1.0 moles, per molecular weight of 196. Found: 1.75 and 0.75, respectively.

(4) Action of Acids on α-Hydroxypropiovanillone

(a) Sulfuric Acid (5%).—α-Hydroxypropiovanillone (1 g.) was refluxed with 50 cc. of sulfuric acid (5%) for twenty-four hours. The resulting dark brown insoluble material was filtered, washed with water, dissolved in acetone (10 cc.) and precipitated into water (200 cc.). The flocculent precipitate was centrifuged, the liquors discarded and the product dried in the vacuum desiccator. It was redissolved in chloroform (10 cc.) and reprecipitated into petroleum ether (b. p. 60–70°) (200 cc.). The centrifuged material was stirred with petroleum ether (b. p. 30–50°), centrifuged and dried in the vacuum desiccator; yield 0.25 g. (25%). The light brown amorphous product was soluble in alkali. *Anal.* Found: C, 70.0; H, 4.94; OCH_3, 17.1.

(b) Methanolic Hydrogen Chloride.—α-Hydroxypropiovanillone (1 g.) treated similarly with a 5% solution of anhydrous hydrogen chloride in methanol (20 cc.) gave a similar dark colored, alkali-soluble, amorphous product; yield, 31%. *Anal.* Found: C, 70.3; H, 4.96; OCH_3, 20.6.

(c) Formic Acid (95%).—α-Hydroxypropiovanillone (1 g.) was treated in the same manner with 95% formic acid (20 cc.). The dark colored, alkali-soluble reaction product was purified similarly. *Anal.* Found: C, 70.0; H, 5.86; OCH_3, 17.3. A condensation trimer of type (A), $C_{27}H_{21}O_5(OCH_3)_3$ (mol. wt. 518) requires C, 69.5; H, 5.8; OCH_3, 17.9.

Acknowledgment.—The authors wish to thank the Carnegie Corporation of New York for kind financial assistance.

Summary

1. A description is given of the synthesis of α-hydroxypropiovanillone, a possible precursor of lignin, and of its behavior toward diazomethane and the Grignard reagent.

2. Hot dilute sulfuric acid, methanol–hydrochloric acid and formic acid (95%) convert it into alkali-soluble, lignin-like products.

MONTREAL, CANADA RECEIVED JUNE 20, 1939

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY, HARVARD UNIVERSITY]

Synthesis of Quinones Related to Vitamins K_1 and K_2

BY LOUIS F. FIESER, WILLIAM P. CAMPBELL[1] AND EDWARD M. FRY[2,3]

In a recent Communication[4] we advanced structural formulas for the antihemorrhagic vitamins which Doisy and co-workers[5] isolated in a condition of demonstrated purity, and there are now further indications that our conception of the structures is essentially correct. Of particular importance is the degradative work on vitamin K_1 by the Doisy group,[6] reported in a Communication submitted about the same time as ours.

Since the evidence from the degradations is still incomplete and in some points uncertain, we shall include in the present paper a fuller account of the previous deductions and report certain observations of significance made in a study of synthetic model substances.

Following Doisy's report of the quinonoid character of vitamins K_1 and K_2, Dr. R. N. Jones pointed out to us that in absorption spectra[5,7] the substances resemble 1,4-naphthoquinones more closely than quinones of other series. Such a structure would account for the known lability to light,[8,9] heat,[5a] and alkali,[7] for the yellow color and for the sensitivity of the hydroquinones to air oxidation.[5b] Anthraquinones possess the last-named property but are far more stable substances. The next clue was the resistance of the dihydro vitamin diacetates to alkaline hydrolysis,[5b] which suggested the presence of hindering substituents in the 2 and 3 positions adjacent to the acetoxyl groups, and an entirely analogous behavior has been encountered in 2,3-diallyl-1,4-naphthohydroquinone diacetate. Hindering substituents are also indicated by the failure of vitamin K_1 concentrates to react with carbonyl reagents.[10,11] From these considerations it seemed

(1) Squibb Research Fellow.

(2) Du Pont Research Fellow.

(3) We are indebted to Mary Fieser and Marshall D. Gates, Jr., for the participation in the synthetic work indicated in the Experimental Part and to Dr. R. Norman Jones and Douglas M. Bowen for the determination of the absorption spectra.

(4) Fieser, Bowen, Campbell, M. Fieser, Fry, Jones, Riegel, Schweitzer and Smith, THIS JOURNAL, **61**, 1925 (1939).

(5) (a) McKee, Binkley, MacCorquodale, Thayer and Doisy, *ibid.*, **61**, 1295 (1939); (b) Binkley, MacCorquodale, Cheney, Thayer, McKee and Doisy, *ibid.*, **61**, 1613 (1939).

(6) MacCorquodale, Binkley, Thayer and Doisy, *ibid.*, **61**, 1928 (1939).

(7) Dam, Geiger, Glavind, P. Karrer, W. Karrer, Rothschild and Solomon, *Helv. Chim. Acta*, **22**, 310 (1939).

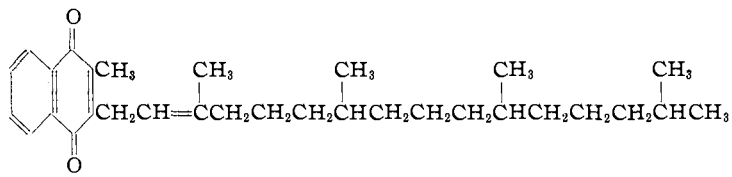
(8) Almquist, *J. Biol. Chem.*, **117**, 517 (1937); **120**, 635 (1937).

(9) MacCorquodale, Binkley, McKee, Thayer and Doisy, *Proc. Soc. Exptl. Biol. Med.*, **40**, 482 (1939).

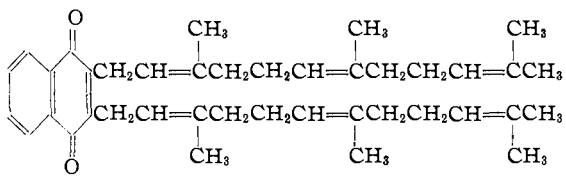
(10) Klose, Almquist and Mecchi, *J. Biol. Chem.*, **125**, 681 (1938). These investigators observed that the antihemorrhagic activity is not destroyed by reduction and concluded that the vitamin is inert to reducing agents, but it is now evident that reoxidation could have occurred before the test was made.

(11) Riegel, Schweitzer and Smith, in press (personal communication from Dr. Riegel).

likely that both vitamins are 2,3-dialkyl-1,4-naphthoquinones, and this was further supported by preliminary data on the oxidation–reduction potential of alfalfa concentrates of which Dr. Byron Riegel kindly informed us.[4]



I



II

If the vitamins are 1,4-naphthoquinones they must, according to Doisy's analyses,[5] have one or more long side chains containing a certain number of double bonds. If the values for the hydrogen absorption observed by Doisy[5a] in microhydrogenation experiments were due entirely to saturation of such linkages, vitamin K_1 would have three side chain double bonds and vitamin K_2 would have eight, but in the naphthoquinone series such a formulation would not be compatible with the analytical figures. We therefore assumed that under the as yet unreported conditions of the hydrogenation the reaction proceeded beyond the first possible stopping point and resulted in saturation of the oxygen-free ring of the naphthalene nucleus, giving a 5,6,7,8-tetrahydro-1,4-naphthohydroquinone which could revert to a quinone on air oxidation,[5a] an interpretation also reached by Doisy.[6] This would mean that vitamins K_1 and K_2 have 1 and 6 lateral double bonds, respectively.

