentially as described above (see part A) to afford about 0.20 g. (8% yield) of vitamin K_1. The Claisen alkali-insoluble fraction was essentially unchanged phytol.

(D) **Boron Trifluoride Etherate as Catalyst.**—A solution of 1.481 g. of phytol dissolved in 4 cc. of dioxane was added dropwise over a 30-minute interval to a stirred mixture (maintained at 50°) of 10.9 g. of the monoacylate IIa, 0.27 cc. of boron trifluoride etherate (47%, Matheson, Coleman & Bell, Inc.) and 10 cc. of dioxane. After the addition of the phytol was complete the dropping funnel was rinsed with 2 cc. of dioxane and the stirring at 50° was continued for 25 minutes. The reaction mixture was cooled, diluted with ether and washed free of the catalyst with a 5% solution of sodium bicarbonate. After washing with water and with a saturated salt solution the organic layer was dried over magnesium sulfate and taken to dryness. The isolation of the unchanged starting material and of the vitamin were carried out as described in part A above. In this manner 1.50 g. (66.5% yield) of vitamin K_1 was obtained,[11,14] $\lambda\lambda_{max.}$ 245 mμ (log ε 4.25), 248 (4.26), 264 (4.19), 271 (4.20), 329 (3.48).

Vitamin K_1 (IV) from 2-Methyl-1,4-naphthohydroquinone (II). (A) Potassium Acid Sulfate with Phytol.—A mixture of 10.0 g. of 2-methyl-1,4-naphthohydroquinone, 3.02 g. of powdered potassium acid sulfate, and 1.483 g. of phytol in 16 cc. of dioxane (purified with sodium) was heated in an oil-bath maintained at 76° for one hour and 20 minutes. The reaction mixture was cooled, the catalyst was removed by filtration and washed with ether. The combined filtrate and washings were extracted with successive 50-cc. portions of 2% aqueous potassium hydroxide solution in which sodium hydrosulfite was dissolved just before use. The alkaline layers were collected in a separatory funnel under ether, acidified with glacial acetic acid and extracted into the organic layer. The aqueous layer was extracted with a fresh portion of ether and the total extracts were dried over magnesium sulfate and concentrated to a very small volume. The residual cake was treated with petroleum ether, collected and washed with petroleum ether affording 8.42 g. of II, m.p. about 164–167°, suitable for use in later experiments.

The slightly yellow ethereal solution remaining after extraction with alkali was washed twice with a dilute solution of sodium hydrosulfite and with a saturated salt solution. The solution was concentrated *in vacuo* until most of the ether had been removed when the solution started to turn red. Without delay 50 cc. of petroleum ether (b.p. 30–60°) was added, the mixture was transferred to a separatory funnel and extracted with Claisen alkali as described above. Processing the latter extract in the usual manner gave, after oxidation and Florisil purification, a 42% yield of vitamin K_1,[11,14] $\lambda\lambda_{max.}$ 244 (4.26), 248 (4.27), 263 (4.18), 270 (4.19), 328 (3.50).

The first petroleum ether fraction containing the Claisen alkali-insoluble products was washed free of base, dried over magnesium sulfate and taken to dryness. The residue amounted to 0.997. The infrared spectrum revealed all the characteristic absorption maxima of the isomeric by-product VI as well as an additional peak of 11.2 μ, the best region for the detection of phytadiene (V) in the presence of VI. The ultraviolet absorption spectrum, $\lambda\lambda_{max.}$ 300 mμ ($E^{1\%}_{1cm.}$ 34), 250 (186), 224 (664), is also consistent with the interpretation that this material is a mixture containing mostly the isomeric by-product[16] and some phytadiene.

(B) **Oxalic Acid with Phytyl Oxalate.**—A mixture of 1.994 g. of diphytyl oxalate (VII) (see below), 6.18 g. of 2-methyl-1,4-naphthohydroquinone and 1.24 g. of oxalic acid in 18.6 cc. of dioxane was heated in an oil-bath maintained at 76° for 36 hours. The solution was cooled and washed into a separatory funnel with ether. The unchanged naphthohydroquinone II as well as the desired condensation product III were isolated from the reaction product as described above (see part A). In this manner there was obtained, after oxidation with silver oxide and passage through Florisil, 0.626 g. of vitamin K_1.

Diphytyl Oxalate (VII).—A mixture of 1.0 g. of phytol, $\lambda^{CH_3OH}_{max}$ 226 mμ ($E^{1\%}_{1cm.}$ 50.7) was heated with 0.675 g. of oxalic acid and 10.1 cc. of dioxane at about 75° for 40 hours. The reaction mixture was cooled, diluted with ether and washed free of acid with water. The ethereal solution was dried over magnesium sulfate and evaporated to dryness to afford a yellow oil exhibiting nearly the same amount of diene absorption in the ultraviolet as the starting material. The infrared spectrum indicated the presence of only small amounts of phytol in this sample of diphytyl oxalate; shoulder at 224 mμ ($E^{1\%}_{1cm.}$ 58), $\lambda\lambda^{oil\ film}_{max}$ 5.70 μ, 5.75 μ.

Essentially the same results were obtained when phytol and oxalic acid were heated in dioxane at 100° for four hours as described by Karrer.[5]

Saponification of Diphytyl Oxalate.—A 5.35-g. sample of the ester VII, prepared essentially as described above, was dissolved in a mixture of 180 cc. of methanol and 75 cc. of tetrahydrofuran and the solution was saponified at room temperature with 28 cc. of 2.5 *N* sodium hydroxide. The mixture was filtered to remove solids which had separated and the filtrate was diluted with 250 cc. of water and concentrated to a volume of about 100 cc. The phytol was extracted into ether and the resulting solution was washed free of base with water and with a saturated salt solution. The solution was dried over magnesium sulfate and taken to dryness to afford 4.47 g. of an oil. The infrared spectrum of this alcohol was identical with that of the phytol employed in the preparation of phytyl oxalate described above.

Pyrolysis of Diphytyl Oxalate.—A 4.62-g. sample of the above ester was distilled *in vacuo* through a short Vigreux column. The distillate amounted to 1.87 g., $\lambda^{CH_3OH}_{max}$ 225–226 mμ ($E^{1\%}_{1cm.}$ ranging from 260–530). The best sample of phytadiene, obtained from chromatography on acid washed alumina exhibited $E^{1\%}_{1cm.}$ of 740 at 227 mμ corresponding to log ε of 4.31.

RAHWAY, NEW JERSEY

(16) In a redetermination of the spectrum of VI[4] in methanol an additional peak at shorter wave length (224 mμ) was observed. This peak is outside the spectral range examined in the original[4] analysis. Our results were as follows: $\lambda\lambda_{max}$ 224 mμ (log ε 4.51), 252 (4.00), 296 (3.29), 303 (3.28). See also: M. Carmack, M. B. Moore and M. B. Bayliss, THIS JOURNAL **72**, 844 (1950).