We have made the observation that solutions of the vitamin, the purified pigment derived from the vitamin by alkaline hydrolysis, the low temperature distillate from the molecular still (contains no vitamin K), and pure phytol all exhibit a characteristic white fluorescence when exposed to the light from an argon lamp. The same fluorescence was noted in samples of vitamin K obtained from Professor E. A. Doisy and Professor P. Karrer. The active nucleus, 2-methyl-1,4-naphthoquinone, does not show this fluorescence.

We prepared 2-methyl-3(?)-phytyl-1,4-naphthoquinone by condensation of 2-methyl-1,4-naphthoquinone with phytol. Purification was effected by repeated molecular distillation. *Anal.* Calcd. for $C_{31}H_{46}O_2$: C, 82.6; H, 10.3. Found: C, 82.5; H, 10.6. The product has the color, oily form and solubilities similar to those of vitamin K from alfalfa and sublimes in the molecular still under the same temperature and pressure. It shows the characteristic white fluorescence previously mentioned and gives the color changes of the natural vitamin in sodium methylate [*ibid.*, **61,** 1610 (1939)], although the transient purple is rather weak. When administered orally to vitamin K deficient chicks three weeks old at a level of 0.2 mg. per chick the compound restored blood clotting power to normal within a few hours. Quantitative assays have not been completed [see *Biochem. J.*, **33,** 1055 (1939)].

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RECEIVED JULY 21, 1939

THE CONSTITUTION AND SYNTHESIS OF VITAMIN K_1

Sir:

In a previous communication [THIS JOURNAL, **61,** 1928 (1939)] we reported some experiments on the oxidation of vitamin K_1, in which we obtained phthalic acid, a quinone acid, and a ketone $C_{18}H_{36}O$. The ketone was identified as 2,6,10-trimethylpentadecanone-14 by means of the semicarbazone, melting point 66–67°. An authentic specimen of this semicarbazone was not available at the time but we have subsequently prepared it from the ketone which we obtained by the oxidation of phytol [F. G. Fischer and K. Löwenberg, *Ann.*, **464,** 69 (1929)]. The melting point was 64–66° and the mixed melting point 64–66°.

The amount of quinone acid obtained was so small (3.5 mg.) that only one analysis was possible, and the results indicated the formula $C_{14}H_{12}O_4$. On the basis of this, it was tentatively suggested that the acid was 2-ethyl-1,4-naphthoquinone-3-acetic acid. When this acid was synthesized and found to be different, we prepared an additional amount of the quinone acid from the vitamin and converted it to the methyl ester (melting point 121–122°). This was found to be identical with a synthetic specimen of the methyl ester of 2-methyl-1,4-naphthoquinone-3-acetic acid. *Anal.* Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.55; H, 5.22. The synthetic ester melted at 121.5–122.5° and the mixture showed no depression.

These results have been confirmed by further experiments with the diacetate of dihydro vitamin K_1 [THIS JOURNAL, **61,** 1612 (1939)]. Oxidation of this with chromic acid gave a good yield of a colorless diacetate acid melting without decomposition at 205°. *Anal.* Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.40, 64.56; H, 5.09, 5.16. Treatment with diazomethane gave the methyl ester which melted at 127.5–128.5°. *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.12; H, 5.36. This was found to be identical with a synthetic specimen of the methyl ester of 1,4-diacetoxy-2-methylnaphthalene-3-acetic acid (melting point 125–126°). The mixed melting point was 126–127°. Chromic acid oxidation of the diacetate acid from the vitamin converted it to the quinone acid which gave a methyl ester identical with the methyl ester of 2-methyl-1,4-naphthoquinone-3-acetic acid. These experiments demonstrate conclusively that the structure of vitamin K_1 is correctly represented by the formula 2-methyl-3-phytyl-1,4-naphthoquinone.

Confirmation of this structural formula for vitamin K_1 has been obtained through synthesis which was easily accomplished through direct alkylation by the method of Claisen [*Ann.*, **442,** 210 (1925)] for direct carbon alkylation of phenols. The reaction of phytyl bromide with a benzene suspension of the monosodium salt of 2-methyl-1,4-naphthohydroquinone produced the hydroquinone of the vitamin which was oxidized by the air to the quinone. This was purified by chromatographic adsorption and by high-vacuum distillation and was then subjected to reductive acetylation. The diacetate obtained in this man-

ner was crystallized from methyl alcohol. *Anal.* Calcd. for $C_{35}H_{52}O_4$: C, 78.33; H, 9.77. Found: C, 78.06; H, 9.81. The mixed melting point with an authentic specimen of diacetate from the natural vitamin showed no depression.