It then occurred to us that the presence of a phytyl group in vitamin K_1 and of two farnesyl groups in vitamin K_2 not only would satisfy these unsaturation requirements but also would give structures of the observed carbon content, interpreted by Doisy[5a] in terms of C_{32} and C_{40} formulas, respectively. It was postulated that vitamin K_1 has the basic structure of 2-methyl-3-phytyl-1,4-naphthoquinone (I), with or without a second methyl group in the benzenoid ring, and that vitamin K_2 is 2,3-difarnesyl-1,4-naphthoquinone (II). There is a certain amount of coincidental circumstance to lend appeal to the hypothesis, considered as a whole. It is striking that among the radicals of the known naturally occurring alcohols those two which give the correct degree of unsaturation are also those which provide the proper number of carbon atoms in the side chains. Naphthoquinone and methylnaphthoquinone derivatives are widely distributed in nature, and it is perhaps significant that the vitamin regarded as a phytyl derivative occurs along with the phytol-containing chlorophyll in green leaves.[12]

According to formula I an interesting relationship exists to another type of vitamin (E). α-Tocopherol apparently arises in nature by the nuclear substitution of a phytyl group into trimethylhydroquinone, followed by ring closure between a hydroxyl group and the double bond in the side chain; vitamin K may arise by a similar condensation of phytol with a 2-alkyl-1,4-naphthohydroquinone, followed by oxidation. The occurrence of vitamin K_2 in putrefied fish meal (Doisy[5a]) is also suggestive of a significant relationship, for the farnesyl group postulated to be present in this substance is associated structually with squalene, a known constituent of fish liver oils, which has the structure di-farnesyl.

According to the suggested structures the vitamins are further related to the natural products lapachol and lomatiol, for these substances are 1,4-naphthoquinones having β-unsaturated, isoprenoid side chains. It is to be noted that the yellow color of the vitamins rules out alternate formulas with double bonds adjacent to the quinonoid nucleus, for such substances are all red or orange.[13] Also of significance is the fact that the spectrum of the highly unsaturated vitamin K_2 is very similar to that of vitamin K_1 and gives no indication of conjugation in the side chains. The distribution of the six double bonds according to the farnesyl pattern is one of a very limited number of ways possible which avoid both conjugation and α-unsaturation.

As mentioned above, Doisy[5] interpreted the analytical results with carefully purified vitamin K_1 in terms of the empirical formula $C_{32}H_{48}O_2$ or $C_{32}H_{50}O_2$. In accordance with the first formula we originally considered the possibility that the substance has a structure similar to I but with a second methyl group in the benzenoid nucleus,

(12) Dam, *Z. Vitaminforsch.*, **8**, 248 (1939).

(13) Hooker, THIS JOURNAL, **58**, 1163, 1174 (1936).

for example at position 6. Our observation[14] that the model substance 2,6-dimethyl-3-allyl-1,4-naphthoquinone has an absorption curve very similar to that of vitamin K_1 but shifted to a considerable extent in the direction of longer wave length led us recently to question the presence of this second nuclear substituent, and Doisy's isolation of phthalic acid as an oxidation product of the vitamin[6] now proves definitely that the benzenoid ring is not substituted. Doisy also has obtained evidence from ozonization experiments which already provides a strong indication of the presence of the phytyl group. In accordance with the C_{32}-formulation, and on the basis of the isolation of an as yet unidentified oxidation product having the composition of 2-ethyl-1,4-naphthoquinone-3-acetic acid, Doisy has suggested the structure of 2-ethyl-3-phytyl-1,4-naphthoquinone. Until the evidence is complete there is little choice between this structure and that of the lower homolog I. We may point out that the C_{31}-formulation is entirely admissible on the basis of the available analytical data, as shown in the table, and that the occurrence of methylnaphthoquinones is common while ethyl derivatives have not previously been encountered.

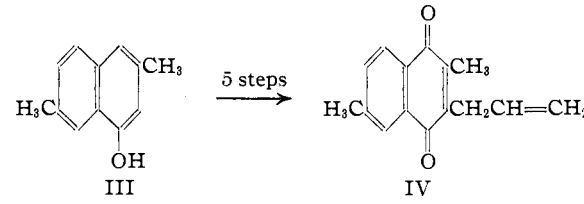
TABLE I

ANALYSES BY DOISY AND CO-WORKERS

	C, %		H, %	
Calcd. for $C_{31}H_{46}O_2$	82.61		10.29	
Vitamin K_1, purified[5a]	82.76	82.54	10.65	10.66
Regenerated from derivative[5b]	82.34		10.13	
Calcd. for $C_{35}H_{52}O_4$	78.31		9.77	
Dihydro K_1 Diacetate[5b]	78.21	78.01	10.07	10.03

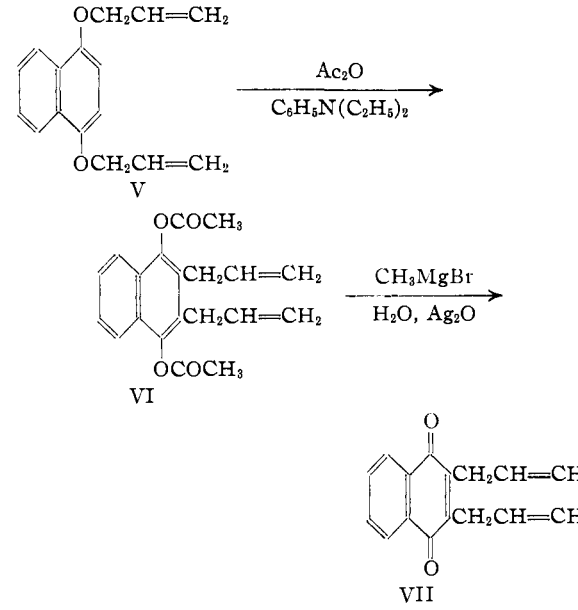
Methods of Synthesis.—In undertaking synthetic work on the problem we thought it of importance first of all to investigate the properties of reasonably accessible allyl derivatives of α-naphthoquinone even though the methods of preparation might not be directly applicable to the synthesis of the vitamins. Thus the allyl group is introduced into phenols more conveniently by the Claisen rearrangement than by direct allylation of the sodium salt, while the intro duction of higher β-unsaturated groups of the desired structure from the available primary halides would require the use of the second method (which is now under investigation).

2-Allyl-1,4-naphthoquinone was obtained from the known 2-allyl-1-naphthol by the standard procedure of coupling with diazotized sulfanilic acid, reduction with hydrosulfite, and oxidation employed previously on numerous occasions in this Laboratory. Hydrogenation, followed by reoxidation of the hydroquinone, gave the 2-*n*-propyl derivative, which was obtained as well from the intermediate allylaminonaphthol. In the same way 2,6-dimethyl-8-naphthol (III) was



III IV

converted through the allyl ether to the 3-allyl derivative and thence to 2,6-dimethyl-3-allyl-1,4-naphthoquinone, IV, which presents an interesting analogy to the structure I. In one of two routes developed for the synthesis of a simple model for structure II, α-naphthohydroquinone was first allylated by Claisen's allyl bromide–potassium carbonate–acetone procedure. The yield was poor, possibly because of appreciable C-allylation,



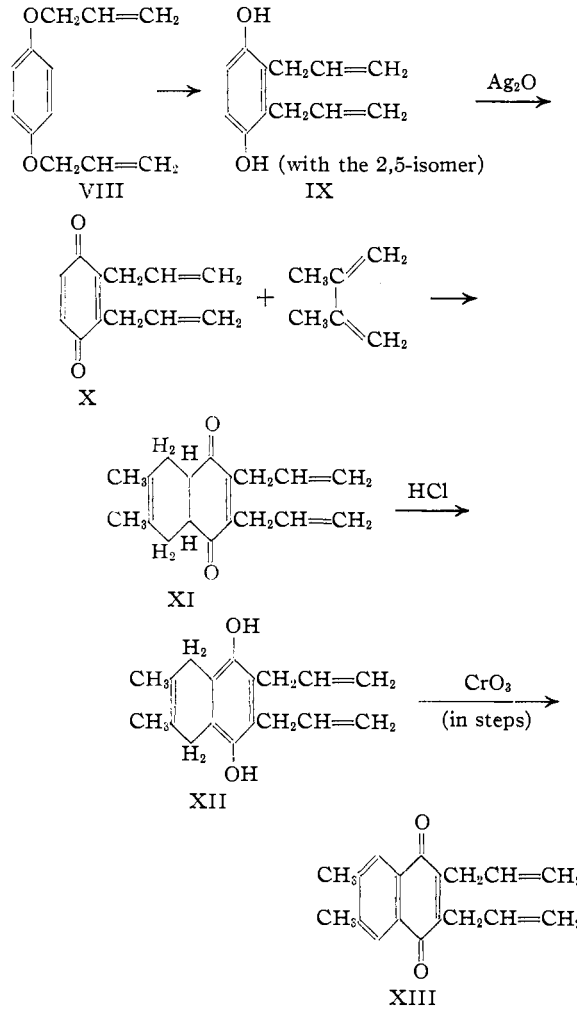
and the crystalline ether V could not be rearranged satisfactorily by the usual methods because of the sensitivity of the product. Good use was made, however, of the device employed on a previous occasion[15] of heating the allyl ether with acetic anhydride in diethylaniline solution. The sensitive hydroquinone is protected as formed by

(14) Fieser, Bowen, Campbell, Fry and Gates, THIS JOURNAL, **61**, 1926 (1939).

