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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RECEIVED AUGUST 21, 1939

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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RECEIVED JULY 25, 1939

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.

The unchanged hydroquinone is removed by extraction from ether with dilute alkaline hydrosulfite and the phytyl-substituted hydroquinone is separated from the ether residue as a waxy, white solid by digestion with petroleum ether and centrifugation. The white sludge is oxidized in dry ether with silver oxide, and evaporation gives 2-methyl-3-phytyl-1,4-naphthoquinone as a pure yellow, rather mobile oil (Calcd. for $C_{31}H_{46}O_2$: C, 82.61; H, 10.29. Found: C, 82.76; H, 10.53). The preparation has been completed successfully ten times under slight variation of the conditions and the pure quinone obtained in yields up to half the weight of the phytol employed. Trichloroacetic acid has been used satisfactorily in place of oxalic acid and the procedure has been applied to the preparation of 2,6-dimethyl-3-phytyl-1,4-naphthoquinone (M. D. Gates, Jr.) and 2-methyl-3-geranyl-1,4-naphthoquinone (yellow oils).

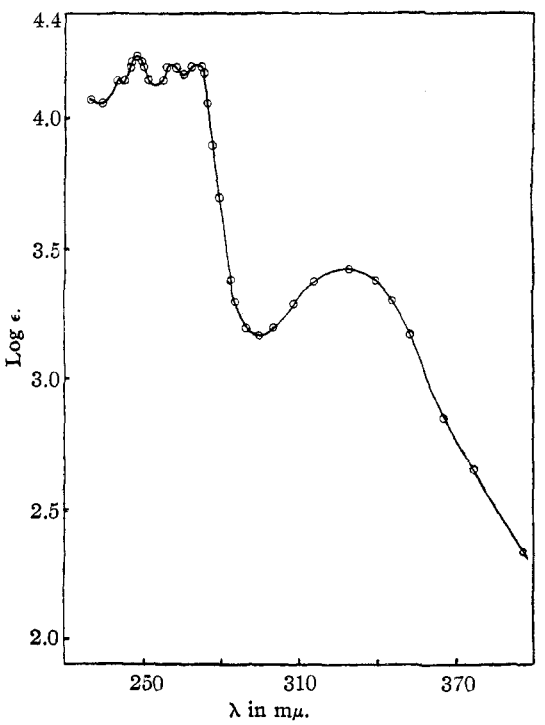

Fig. 1.—2-Methyl-3-phytyl-1,4-naphthoquinone in absolute alcohol. Maxima in mμ (with log ε values in parentheses): 241 (4.15), 248 (4.24), 260.5 (4.20), 270.5 (4.20), 328 (2.42).

In the Dam–Karrer test with alcoholic alkali, 2-methyl-3-phytyl-1,4-naphthoquinone gives striking purple or deep blue colors, depending upon the concentrations. The absorption spectrum, kindly determined by D. M. Bowen, closely resembles that reported for vitamin K_1, the curve being practically identical in form with that given by Dam, Karrer, *et al.* [*Helv. Chim. Acta*, **21**, 310 (1939)]. The positions of the maxima correspond closely with the values given for the vitamin by Dam, Karrer, *et al.*, and by Doisy, *et al.*, THIS JOURNAL, **61**, 1295, 1612 (1939), although the high extinction coefficient reported by Doisy has not been observed.

Dr. W. L. Sampson has found synthetic 2-methyl-3-phytyl-1,4-naphthoquinone to have marked antihemorrhagic activity. The substance was administered in 0.1 cc. of peanut oil to chicks which had been on a vitamin K deficient diet for two weeks and the blood clotting time determined eighteen hours after administration. The control birds all showed a clotting time of more than two hours and the following assays were made on the same day with the same group of chicks. With the Walker–Gordon standard alfalfa 75 mg. reduced the clotting time of 90% of the birds below ten minutes (av. 6.1 min.). With 2-methyl-3-phytyl-1,4-naphthoquinone a dose of 4 γ reduced the c. t. below ten minutes in 90% of the birds (av. 5 min.), while 2 γ was effective in 50%; thus 2–4 γ of the quinone is equivalent to approximately 75 mg. of alfalfa. Doses of 1 γ and 0.5 γ of 2-methyl-1,4-naphthoquinone were effective in 90% (av. c. t. 5 min.) and 30%, respectively, indicating an activity definitely greater than that of the phytyl derivative.

