considerable amount. This was phenolic in nature and in an impure condition melted at 153–156°. It has now been determined that the same substance results from heating *p*-fluorophenol with benzene and aluminum chloride. When purified it melted at 163.5–164° and upon oxidation gave a high yield of benzoic acid. No depression of the melting point occurred when a sample of the unknown was mixed with *p*-hydroxybiphenyl. Hence

$$C_6H_6 + FC_6H_4OH \xrightarrow{AlCl_3} C_6H_5C_6H_4OH\ [+ HF]$$

p-fluorophenol must react as shown and the *p*-hydroxybiphenyl obtained in the deëthylation of *p*-fluorophenetole also results from this reaction.

Attempts to extend the reaction in various directions have been without success. Because aromatic fluorine may be under some conditions replaced by chlorine,[3] it seemed possible that *p*-chlorophenol was an intermediate in the reaction. However, *p*-chlorophenol showed no activity toward benzene in the presence of aluminum chloride. None of the corresponding hydroxybiphenyl was isolated when *p*-fluorophenol and aluminum chloride were heated with toluene or chlorobenzene.

By heating a mixture of 3 g. of *p*-fluorophenol, 7 ml. of benzene and 7 g. of aluminum chloride under reflux for two and one-half hours there was obtained about 1 g. of *p*-hydroxybiphenyl, m. p. 164°. The 51 g. obtained in the deëthylation of *p*-fluorophenetole[2] corresponds to 13% of the *p*-fluorophenol reacting with the benzene.

(3) Bacon and Gardiner, *J. Org. Chem.*, **3**, 281 (1938).

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COMMUNICATIONS TO THE EDITOR

SYNTHETIC AND NATURAL ANTIHEMORRHAGIC COMPOUNDS

Sir:

In our last communication [THIS JOURNAL, **61,** 1923 (1939)] the reported antihemorrhagic activity of 2-methyl-1,4-naphthoquinone was a minimum assay result. The total comparative activity of this compound is given in Table I. It is by no means as active as vitamin K [Ansbacher and Fernholz, *ibid.*, **61,** 1924 (1939)] or as low in activity as reported by Thayer, *et al.*, [*ibid.*, **61,** 1932 (1939)] and would seem to provide an effective, cheap, synthetic substitute for vitamin K. This compound, like phthiocol and others, is capable of maintaining the prothrombin level of chick blood at a normal value when sufficient is given.

We have purified or synthesized and tested a number of naphthoquinones and related compounds (Table I). Assays were conducted and results expressed as noted previously [*ibid.*, **61,** 1923 (1939)]. Entirely negative results were obtained with 1,4-benzoquinone, naphthalene, 1,4-naphthoquinone, anthraquinone, 1,2-dihydroxyanthraquinone, and hydrolapachol at levels of 100 mg. or more per kg. of diet. Thayer, *et al.*, [*ibid.*, **61,** 1932 (1939)] have reported some activity in 1,4-naphthoquinone. Fieser, *et al.*, [*ibid.*, **61,** 1925 (1939)] have indicated activity in lomatiol, lapachol and hydrolapachol. We have previously found lomatiol and lapachol to be inactive [*ibid.*, **61,** 1923 (1939)]. These other workers employ assay methods which require only twenty-four hours or less but which are, in our experience, likely to give misleading results.

TABLE I

ANTIHEMORRHAGIC ACTIVITY OF NAPTHOQUINONES

Substance	Level fed per kg. of diet, mg.	Activity in terms of cc. of ref. standard per g.[a]
2-Methyl-1,4-naphthoquinone	10	> 2400
2-Methyl-1,4-naphthoquinone	2.5	5150
2-Hydroxy-1,4-naphthoquinone	75	139
Phthiocol	20	287
Phthiocol ethyl ether	15	100
Phthiocol octadecyl ether	20	95
Phthiocol phytyl ether	20	< 50
Phthiocol monoacetate	15	420
Phthiocol triacetate	15	192
Alfalfa concentrate	0.5	>53600
Alfalfa concentrates[b]	0.2 to 0.3	63000

[a] Standard hexane extract of dried alfalfa representing 1 g. per cc. [b] From preliminary assays of alfalfa preparations (E. A. Doisy, P. Karrer).

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-