(15) Fieser and Lothrop, *ibid.*, **58**, 749 (1936).

acetylation and the diacetate VI is obtained in excellent yield. The hindered character of the acetoxyl groups of this compound and its analogy to the corresponding vitamin derivatives already has been mentioned. The best method found for effecting hydrolysis is exactly that employed in the vitamin series by Doisy,[5b] namely, interaction with a methyl Grignard reagent and oxidation in ethereal solution with either air or silver oxide. The resulting 2,3-diallyl-1,4-naphthoquinone (VII) is a low melting yellow solid (m. p. 29–30°) resembling the vitamins in general properties. When the diacetate VI was refluxed for prolonged periods with ethyl or *n*-butylmagnesium bromide the reagent apparently exerted a reducing action, for there was isolated a small amount of a quinone having two hydrogen atoms more than the normal product VII. The spectrum[4] is very similar to that of 2,3-dimethyl-1,4-naphthoquinone, showing that the naphthoquinone nucleus is intact and that the reduction occurs in the side chain or chains, possibly with condensation to give a third ring.

Another route to 2,3-diallyl derivatives of 1,4-naphthoquinones was found starting with hydroquinone diallyl ether. This method was based upon preliminary observations of H. B. Dunkle.[16] The diallyl ether VIII rearranges smoothly when heated in kerosene solution, from which the phenolic product crystallizes, giving a mixture of two isomers. The higher melting substance presumably is 2,5-diallylhydroquinone, but the structure was not established; the other compound is identified as the 2,3-isomer IX by the successful outcome of the following synthesis. The corresponding quinone X, employed as an unpurified oil, was condensed with 2,3-dimethylbutadiene and the product (XI) isomerized with acid to the dihydronaphthohydroquinone XII. As with simpler examples reported in the patent literature,[17] it was found that treatment of this with chromic acid under rather mild conditions gives a yellow crystalline complex intermediate in composition between the desired naphthoquinone and its dihydride. Further oxidation with excess reagent at 90–100° gave the unsaturated naphthoquinone derivative XIII in a pure condition and in reasonably good yield; probably a portion of the quinone is exhaustively oxidized to easily



eliminated products. Similar intermediate complexes were isolated in syntheses of 6,7-dimethyl-1,4-naphthoquinone and 2,3-diallyl-1,4-naphthoquinone involving the same type of oxidation. The substances do not have the deep color characteristic of quinhydrones and their nature is still obscure.

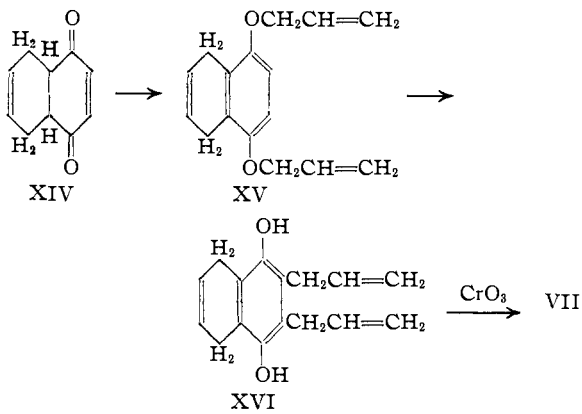
The above diene synthesis makes possible the introduction of substituents in the benzenoid nucleus of the naphthoquinone. By reversing the sequence of the Claisen rearrangement and the diene addition a practical method was found which permits variation in the nature of the unsaturated side chain. The product XIV of the addition of butadiene to quinone is known to be isomerized easily by acids or bases to 5,8-dihydro-1,4-naphthohydroquinone,[18] and it was found that the change occurs in the presence of potassium carbonate, allyl bromide, and acetone, for the

(16) H. B. Dunkle, Dissertation, Harvard University, 1937.

(17) I. G. Farbenindustrie A.-G., English Patent 324,661 (1930); German Patent 521,621 (1931) [*Chem. Zentr.*, **101**, 2, 809 (1930); **102**, 2, 1758 (1931)].

(18) Diels and Alder, *Ber.*, **62**, 2337 (1929).

crystalline ether XV was obtained satisfactorily from this reaction mixture. The ether rearranged smoothly in boiling kerosene to XVI, and the latter on stepwise oxidation with chromic acid gave 2,3-diallyl-1,4-naphthoquinone, identical



with the material obtained by the synthesis from α-naphthohydroquinone.

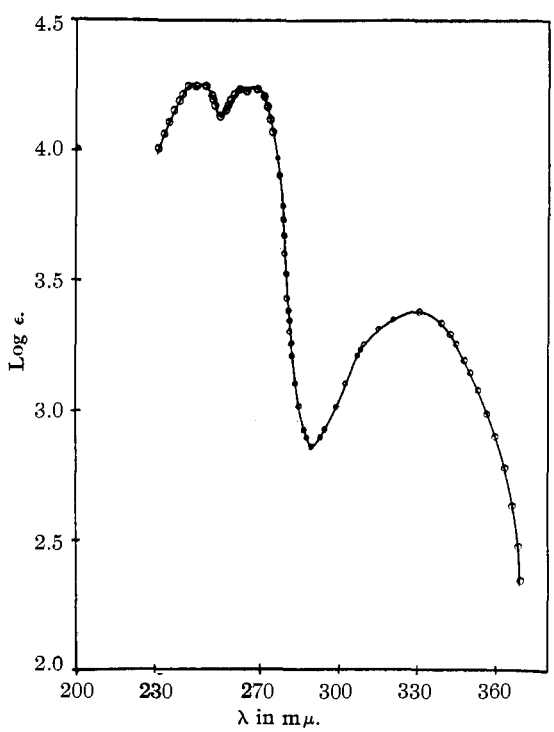


Fig. 1.—2,3-Dimethyl-1,4-naphthoquinone in absolute alcohol. Maxima in mμ (with log ε values in parentheses): 243, 249 (4.26); 262, 267 (4.24); 330 (3.38).

