

TABLE I  
BIOLOGICAL DATA OF TEST SUBSTANCES

Amount administered $\gamma$	No. of chicks	B. C. T., <sup>a</sup> min. before treatment	min. after treatment
2-Methyl-1,4-naphthoquinone			
2500	10	>90	<1 <sup>b</sup>
1000	20	>90	<1
500	10	>90	<1
333	10	>90	<1
100	10	>90	<1
10	10	>90	<2
5	10	>90	<3
1/2	10	>90	<6
2-Methyl-1,4-acetoxynaphthalene			
1000	10	>90	<1 <sup>b</sup>
100	10	>90	<1
10	10	>90	<4
5	10	>90	<8
2-Methyl-3-hydroxy-1,4-naphthoquinone			
1000	10	>90	<2 <sup>c</sup>
100	20	>90	>30 <sup>d</sup>
10	5	>90	>30
Duroquinone			
1000	10	>90	>30

<sup>a</sup>B. C. T. = blood clotting time.

<sup>b</sup>All vitamin K-deficiency symptoms disappeared within twenty-four hours and the chicks doubled their weight within ten days.

<sup>c</sup>Three chicks died during the six-hour test period.

<sup>d</sup>Four chicks died during the six-hour test period.

We are preparing and investigating a large number of quinones and hydroquinones, particularly those with a long aliphatic side chain to which class vitamins K<sub>1</sub> and K<sub>2</sub> [Binkley, *et al.*, THIS JOURNAL, **61**, 1612 (1939)] appear to belong.

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#### QUINONES HAVING VITAMIN K ACTIVITY

Sir:

Certain indications from recent publications of others and from preliminary oxido-reduction potential measurements conducted at Northwestern University have led us to postulate that the anti-hemorrhagic vitamin K<sub>1</sub> of alfalfa is a 2,3-dialkyl-1,4-naphthoquinone. From the similarity of vitamin K<sub>2</sub> [Doisy, *et al.*, THIS JOURNAL, **61**, 1295, 1612 (1939)] in absorption spectrum, ease of oxidation of the hydroquinone and other properties, it is probable that this substance is of the same type. As a specific hypothesis it is suggested (L. F. F.) that vitamin K<sub>1</sub> may be 2,6(?) -dimethyl-

3-phytyl-1,4-naphthoquinone (or the 2-mono-methyl compound) and vitamin K<sub>2</sub> 2,3-difarnesyl-1,4-naphthoquinone. These structures seem consistent with the spectra [Doisy, *et al.*; Dam, Karrer, *et al.*, *Helv. Chim. Acta.* **22**, 310 (1939)], the analyses and hydrogen absorption [Doisy, *et al.* (assuming the saturation of one ring of the naphthalene nucleus)], the sensitivity to heat and light, and the hindered character of the functional groups of the quinone (K<sub>1</sub>) [Almquist, *et al.*, *J. Biol. Chem.*, **125**, 681 (1938); Riegel, Schweitzer and Smith, in press] and hydroquinone diacetates (K<sub>1</sub> and K<sub>2</sub>) [Doisy, *et al.*]. They also accord with recognized processes of biogenesis: K<sub>1</sub> (alfalfa) from dimethylnaphthoquinone (or toluquinone plus isoprene) and phytol [occurrence in green leaves: Dam, *Z. Vitaminforsch.*, **8**, 248 (1938-39); relationship between vitamins E and K<sub>1</sub>]; K<sub>2</sub> (putrefied sardine meal) from naphthoquinone and farnesol (relationship of the alcohol to squalene).

These considerations suggested (B. R. and L. F. F.) the testing of various quinones available from previous researches or from the collection of the late Samuel C. Hooker. The synthesis of compounds of the type indicated has been undertaken at Harvard. Exploratory assays of ten compounds were kindly carried out by Dr. W. L. Sampson of the Merck Institute by a procedure based on that of Ansbacher [*J. Nutrition*, **17**, 303 (1939)]. Day old chicks were placed on the Almquist vitamin K deficient diet for twelve days and given a dose of 250  $\gamma$  of substance in 1 cc. of peanut oil, administered by a tube into the crop, and the blood clotting time determined (Almquist method) the following morning.

The preliminary results suggest that some of the 2-hydroxy-3-alkyl-1,4-naphthoquinones possess positive vitamin K activity at the dose level fed [compare phthiocol, Almquist and Klose, THIS JOURNAL, **61**, 1611 (1939)] and that the 2,3-dimethyl derivative is at least 1/250 as active as Doisy's vitamin K<sub>1</sub>.