That the phytyl group very probably is linked through the terminal carbon atom is inferred from (1) analogy to the synthetic compounds of the vitamin E group, (2) analogy to similar condensations observed with cinnamyl alcohol and benzyl alcohol, and (3) the color reaction, which is interpreted as requiring an enolizable hydrogen on the α-carbon of the unsaturated side chain. Reductive acetylation gave the hydroquinone diacetate as a nearly colorless oil (Calcd. for $C_{35}H_{52}O_4$: C, 78.31; H, 9.77. Found: C, 78.43; H, 10.01), which resisted first attempts to effect crystallization but which eventually separated in part from methanol as colorless nodules after exposure of the solution in a Pyrex flask to sunlight, although it is not yet established that this treatment is essential. Recrystallized from methanol, the diacetate melted at 57–59° (Found: C, 78.34; H, 9.87). The hydroquinone dibenzoate, obtained as a solid after exposure to sunlight, melted at 85–86° (Calcd. for $C_{45}H_{56}O_4$: C, 81.77; H, 8.54.

Found: C, 81.63; H, 8.59). For the corresponding diacetyl derivative of natural vitamin K_1 Doisy (*loc. cit.*) found the m. p. 59°.

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RECEIVED AUGUST 12, 1939

IDENTITY OF SYNTHETIC 2-METHYL-3-PHYTYL-1,4-NAPHTHOQUINONE AND VITAMIN K_1

Sir:

A comparison of the synthetic product described earlier with the natural vitamin was made possible by Dr. Byron Riegel, who generously supplied me with a highly purified 3–5% alfalfa concentrate [Riegel, Schweitzer and Smith, *J. Biol. Chem.*, **129**, 495 (1939)]. An alcoholic suspension of 5.3 g. of this oil was shaken with aqueous hydrosulfite and the vitamin hydroquinone taken into petroleum ether, extracted with Claisen's alkali containing hydrosulfite, and recovered from the yellow liquor by dilution with water and extraction with ether. Digestion with petroleum ether and centrifugation, following the procedure of the synthesis, gave a white solid yielding on oxidation 60 mg. of vitamin K_1 as a yellow oil (Found: C, 82.64; H, 10.20). The substance gives the characteristic Dam–Karrer color test, the spectrum agrees very closely with that of the synthetic quinone (T. J. Webb), and in antihemorrhagic activity the two substances appear identical within the limit of error (W. L. Sampson). Reductive acetylation gave a diacetate, m. p. 58.5–60° (Found: C, 78.13; H, 10.11) showing no depression when mixed with synthetic 2-methyl-3-phytyl-1,4-naphthohydroquinone diacetate (purified sample, m. p. 60–61.5°, remelting at 60–60.5°). Subsequent to my comparison, this finding has been confirmed by Dr. E. A. Doisy, who kindly examined my synthetic diacetate and found that it did not depress the m. p. of a purified sample of his diacetate from natural vitamin K_1. The sample was sent, at Dr. Doisy's stipulation, at the conclusion of his own work (sample received August 21, examined August 22). In contrast to the behavior noted with the synthetic compound of the methyl series and with the natural vitamin, synthetic 2-ethyl-3-phytyl-1,4-naphthohydroquinone did not separate from petroleum ether even after considerable purification had been effected by extraction with Claisen's alkali, and a sample of the quinone showing a strong color test was found inactive in fairly high dosage. The conclusion from this work is indicated by the title. A further observation, made with a sample of the synthetic material, is that the Dam–Karrer reaction results in the formation of phthiocol, m. p. 171–172°, mixed m. p. 171.5–172.5°.

In a clinical trial Drs. H. A. Frank and A. M. Seligman of the Beth Israel Hospital, Boston, found that 10 mg. of the synthetic vitamin given by mouth with 3 g. of ox bile to a patient with a complete malignant biliary obstruction reduced the prothrombin clotting time (method of Quick) from 37.5 to 17 seconds on one occasion and from 55 to 28 seconds on another. Intravenous injection of the quinone (10 mg.) in dispersion in 10% glucose solution (1 liter) was also successful and the patient was carried through operation without abnormal bleeding.

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RECEIVED AUGUST 25, 1939

NEW THERMODYNAMIC DATA FOR THE CYCLOHEXANE–METHYLCYCLOPENTANE ISOMERIZATION

Sir:

The equilibria at several temperatures in the isomerization reaction Cyclohexane (liq.) $\rightleftarrows$ Methylcyclopentane (liq.) have been studied carefully by Glasebrook and Lovell [THIS JOURNAL, **61**, 1717 (1939)]. From their measurements on this reaction they have calculated the thermodynamic data at 25° which appear in the second column of Table I and then have compared these results with similar ones (Column 3) derived from the free energy studies of Parks and Huffman ["The Free Energies of Some Organic Compounds," The Chemical Catalog Co., New York, 1932, p. 90]. Here the Parks–Huffman value for ΔS, which should be quite reliable, is in fairly good agreement with the value derived indirectly by Glasebrook and Lovell but the ΔH and $\Delta F°$ values differ even in sign. These discrepancies are undoubtedly due to the fact that the Parks–Huffman ΔH value (and therefore also their $\Delta F°$) is based on early and somewhat uncertain combustion data for these two hydrocarbons. Indeed an error of only 0.25% in the two heats of combustion might conceivably account for this difference.