Absorption Spectra.—Table II of our second Communication[14] summarizes the spectrographic data on most of the above synthetic naphthoquinones except the 2,3-diallyl derivative, and the

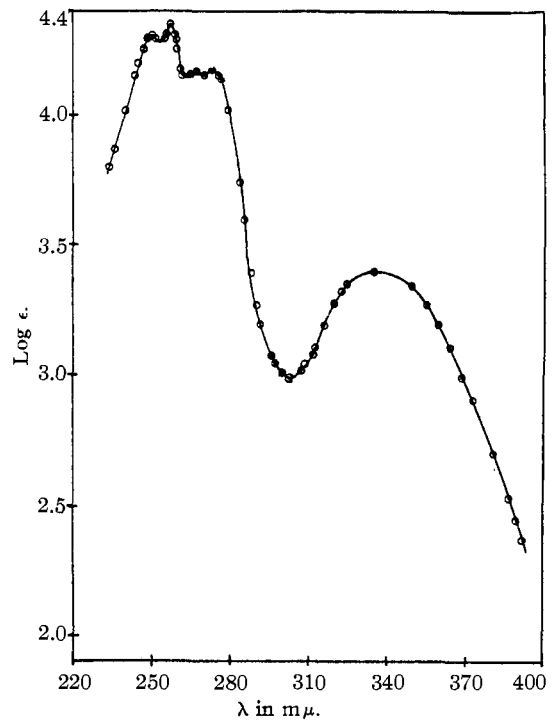


Fig. 2.—2,6-Dimethyl-3-allyl-1,4-naphthoquinone in absolute alcohol. Maxima in mμ: 249 (4.30), 256 (4.35); 265, 272 (4.17); 335 (3.39).

absorption curves for this and other compounds of interest are given in Figs. 1–4. The only set of complete data for comparison consists in the curve published by Dam, Karrer, *et al.*,[7] for a purified preparation from alfalfa consisting largely of vitamin K_1, but the positions of the maxima are very close to those reported by Doisy[5] for pure K_1. According to Doisy vitamins K_1 and K_2 are spectrographically almost identical. As the chief characteristics the spectra show two intense bands, centering in the neighborhood of 245 and 265 mμ, and a broader band of low intensity at about 324 mμ. The first intense band shows some evidence of resolution, with maxima at 243 and 248 mμ (Doisy, K_1) while the second one has definite fine structure with peaks at 261 and 270 mμ (K_1 and K_2). In comparing the synthetic compounds with the vitamins it is significant that naphthoquinones which depart appreciably from the suggested structures I and II of 2,3-dialkyl derivatives diverge considerably in spectrographic characteristics. Thus the 2,6-dimethyl compound has only one intense absorption band and the 2-methyl derivative has two such bands but both are lacking in fine structure. 2,3-Dimethyl-1,4-naphthoquinone, however, gives

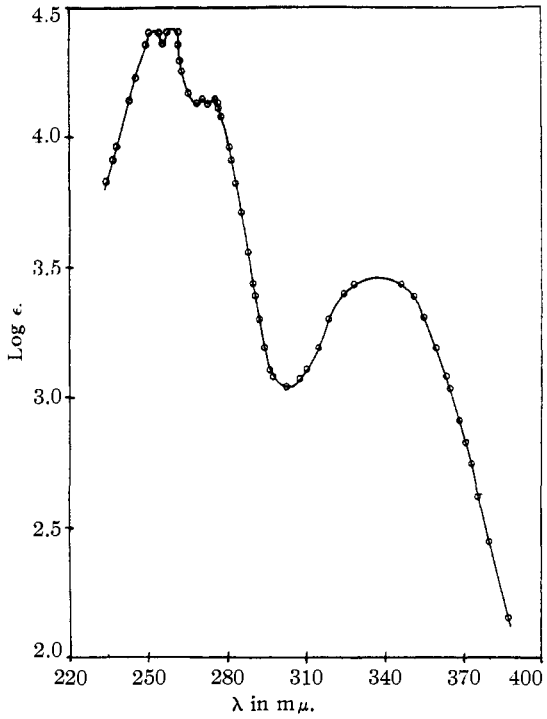


Fig. 3.—6,7-Dimethyl-2,3-diallyl-1,4-naphthoquinone in hexane. Maxima in mμ: 253, 260 (4.41); 271, 276 (4.14); 338 (3.46).

indications of resolution in the first intense band and the second one is definitely resolvable. This fine structure was first pointed out to us by Dr. T. J. Webb of the Merck Research Laboratories, and decisive evidence on the question has been obtained through the kind coöperation of Dr. H. H. Darby, Columbia University. Dr. Darby examined the plates prepared by D. M. Bowen using the Krüss densitometer at the Bartol Institute and found unquestioned resolution of the second band, as shown in Fig. 1, and probable resolution of the first band. In both the positions and the special characteristics of all three principal absorption bands this 2,3-dialkyl-1,4-naphthoquinone corresponds very closely with the natural vitamins, and the only difference is that in the Dam–Karrer curve the second intense band is somewhat less intense than the first. This same characteristic is met with in 2,6-dimethyl-3-allyl-1,4-naphthoquinone (Fig. 2), and indeed the form of the curve throughout almost duplicates that given by Dam, Karrer, *et al.* The reading of the plates in this case was verified by Dr. Darby with the densitometer and the more accurate values for the maxima are recorded in the legend of Fig. 2. The whole curve for the 2,6-dimethyl-3-allyl compound, however, is shifted about 5 mμ toward the red end of the spectrum, and we interpret this difference as due to the presence of a 6-methyl group in the model substance and not in the vitamins. A smilar and even more pronounced shift (av. 11 mμ) is observable in the 6,7-dimethyl-2,3-diallyl compound (Fig. 3) as compared with 2,3-diallyl-1,4-naphthoquinone (Fig. 4). Examination of the previously reported[14] data for 2-allyl-1,4-naphthoquinone will show that a second band of high intensity is clearly resolvable only when hexane is used as the solvent and that this is relatively closer to the first band than in the case of the synthetic 2,3-dialkyl derivatives and the natural vitamins; the 2-allyl compound indeed seems related more closely to the 2-methyl quinone than to these substances.

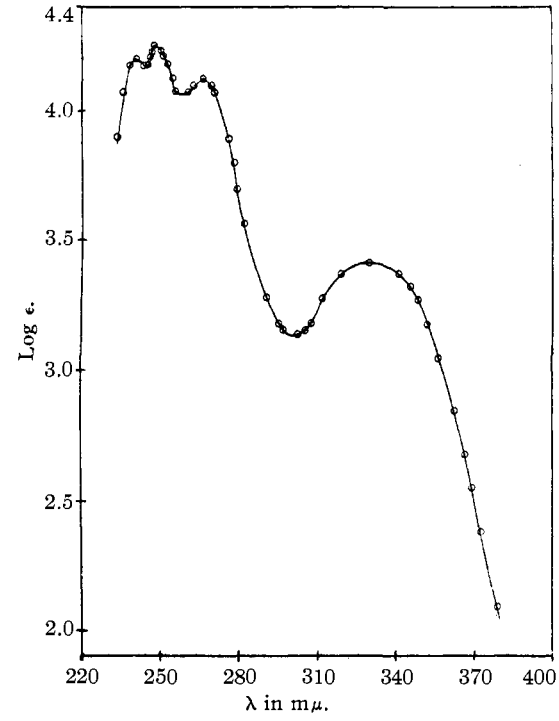


Fig. 4.—2,3-Diallyl-1,4-naphthoquinone in absolute alcohol. Maxima in mμ: 240 (4.20); 249 (4.24); 267 (4.12); 330 (3.42).

The spectrographic evidence as a whole provides convincing evidence for the proposed formulations I and II. From the form of the curves and the positions of the maxima it is evident that 2,3-dimethyl and 2,3-diallyl-1,4-naphthoquinone constitute very close optical models for the vitamins, whereas nuclear homologs and compounds lacking the feature of 2,3-disubstitution depart signifi-

cantly from the natural pattern. An alteration in the size of the alkyl substituents in the quinonoid ring clearly does not influence the spectrum, and 2-methyl and 2-ethyl-3-phytyl-1,4-naphthoquinone would of course be spectrographically equivalent.

Bio-assays.—We had hoped to gain an insight into the nature of the antihemorrhagic vitamins from a knowledge of the biological properties of synthetic models, and we are of course also interested in producing synthetic vitamins or synthetic substitutes. Indeed Doisy's isolation[5a] of two antihemorrhagically active substances differing by as much as eight or nine carbon atoms and containing from one to six lateral double bonds adequately demonstrates that vitamin K activity is not specific to a single structure. Our new compounds, as well as various known substances, have been examined in exploratory assays by Dr. W. L. Sampson of the Merck Institute, through the courtesy of Dr. R. T. Major, and most of the results have been reported in our two Communications.[4,14] These assays by the rapid Ansbacher procedure[19] were recognized as preliminary and now seem rather uncertain. Thus 2-allyl-1,4-naphthoquinone gave evidence of high vitamin K potency in an assay with one series of chicks[14] but in a subsequent test it appeared to be inactive even at a higher dosage level. A similar inconsistency appears in recent reports concerning 2-methyl-1,4-naphthoquinone. The Doisy group[20] find the 2-methyl compound to be only slightly more potent than phthiocol, which various workers have described as greatly inferior to the natural vitamins in activity.[20,21,22] Ansbacher and Fernholz,[22] on the other hand, state that 2-methyl-1,4-naphthoquinone is practically as active as vitamin K. Evidently the rapid assay procedures require considerable further investigation for application to the testing of pure compounds, and for the present it is necessary to reserve judgment on the preliminary results.