2-Allyl-1,4-naphthoquinone (m. p. 36-36.5°, found: C, 78.82; H, 5.14) was prepared from 2-allyl-1-naphthol through the azo compound and amine (W. P. C.). 2,3-Diallyl-1,4-naphthoquinone diacetate (m. p. 92.5-93°, found: C, 74.18; H, 6.33) was obtained by heating 1,4-naphthohydroquinone diallyl ether (m. p. 49.5-50°, found: C, 80.09; H, 6.74) with diethylaniline and acetic anhydride (M. F.). The diacetate is

TABLE I

Compound	No. of birds	Clotting times, min.					Per cent. 10-min. birds	Remarks
		5	5-10	10-20	20-30	>30		
Controls	20	1	3	2	..	14	20	
2,3-Dimethyl-1,4-naphthoquinone	10	10	..	..	..	..	100	Very effective
Lomatiol	9	5	2	1	..	1	77	Effective
Hydroxyhydrolapachol	9	5	1	1	..	2	67	Effective
Lapachol	9	1	3	4	1	..	45	Borderline
Diallyl-1,4-hydroquinone <sup>1</sup>	10	3	2	2	..	3	50	Borderline
Lomatiol methyl ether <sup>2</sup>	9	1	3	..	..	5	45	Doubtful
Hydrolapachol	9	2	2	2	..	3	45	Borderline
Diallyl-1,4-hydroquinone diacetate <sup>3</sup>	8	..	3	3	2	..	37	Probably not effective
Lapachol methyl ether <sup>4</sup>	9	..	3	..	1	6	35	Not effective
Diallyl-1,4-benzoquinone <sup>5</sup>	10	3	..	..	..	7	30	Not effective

<sup>1</sup> M. p. 130–131°, found: C, 75.80; H, 7.40. By rearrangement of hydroquinone diallyl ether (H. B. Dunkle, Dissertation, Harvard University) along with an isomer, m. p. 87–90°, found: C, 76.17; H, 7.60 (E. M. F.).

<sup>2</sup> M. p. 61.5–62°, found: C, 70.96; H, 6.05; prepared with diazomethane (W. P. C.).

<sup>3</sup> M. p. 111–112°, found: C, 70.25; H, 6.70; from the higher melting isomer (E. M. F.).

<sup>4</sup> M. p. 51.5–52°, found: C, 74.76; H, 6.34 (W. P. C.).

<sup>5</sup> M. p. 16°, found: C, 76.71; H, 6.75; by oxidation of the 130–131° isomer with silver oxide (E. M. F.).

resistant to alkaline hydrolysis (compare Doisy's dihydro vitamin diacetates); on cleavage with a Grignard reagent and air oxidation in ether it gave a quinone, m. p. 129–130° (absorption maxima at 245, 267, and 330 m $\mu$  in ethanol). 2,3-Dimethyl-1,4-naphthoquinone shows maxima at 246 and 265 m $\mu$  (log  $\epsilon$  between 4.2 and 4.3) and 330 m $\mu$  (log  $\epsilon$  = 3.4). The spectra (R. N. J. and D. M. B.) resemble those reported for vitamins K<sub>1</sub> and K<sub>2</sub> (Doisy, *et al.*, Dam, Karrer, *et al.*) except for the absence of fine structure in the two intense bands.

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#### SYNTHESIS OF ANTIHEMORRHAGIC COMPOUNDS *Sir:*

The further bio-assays by Dr. W. L. Sampson given in Table I lend added support to our conception of the nature of vitamin K<sub>1</sub> and K<sub>2</sub>. Of special significance is the contrast between the highly active 2,3-dimethyl-1,4-naphthoquinone and the much less potent 2,6- and 2,7-isomers, the contrast between quinones of the benzene and naphthalene series, and the high potency encountered in a 1,4-naphthoquinone having a  $\beta$ -unsaturated side-chain (allyl) in the quinonoid

ring, as postulated for both vitamins. The spectrographic data of Table II also indicate a close correspondence between the natural vitamins and model substances of the postulated structure of 2,3-dialkyl-1,4-naphthoquinones. Dr. T. J. Webb of the Merck Research Laboratories independently examined 2,3-dimethyl-1,4-naphthoquinone and pointed out to us definite indications of fine structure in the two intense bands; this was subsequently discerned in a new reading of our plates. The resolution of the most intense band of the 6,7-dimethyl-2,3-diallyl compound is still more distinct, particularly in hexane. We are indebted to Dr. Webb for the other determinations indicated.

The following examples illustrate methods developed for the synthesis of quinones of the type considered favorable for vitamin K activity. (1) 2,6-Dimethyl-8-naphthol was allylated, the ether rearranged, and the once distilled allyl-dimethylnaphthol (b. p. 152–157° at 2 mm. Found: C, 84.20; H, 7.74) converted to the 5-amine and this oxidized in acetone suspension with ferric chloride to give 2,6-dimethyl-3-allyl-1,4-naphthoquinone, m. p. 42–42.5° (Found: C, 79.82; H, 6.36). (2) The lower melting diallyl-hydroquinone (87–90°) was oxidized with silver oxide to the quinone (oil); 2,3-dimethylbutadiene was added to this, the product was isomerized to a hydroquinone, and on oxidation with chromic acid this afforded 6,7-dimethyl-2,3-diallyl-1,4-naphthoquinone, m. p. 69.5–70.7° (Found: C, 81.46; H, 6.96). 6,7-Dimethyl-1,4-naphthoqui-