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SYNTHETIC APPROACH TO VITAMIN K1

Sir:

In seeking a method for the introduction of the phytyl group into the 3-position of 2-alkyl-1,4-naphthoquinones we have investigated various procedures for condensing 2-methyl-1,4-naphthohydroquinone with phytol, geraniol and simpler β-unsaturated alcohols, and with dienes. In the work on vitamin E such condensations have been brought about in the presence of mineral acids (either added or liberated in the reaction) or zinc chloride and have been attended with cyclization to compounds of the tocopherol type. Since cyclization introduces a complication in the case at hand, trial was made of less powerful agents and it was found that, with anhydrous oxalic acid in dioxane solution, methylnaphthohydroquinone can be condensed with simple β-unsaturated alcohols and dienes to give considerable amounts of the uncyclized substituted hydroquinones. With 2,3-dimethylbutadiene, after refluxing for twenty-four hours, there was obtained 29% of the substituted hydroquinone, characterized as the diacetate (m. p. 119–120°, found: C, 74.04; H, 7.23), and 13% of a stable substance, m. p. 73–73.5°, which appears to be of the tocopherol type (found: C, 79.95; H, 7.63). The crude hydroquinone was converted quantitatively on oxidation to 2-methyl-3-(β,γ,γ-trimethylallyl)-1,4-naphthoquinone, m. p. 95–95.5° (found: C, 80.33; H, 7.25); this gives the above diacetate on treatment with pyridine, acetic anhydride, and zinc dust. Condensation with cinnamyl alcohol gave a hydroquinone (extracted with 10% sodium hydroxide) which formed a diacetate, m. p. 167.5–168° (found: C, 77.17; H, 6.09) and a quinone, m. p. 127–127.5° (found: C, 83.63; H, 5.71).

The reaction is being extended to other examples, including the isoprenoid alcohols, and the use of esters and ethers of the hydroquinone is being investigated. We have ascertained that phytol enters into the condensation under the above conditions or at 140°, and viscous oils have been obtained of the composition of the substituted hydroquinone or tocopherol. One preparation, purified by rather drastic treatment with alkali and by high vacuum distillation, gave C, 82.62; H, 10.52 ($C_{31}H_{48}O_2$ requires C, 82.24; H, 10.69); another after distillation gave C, 82.36; H, 10.71. The general character of the distilled material suggests that it is the tocopherol. In the geranyl series a similar product was oxidized with lead tetraacetate to a substance having the composition of the acetoxyquinone (found: C, 74.92; H, 8.15; $C_{23}H_{28}O_4$ requires C, 74.93; H, 7.69), and this route is under investigation.

Synthesis by the addition of a Grignard reagent to a 2-alkyl-1,4-naphthoquinone oxide does not appear promising. Such oxides (2-methyl, 2,6- and 2,7-dimethyl) are conveniently prepared by adding aqueous sodium carbonate to an alcoholic solution of the quinone and excess hydrogen peroxide. The 2,6-dimethyl compound, m. p. 97–98° (found: C, 71.23; H, 5.07), with either allylmagnesium bromide or magnesium bromide in ether gave a considerable amount of the bromohydrin, m. p. 146–148° (found: C, 51.05; H, 4.18; Br, 28.33), characterized by conversion to the bromodimethylnaphthoquinone, m. p. 114–114.7° (found: C, 54.64; H, 3.61).

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SYNTHESIS OF 2-METHYL-3-PHYTYL-1,4-NAPHTHOQUINONE

Sir:

When equivalent amounts of phytol and 2-methyl-1,4-naphthohydroquinone are heated in dioxane solution in the presence of anhydrous oxalic acid at the reflux temperature, condensation occurs readily but the methylphytylnaphthohydroquinone produced is cyclized about as rapidly as formed and the chief reaction product appears to be the naphthotocopherol. By using a large excess of methylnaphthohydroquinone to accelerate the bimolecular condensation reaction and by operating at a temperature (75°) where cyclization is slow, it is possible to produce a considerable amount of the substituted hydroquinone.