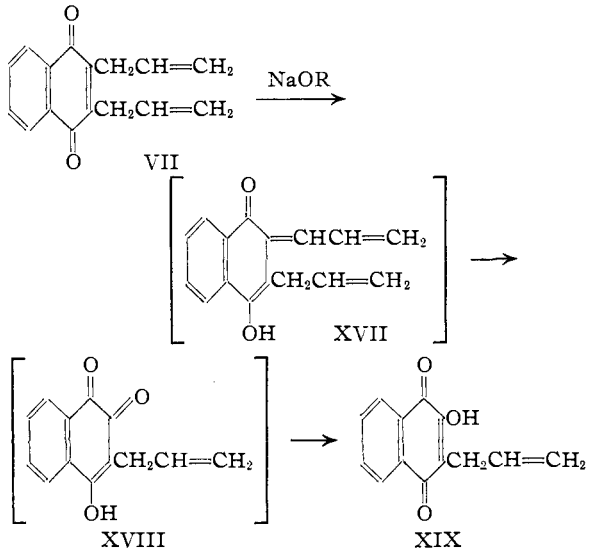
Dr. Sampson has tested three compounds from our Laboratory by the Almquist procedure.[23] Lapachol, tested at a level of 8 mg. and 15 mg. per kilogram of diet was entirely inactive, as was lomatiol at the 5-mg. and 10-mg. levels. Almquist and Klose obtained similar results at still higher levels. 2,3-Dimethyl-1,4-naphthoquinone was dosed at 8 mg., 3 mg., and 0.5 mg. The 8 mg. level was about as effective as 2 g. of the Walker–Gordon standard, giving an average blood clotting time of 7.5 minutes for 8 birds (two prolonged). The birds on the two lower doses were but slightly different from the controls.

Color Reaction with Sodium Ethylate.—Dam, Karrer, *et al.*,[7] reported that their highly purified vitamin K_1 preparation gave with sodium ethylate in alcohol a transient purple color changing to reddish-brown, and Almquist and Klose[24] have published an extensive comparison of the color reactions and bio-assays of concentrates which strongly indicates that the color is due to the vitamin. Fernholz, Ansbacher and Moore,[25] however, question this conclusion and the matter is still unsettled; unfortunately the behavior of pure vitamins K_1 and K_2 in the color reaction has not been reported.

The response of our synthetic models to treatment with alcoholic alkalies presents certain points of special interest. All of the above 1,4-naphthoquinones containing at least one allyl group in the quinonoid ring give strikingly beautiful purple or blue solutions changing in a minute or two to dull brown-red, whereas naphthoquinones containing saturated alkyl groups show no purple or blue phase. The contrast between 2-allyl and 2-*n*-propyl-1,4-naphthoquinone is so marked that the color test was used to determine when traces of the former substance had been removed completely from a preparation of the latter.

Speculating on the nature of the changes involved, we were impressed by a similarity to observations on the behavior of 2-hydroxy-3-alkenyl-1,4-naphthoquinones on treatment with sodium acetate and acetic anhydride. Lapachol gives an unusual reaction product referred to in the early literature as Paternò's isolapachone, and the structure of this substance was fully established in the later researches of Hooker.[26] In connection with a recent study of the tautomerism of certain alkylated β-naphthoquinones in this Laboratory,[27] the abnormal reaction was interpreted as involving in the essential step a tautomeric shift of hydrogen from the activated methylene group between the unsaturated quinone ring and the external double bond and it was noted that similar

(19) Ansbacher, *J. Nutrition*, **17**, 303 (1939).
(20) Thayer, Cheney, Binkley, MacCorquodale and Doisy, THIS JOURNAL, **61**, 1932 (1939).
(21) Almquist and Klose, *ibid.*, **61**, 1923 (1939).
(22) Ansbacher and Fernholz, *ibid.*, **61**, 1925 (1939).
(23) Almquist, Mecchi and Klose, *Biochem. J.*, **32**, 1897 (1938).
(24) Almquist and Klose, THIS JOURNAL, **61**, 1610 (1939).
(25) Fernholz, Ansbacher and Moore, *ibid.*, **61**, 1613 (1939).
(26) Hooker, *ibid.*, **58**, 1190 (1936).
(27) Fieser and Fieser, *ibid.*, **61**, 596 (1939).



abnormal acylations occur with the 3-allyl[28] and 3-benzyl derivatives of 2-hydroxy-1,4-naphthoquinone, but not with substances having no activating double bond or phenyl group attached to the α-carbon atom of the side chain.

Applied to the case at hand, these inferences suggested that the color reaction of 2,3-diallyl-1,4-naphthoquinone, for example, may be due to a similar tautomeric shift to the hydroxyquinonemethane XVII, the intense color being due to the orthoquinonoid group and salt formation with the acidic hydroxyl substituent. Such an intermediate might well be subject to fission by hydrolysis, or by some process involving disproportionation and cleavage, and we consequently sought to isolate the pigment from the dull red end solution by a procedure adapted to the properties of a 2-hydroxy-3-alkyl-1,4-naphthoquinone. These substances are strongly acidic and give cherry-red or orange-red solutions in aqueous sodium carbonate, and indeed soda extraction of the pigment from the 2,3-diallyl compound gave an easily purified yellow substance identified as 2-hydroxy-3-allyl-1,4-naphthoquinone by analysis and by direct comparison with a sample available from a previous synthesis.[28] The color reaction with alcoholic alkali, which in the above case goes to completion at room temperature in less than ten minutes, thus involves the cleavage of one allyl group and its replacement by hydroxyl. 2-Allyl-1,4-naphthoquinone similarly gives a substance very probably identical with 2-hydroxy-1,4-naphthoquinone.

(28) Fieser, THIS JOURNAL, **48**, 3201 (1926).

This observation probably is of considerable significance to the vitamin K problem although application of the information must remain somewhat uncertain until more is known of the behavior of the vitamins. If the pure substances K_1 and K_2 are found to give the color test, the present experiments will afford a good indication of the presence of a β-unsaturated side chain. Furthermore, it should be possible to degrade vitamin K_1 to phthiocol or to the ethyl homolog, and to convert K_2 to a 2-hydroxy-3-alkyl(farnesyl ?)-1,4-naphthoquinone which should be obtainable by a known process of synthesis.[28,29]

Of considerable interest is the observation of Almquist and Klose[21] that the pigment resulting as the end-product of the action of sodium methylate on vitamin K concentrates gives color changes and tests very similar to those exhibited by phthiocol and its homologs. This provides at least a preliminary confirmation of the above prediction and encourages us to mention tentatively a further speculation. Almquist and co-workers[30] have demonstrated that various bacteria are capable of producing vitamin K, including *Mycobacterium tuberculosis*, from which Anderson and Newman[31] isolated phthiocol. Since their isolation procedure involved saponification with alcoholic potassium hydroxide, it is conceivable that the phthiocol was not a true natural constituent of the organism but arose as a product of the alkaline cleavage of vitamin K_1 or a homolog.

Experimental Part[32]

2-Allyl- and 2-*n*-Propyl-1,4-naphthoquinone (W. P. C.).—2-Allyl-1-naphthol was prepared from α-naphthol by allylation in acetone and rearrangement of the ether according to Claisen and Eisleb[33]; over-all yield 67%, b. p. 144° at 4 mm. The coupling of this substance (2.02 g.) with diazotized sulfanilic acid and reduction of the dye was conducted by exactly the procedure given for α-naphthol[34] except that more water was required in dissolving the amine hydrochloride, which is rather sparingly soluble. After one recrystallization from a solution containing excess hydrochloric acid and a trace of stannous chloride, **2-allyl-4-amino-1-naphthol hydrochloride** was obtained as colorless needles; yield 1.60 g. (62%). The sample for analysis was dried at 110° and 15 mm.

