

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 ¹	10	3	2	2	..	3	50	Borderline
Lomatiol methyl ether ²	9	1	3	5	45	Doubtful
Hydrolapachol	9	2	2	2	..	3	45	Borderline
Diallyl-1,4-hydroquinone diacetate ³	8	..	3	3	2	..	37	Probably not effective
Lapachol methyl ether ⁴	9	..	3	..	1	6	35	Not effective
Diallyl-1,4-benzoquinone ⁵	10	3	7	30	Not effective

¹ 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.).

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

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

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

⁵ 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 μ in ethanol). 2,3-Dimethyl-1,4-naphthoquinone shows maxima at 246 and 265 m μ (log ϵ between 4.2 and 4.3) and 330 m μ (log ϵ = 3.4). The spectra (R. N. J. and D. M. B.) resemble those reported for vitamins K₁ and K₂ (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 K₁ and K₂. 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 β -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-

TABLE I
 BIO-ASSAYS BY THE ANSBACHER PROCEDURE

Substance (In 1 cc. peanut oil)	No. of birds	Clotting times, min.					% 10-min. birds	Remarks
		5	10-20	20-30	> 30			
Controls (1st series)	20	2	4	6	..	8	30	
Peanut oil (1 cc.)	10	..	3	7	30	
Alfalfa (100 mg.)	10	5	3	1	1	..	80	
Alfalfa (50 mg.)	9	2	5	1	1	..	77	
Alfalfa (25 mg.)	10	1	4	2	1	2	50	
Alfalfa (10 mg.)	10	1	3	2	2	2	40	
2- α -Heptenyl-3-hydroxy-1,4-naphthoquinone (0.2 mg.)	10	3	4	2	..	1	70	Some activity
2- <i>n</i> -Heptyl-3-hydroxy-1,4-naphthoquinone (0.2 mg.)	10	2	6	2	80	Some activity
2-Allyl-1,4-naphthoquinone (0.2 mg.)	10	10	100	Very active
Controls (2nd series)	11	11	0	All over 60 min.
Alfalfa (150 mg.)	10	7	3	100	
2,3-Diallyl-1,4-naphthohydroquinone diacetate (0.2 mg.)	10	..	1	1	5	3	10	Inactive
2,6-Dimethyl-1,4-naphthoquinone (0.2 mg.)	10	..	4	6	40	Very sl. act.
2,7-Dimethyl-1,4-naphthoquinone (0.2 mg.)	10	3	3	2	..	2	60	Active

 TABLE II
 ABSORPTION MAXIMA

 In ethanol, except as noted; log ϵ values given in parentheses

	Maxima (in m μ)		
Vitamin K ₁ (Doisy, <i>et al.</i>)	243, 248	261, 270	323
(Dam, Karrer, <i>et al.</i>)	248	261, 270	328
Vitamin K ₂ (Doisy, <i>et al.</i>)	249	261, 269	320
2,3-Dimethyl-1,4-naphthoquinone (T. J. Webb)	244, 249 (4.29)	264, 270 (4.27)	332 (3.39)
(D. M. B., new reading)	243, 249 (4.26)	262, 267 (4.24)	330 (3.38)
6,7-Dimethyl-2,3-diallyl-1,4-naphthoquinone	253, 260 (4.40)	273, 278 (4.12)	343 (3.45)
(In hexane)	253, 260 (4.41)	271, 276 (4.14)	338 (3.46)
2-Allyl-1,4-naphthoquinone	246, 251 (4.31)	Shoulder	332 (3.43)
(In hexane)	243, 251 (4.1)	260 (3.9)	Not measured
2-Methyl-1,4-naphthoquinone (T. J. Webb)	250 (4.29)	263 (4.24)	334 (3.38)
2,6-Dimethyl-1,4-naphthoquinone (T. J. Webb)	256 (4.33)		340 (3.47)
2,6-Dimethyl-3-allyl-1,4-naphthoquinone ^a	249 (4.30) 256 (4.35)	266, 272 (4.17)	335 (3.39)

none, m. p. 118–119° (Found: C, 77.43; H, 5.61), was similarly prepared from the known diene addition product. (3) Monobutadiene-1,4-benzoquinone with allyl bromide and potassium carbonate in acetone gave 5,8-dihydro-1,4-naphthohydroquinone diallyl ether, m. p. 64–65° (Found: C, 79.51; H, 7.55), and when heated in kerosene this rearranged smoothly to 5,8-dihydro-2,3-diallyl-1,4-naphthohydroquinone, m. p. 108–109° (Found: C, 79.36; H, 7.78). Chromic acid oxidation in acetic acid gave 2,3-diallyl-1,4-naphthoquinone, m. p. 29–30° (Found: C, 80.53; H, 6.02). The substance (m. p. 130°) obtained previously by the action of ethyl or *n*-butylmagnesium bromide on 2,3-diallyl-1,4-naphthohydroquinone diacetate is a naphthoquinone (spectrum) having two hydrogen atoms more than the expected diallyl compound (Calcd. for C₁₈H₁₆O₂: C, 79.97; H, 6.71. Found: C, 80.06, 79.93; H, 6.78, 6.76). More gentle cleavage with methylmagnesium bromide and

silver oxide oxidation gave 2,3-diallyl-1,4-naphthoquinone, m. p. 28.5–29.5°, identical with the above sample.

In the Dam-Karrer color test with sodium ethylate in ethanol, regarded by some as characteristic of vitamin K₁ (Almquist and Klose, *THIS JOURNAL*, **61**, 1610 (1939); see, however, Fernholz, *et al.*, *ibid.*, **61**, 1613 (1939)), our synthetic naphthoquinones having at least one allyl group in the quinonoid ring all give intense and transient blue or purple colors and contrast sharply with the 2,3-dimethyl compound (weak, purplish color).^a

^a Received June 26, 1939.

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THE STEREOCHEMISTRY OF TERVALENT NITROGEN

Sir:

Jackson and Kenner [*J. Chem. Soc.*, 573 (1928)] briefly reviewed the existing evidence bearing