Anal. Calcd. for $C_{13}H_{14}ONCl$: N, 5.94. Found: N, 5.90 (Kjeldahl).

(29) Synthesis of lapachol, Fieser, *ibid.*, **49**, 857 (1927).

(30) Almquist, Pentler and Mecchi, *Proc. Soc. Exptl. Biol. Med.*, **38**, 336 (1938).

(31) Anderson and Newman, *J. Biol. Chem.*, **101**, 773 (1933).

(32) All melting points are corrected. Microanalyses by Lyon Southworth and Herbert S. Wight.

(33) Claisen and Eisleb, *Ann.*, **401**, 21 (1913).

(34) Fieser and Fieser, THIS JOURNAL, **57**, 491 (1935); Fieser, *Org. Syn.*, **17**, 9 (1937).

2-Allyl-1,4-naphthoquinone.—On adding a solution of 2.7 g. of ferric chloride crystals and 1 cc. of concentrated hydrochloric acid in 5 cc. of water to a solution of 1 g. of the above hydrochloride and 0.5 cc. of concentrated hydrochloric acid in 90 cc. of warm water the solution turned deep orange and deposited a greenish-black solid. After cooling, this was collected and extracted while moist with ether and the solution was clarified with Norite and evaporated. The yellow residue was obtained crystalline from ether–petroleum ether and afforded 0.65 g. (76%) of product in the form of yellow needles melting constantly at 36–36.5°.

Anal. Calcd. for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.82; H, 5.14.

The quinone darkens rapidly in direct sunlight. It reacts with acetic anhydride–sulfuric acid in the cold to give an apparently colorless substance very soluble in organic solvents. It is very readily soluble in ether or alcohol, less so in petroleum ether, and sparingly soluble in water. On adding 0.5 cc. of a solution prepared from 0.5 g. of sodium and 25 cc. of alcohol (95%) to a solution of 1–2 mg. of the quinone in 1 cc. of alcohol the solution at once acquires an intense, vivid purple color, and after about one minute this changes to dull red. The color changes were similar when 2 cc. of 10% aqueous potassium hydroxide was added to 0.2 g. of the quinone in 5 cc. of alcohol (L. F. F.); on diluting and acidifying the red solution a gelatinous precipitate separated which yielded only a trace of a yellow hydroxyquinone on extraction with ether or hot water. In repeating the experiment two drops of 30% hydrogen peroxide was added to the alcoholic solution and after dilution of the final red solution this was extracted with ether and the acidic material separated with soda solution, taken into ether, crystallized from dilute alcohol, and sublimed. There was obtained 5 mg. of yellow material giving the color reactions of hydroxynaphthoquinone and melting at 178–180°, dec. Mixed with an authentic sample, m. p. 186–188°, dec., the m. p. was 180–181°. The purple phase in the color test is seen best in a dilute solution with a very small amount of alkali. With one drop of 10% methyl alcoholic potassium hydroxide added to 1–2 mg. of the quinone in 25 cc. of alcohol the solution becomes so strongly purple that it is not transparent when viewed lengthwise in a 2 × 15-cm. test-tube and the purple phase persists for about thirty minutes before fading.

2-*n*-Propyl-1,4-naphthoquinone.—On shaking a solution of 2 g. of the allylaminonaphthol hydrochloride in 200 cc. of water with 0.1 g. of Adams catalyst and hydrogen, one mole of gas was absorbed in about twenty-four hours. After removing the catalyst, hydrochloric acid was added to turbidity at the boiling point and the reduction product was obtained as nearly colorless needles. The material was dissolved while still moist in 175 cc. of hot water and a solution of 6 g. of ferric chloride crystals and 2 cc. of concentrated hydrochloric acid in 15 cc. of water added. The quinone separating as a red oil was extracted with ether and the solution was washed, dried, clarified with Norite, and concentrated. Crystallization from ether–petroleum ether gave 1 g. (59%) of crude product sintering at 36° and melting at 38–39.5°. This gave a purple color in the test with alcoholic potassium hydroxide, indicating contamination with allylnaphthoquinone. Several recrystallizations from petroleum ether gave pure material crystallizing in clusters of pale yellow needles, m. p. 39–39.5° (no previous sintering). This gave an immediate red color with alcoholic alkali, with no blue or purple phase.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.97; H, 6.07. Found: C, 78.06; H, 6.21.

The allylnaphthoquinone was also hydrogenated (1 g. in 25 cc. of absolute alcohol), 2 moles of gas being absorbed in about three minutes. After oxidation in ether with silver oxide, the propylnaphthoquinone was obtained pure in 70% yield.

2,6-Dimethyl-3-allyl-1,4-naphthoquinone (M. D. G., W. P. C.).—2,6-Dimethyl-8-naphthol[35] was converted into the allyl ether by heating a mixture of 5 g. of the material with 3 g. of allyl bromide, 8 g. of finely powdered potassium carbonate, and 75 cc. of purified acetone for fifteen hours on the steam-bath with mechanical stirring. The mixture was diluted with water, extracted with ether, and, after extraction of a trace of phenolic material with 10% potassium hydroxide containing sodium hydrosulfite, the ethereal solution was dried and evaporated. The oily residue of the crude ether was heated with 30 cc. of freshly distilled dimethylaniline in an atmosphere of nitrogen for two and three-quarters hours in a salt-bath maintained at 240°, and the cooled solution taken up in ether and extracted with dilute hydrochloric acid. For separation of the **2,6-dimethyl-3-allyl-8-naphthol** the ethereal solution was extracted several times with 10% potassium hydroxide, which removed successive small amounts, and then with Claisen's aqueous alkali–methanol mixture. The combined extracts were acidified and extracted with ether. The product distilled at 152–157° (2 mm.) as a rather dark oil (3 g., 49%) which was used directly without further purification.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.20; H, 7.74.

In an early experiment using crude starting material containing 2,6-dimethyl-3-naphthol the rearrangement gave a small amount of a crystalline product which forms long fibrous needles, m. p. 109–110°, from ligroin (b. p. 70–90°). The substance fails to couple with diazotized amines and evidently is **2,6-dimethyl-4-allyl-3-naphthol.**

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.69; H, 7.67.

The introduction of an amino group into the liquid isomer was conducted as above and the crude **2,6-dimethyl-7-allyl-5-amino-8-naphthol** collected as a nearly colorless precipitate; yield 2.3 g. (72%). The substance is very sparingly soluble in the usual solvents and dissolves to only a slight extent in a large volume of boiling, dilute hydrochloric acid. The filtered solution on cooling deposits very fine, colorless needles of the **hydrochloride,** which apparently forms a stable trihydrate.

Anal. Calcd. for $C_{15}H_{15}ONCl\cdot 3H_2O$: N, 4.41. Found: N, 4.32 (Kjeldahl), 4.39 (Dumas).

Conversion to the Quinone.—For oxidation, 1.3 g. of the free amine was suspended in 50 cc. of acetone and treated

(35) Weissgerber and Kruber, *Ber.*, **52**, 360 (1919).

with 30 cc. of a solution of 27 g. of ferric chloride crystals and 10 cc. of concentrated hydrochloric acid diluted to 245 cc. On warming and stirring the solid dissolved (ten minutes) and the cooled solution was diluted and extracted with ether. After clarification and drying the solvent was removed in vacuum and the residual oil taken up in petroleum ether. On cooling, the quinone separated as yellow needles, m. p. 42–42.5°, and the melting point was not raised on recrystallization; yield 0.75 g. (57%).

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.82; H, 6.36.

In the color test with sodium ethylate in alcohol the quinone gives first a deep blue solution, changing to purple and then brown. Treated with 5% methyl alcoholic potassium hydroxide, the quinone gives a deep blue solution which changes in one to two minutes to a dull greenish-brown and then to a dull red; the diluted solution gives a gelatinous precipitate on acidification. Intense coloration does not develop if much water is present; the addition of 10% aqueous potassium hydroxide to a solution in alcohol gave a faint dull green color changing to weak purplish-red and then to a dull, weak red.

2,3-Diallyl-1,4-naphthoquinone from α-Naphthoquinone (M. F.)

α-Naphthohydroquinone Diallyl Ether.—The α-naphthohydroquinone required as starting material was prepared by dissolving 10 g. of the quinone in 50–75 cc. of hot alcohol and adding gradually a solution of 20 g. of stannous chloride crystals and 20 cc. of concentrated hydrochloric acid in 50 cc. of water. After heating gently until the color faded to pale yellow, and filtering if necessary, the solution was diluted with water and cooled in an ice-bath. The product separated as colorless or gray needles; yield 8.2–8.8 g.

For allylation, 6.1 g. of α-naphthohydroquinone was refluxed for ten to fifteen hours with 6.5 cc. of allyl bromide, 10.4 g. of potassium carbonate, and 20 cc. of acetone. The mixture usually became very dark, even in an atmosphere of nitrogen, and when the ether extract was shaken with alkali containing hydrosulfite considerable phenolic material was removed. After drying with magnesium sulfate the ethereal solution was cooled in a solid carbon dioxide bath, when the diallyl ether separated as a pasty solid. After adding petroleum ether, the crystalline material was collected, and an additional quantity was obtained by diluting the mother liquor with petroleum ether, filtering the solution through a tower of activated alumina, concentrating, and cooling as before. The yield of satisfactory material was 2–3.5 g. (22–38%). Repeated crystallization from petroleum ether containing a trace of ether gave colorless plates, m. p. 49.5–50°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.96; H, 6.72. Found: C, 80.09; H, 6.74.

2,3-Diallyl-1,4-naphthohydroquinone Diacetate.—Attempted rearrangement of the ether in kerosene in an atmosphere of nitrogen gave only dark tars, but the expedient of acetylating the reaction product as produced[15] gave satisfactory results. A mixture of 3 g. of the diallyl ether, 3 cc. of acetic anhydride, and 3 cc. of diethylaniline was heated under reflux in a stream of hydrogen at 200–210° for five hours. The cooled mixture was taken into ether and the solution extracted with dilute hydrochloric acid, dried, and evaporated to a small volume. On slow cooling the diacetate separated as large hexagonal prisms; yield 3.2 g. (79%). The substance is very readily soluble in benzene or alcohol and moderately soluble in ligroin. Recrystallized from ether–petroleum ether or from ligroin (b. p. 70–90°) it formed large, colorless prisms, m. p. 92.5–93°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 74.18; H, 6.33.

2,3-Diallyl-1,4-naphthoquinone (M. D. G.).—The diacetate is resistant to hydrolysis by alkalies, and considerable material was recovered unchanged after boiling for two hours with 12% sodium hydroxide solution. Hydrolysis occurs with mixtures of alcohol and 25% alkali on warming, but the isolation of a satisfactory reaction product is not easily accomplished. For best results the diacetate is cleaved with a Grignard reagent having little reducing action.

To the Grignard solution prepared under nitrogen from 3 g. of magnesium, 100 cc. of absolute ether and sufficient methyl bromide to give complete reaction, was added 2.86 g. of 2,3-diallyl-1,4-naphthohydroquinone diacetate. The solution was refluxed for forty-five minutes, the ether was largely replaced with dry benzene, and after refluxing for one-half hour longer the mixture was decomposed with 25% ammonium chloride solution and a little acid. The organic layer was washed and dried and stirred mechanically with 2.05 g. of silver oxide and 10 g. of Drierite for fifteen minutes (oxidation can be accomplished also by shaking with air). The filtered, yellow solution was concentrated, eventually under vacuum, and the residual, dark yellow oil was cooled well and caused to solidify. After two crystallizations from alcohol (collecting the crystals in the cold room) the substance formed glistening yellow blades, m. p. 29–30°. It gave no depression when mixed with the analyzed sample prepared by the synthesis described below. The total yield of pure material was 1.05 g. (50%). The quinone is very readily soluble in ether or petroleum ether, sparingly soluble in water. It gives a yellow or brown solution in concentrated sulfuric acid.

Alkaline Cleavage of the Quinone (L. F. F.).—2,3-Diallyl-1,4-naphthoquinone gives a characteristic, intense color reaction with alcoholic alkali. When one drop of 10% aqueous alkali is added to a dilute solution of the substance in 1–2 cc. of alcohol, the solution becomes pale greenish-blue, then deep blue, slowly fading to a dull, weak green. With a larger amount of aqueous or alcoholic alkali the green phase is not observed and at the end the solution is red. In one experiment a solution of 0.1 g. of the quinone in 5 cc. of alcohol was treated with 1 cc. of 10% aqueous potassium hydroxide. The solution became deep indigo blue (ten seconds), purplish blue (forty seconds), intense purple (about one minute); a small amount of a cloudy gray precipitate then separated (two minutes) and the solution soon became dull red (two to three minutes) and underwent no further change on standing or heating. After dilution with water, which caused more of the gray material to separate, the mixture was acidified and shaken with ether, when all of the precipitated ma-

terial dissolved. Extraction of the ether solution with sodium carbonate gave a cherry-red aqueous layer and left a dark brown ether layer which gave on evaporation a resin showing no blue color with alcoholic alkali. After washing the red aqueous extract once with ether it gave on acidification a yellow emulsion of crude **2-hydroxy-3-allyl-1,4-naphthoquinone.** This was taken into ether and the solution dried and evaporated. The glassy residue largely dissolved in boiling ligroin (b. p. 70–90°) and after clarification and cooling the hydroxyquinone separated as bright yellow prism clusters, m. p. 115–116°; yield 5 mg. This was combined with material from two other experiments and recrystallized from dilute alcohol–acetic acid, giving fine yellow needles, m. p. 115.5–116°.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.88; H, 4.71. Found: C, 73.19; H, 5.02.

Mixed with synthetic 2-hydroxy-3-allyl-1,4-naphthoquinone,[28] m. p. 115.5–116°, the above sample gave no depression; other preparations were compared with similar results. In a further experiment the hydroxyquinone was purified by sublimation at 2 mm. pressure and the product dissolved in concentrated sulfuric acid. The red solution was poured into water and the product extracted and dried in ether and crystallized from ligroin (b. p. 70–90°), giving ball-like clusters of red microcrystals, m. p. 130–131.5°. A mixture with a synthetic sample of 1-methyl-3,4-benzo-5,6-coumaranequinone[28] (m. p. 134.5–135°, purified with bisulfite) melted at 131–132°.

Reducing Action of the Grignard Reagent (L. F. F.).—On cleavage of 2,3-diallyl-1,4-naphthohydroquinone diacetate by refluxing overnight with excess ethyl or *n*-butylmagnesium bromide in ether and working up the reaction mixture as before, small amounts of a quinone much less soluble than the main reaction product separated in a crystalline condition on concentrating the final ethereal solution to a small volume. Washed free of adhering oil with ether, the substance was obtained as bright yellow prisms, m. p. 127–128°. It was purified by crystallization from dilute alcohol and sublimation at 1 mm. pressure (about 125°), giving bright yellow needles, m. p. 129–130°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.93, 80.32, 80.06; H, 6.76, 6.91, 6.78.

The absorption spectrum is very similar to that of 2,3-dimethyl-1,4-naphthoquinone. The addition of dilute alkali to an alcoholic solution of the quinone gives a weak purplish-pink color which develops rather slowly and gradually changes to red.

Preparation of the Diallylbenzoquinones (E. M. F.)

Hydroquinone diallyl ether was prepared more satisfactorily by the following method than by that described by Hahn and Stenner.[36] A mixture of 44 g. of hydroquinone, 200 cc. of acetone, 96.8 g. of allyl bromide, and 112 g. of potassium carbonate was refluxed for nine hours, water was added to dissolve the inorganic salts, and the reaction product was extracted with ether. Phenolic material was removed by extraction with 1 *N* sodium hydroxide and the solution was washed well with water, dried and evaporated. The orange-yellow residue was induced to crystallize from a cooled solution in dilute alcohol, giving 52 g. of colorless, lustrous plates, m. p. 33–34°; 5 g. of yellowish material was obtained in a second crop, making the total yield 75%.

Rearrangement.—A solution of 53 g. of hydroquinone diallyl ether in 330 cc. of kerosene (b. p. 210–215°) was refluxed vigorously under a stream of nitrogen for two and one-quarter hours. The phenolic reaction product largely crystallized on cooling, and a small additional quantity was obtained on concentrating the mother liquor. The combined, almost colorless material was washed with petroleum ether to remove most of the kerosene and dried at 50°; yield 57.5 g.

2,5-Diallylhydroquinone was separated from this mixture by crystallization from water and the 2,3-isomer subsequently was isolated from the aqueous liquors. The crude rearrangement product was heated to boiling with 2 l. of water containing a little sodium hydrosulfite and steam distilled to remove kerosene still present. A considerable amount of material remained undissolved as an oily solid and the hot solution was decanted from this and filtered. On cooling the colorless filtrate a large crop of 2,5-diallylhydroquinone crystallized, and after collecting this the mother liquor was used to extract a further quantity of material from the semi-solid residue. After heating to boiling, the solution was filtered from a small amount of dark brown oil and cooled, giving another crop of colorless crystals. The total yield of crude 2,5-isomer was 25 g.; recrystallization from 2 l. of water gave 15.2 g. (29%) of pure product in the form of broad, flat needles, m. p. 129.5–131°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found (H. B. Dunkle): C, 75.80; H, 7.40.

The **diacetate** was prepared by adding 1.5 cc. of pyridine to a supension of 1.5 g. of the hydroquinone in 3 cc. of acetic anhydride. The mixture became warm, the solid dissolved, and on cooling the product crystallized. It separated from dilute alcohol as colorless needles, m. p. 111–112° (1.8 g.).

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.62. Found: C, 70.25; H, 6.70.

The dimethyl ether was prepared by the action of dimethyl sulfate in alkali containing hydrosulfite and the chief fraction boiled at 132–135° (1.5 mm.) and melted at about 40°. On oxidation with alkaline permanganate at 30–40° the ether gave a high yield of oxalic acid as the only observed product.

2,3-Diallylhydroquinone.—The combined aqueous mother liquors remaining from the above experiment after removal of the 2,5-isomer on extraction with ether gave 22.2 g. of colorless, crystalline material consisting largely of 2,3-diallylhydroquinone. This is very soluble in hot water but crystallizes satisfactorily from this solvent in fine, colorless needles, m. p. 87–90°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 76.17; H, 7.60.

2,5-Diallyl-1,4-benzoquinone.—A solution of 2.5 g. of the hydroquinone in 150 cc. of dry ether was stirred mechanically for two hours with 6.3 g. of silver oxide and 6.5 g. of anhydrous sodium sulfate with exclusion of air. The course of the oxidation can be followed by transfer-

(36) Hahn and Stenner, *Z. physiol. Chem.*, **181**, 88 (1929).

ring a drop of the solution to a watch glass; a violet color appears if hydroquinone is still present, otherwise the spot is completely yellow. The yellow solution was filtered and evaporated, leaving the quinone as a dark orange-yellow oil. It was purified by careful distillation from a salt-bath, b. p. 105–106° (1 mm.), which gave 1.6 g. of a clear yellow oil. Local overheating or distillation at a higher pressure results in decomposition, as evidenced by darkening or by the appearance of a green coloration. The yellow distillate crystallized on cooling in rectangular tablets, m. p. 16°.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.71; H, 6.75.

2,3-Diallyl-1,4-benzoquinone was prepared from the corresponding hydroquinone (2.5 g.) in an analogous manner and the dark reddish-yellow oil (2.4 g.) remaining after evaporation of the ether was used directly in the synthesis and not purified further.

Diene Synthesis of Naphthoquinones (E. M. F.)

6,7-Dimethyl-1,4-naphthoquinone was prepared essentially as described in the patent literature.[17] A solution of 1 g. each of benzoquinone and 2,3-dimethylbutadiene in 2 cc. of benzene was refluxed for five hours and the addition product which crystallized on cooling (1.9 g.) was purified from dilute alcohol and thus separated from a little high melting material. The substance (m. p. 113–115°) was isomerized with 1 *N* alkali under nitrogen and acidification, or by adding dilute hydrochloric acid to a warm solution of the addition product in alcohol (nearly quantitative). The once crystallized (alcohol) dihydronaphthohydroquinone derivative (0.4 g.), m. p. 232–238°, was dissolved in glacial acetic acid (2 cc.) and treated with 0.3 g. of chromic anhydride, when a sharp temperature rise was noted. After a short period water was added and the yellow precipitate purified from alcohol (0.37 g.). It formed somewhat dull yellow crystals, m. p. 120–126°, dec. (blackening). The substance is intermediate in composition between the naphthoquinone and its dihydride and appears to be a complex.

Anal. Calcd. for $(C_{12}H_{11}O_2)_x$: C, 76.98; H, 5.92. Found: C, 77.19, 76.98; H, 6.14, 6.08.

Further treatment of the intermediate with chromic anhydride gave 6,7-dimethyl-1,4-naphthoquinone, which crystallized from alcohol in bright yellow needles of constant m. p. 118–119°.

Anal. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.43; H, 5.61.

6,7-Dimethyl-2,3-diallyl-1,4-naphthoquinone.—The addition product which separated after refluxing 2.4 g. of 2,3-diallyl-1,4-benzoquinone and 3.4 cc. of 2,3-dimethylbutadiene in 3 cc. of benzene for twenty hours was isomerized by short boiling with dilute alcoholic hydrochloric acid to **6,7-dimethyl-2,3-diallyl-5,8-dihydro-1,4-naphthohydroquinone**, which formed somewhat brownish crystals from alcohol, m. p. 156.5–159° (2.3 g.).

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.27; H, 8.15.

A solution of 0.5 g. of this material in acetic acid was treated at room temperature with 0.25 g. of chromic anhydride in glacial acetic acid. A rapid reaction ensued with rise in temperature (40°). After heating to 60° the solution was cooled and a dull yellow intermediate precipitated with water. This formed rectangular plates from alcohol, m. p. 54–56° with previous sintering; yield 0.4 g.

Anal. Calcd. for $(C_{18}H_{19}O_2)_x$: C, 80.87; H, 7.16. Found: C, 80.80; H, 7.17.

For further oxidation to the naphthoquinone 1 g. of the intermediate in 20 cc. of solvent was heated with 0.3 g. of chromic anhydride to 80°, when the solution warmed spontaneously to 90°, and then to 100°. The product then crystallized from alcohol in long flat needles or rectangular plates; both forms are bright yellow and melt at 69.5–70.7°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.46; H, 6.96.

The color changes in the reaction with sodium ethylate are similar to those of 2,3-diallyl-1,4-naphthoquinone.

2,3-Diallyl-1,4-naphthoquinone from Butadiene-benzoquinone (L. F. F.)

5,8-Dihydro-1,4-naphthohydroquinone Diallyl Ether.—A mixture of 7 g. of monobutadiene-*p*-benzoquinone,[18] 10 cc. of allyl bromide, 23.8 g. of finely powdered potassium carbonate, and 150 cc. of purified acetone was refluxed overnight, diluted with water and extracted with ether. After washing with alkali-hydrosulfite and water the light yellow ethereal solution was dried and evaporated, eventually with suction. The residue was taken up in warm methanol and on cooling the ether crystallized in colorless, pearly plates, m. p. 63–64°; yield 5.6 g. (54%). Recrystallized twice from methanol it melted at 64–65°.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.30; H, 7.49. Found: C, 79.51; H, 7.55.

2,3-Diallyl-5,8-dihydro-1,4-naphthohydroquinone.—A solution of 5.6 g. of the diallyl ether in 34 cc. of kerosene was heated under nitrogen in a bath maintained at 240–250° for two hours, and on cooling (under nitrogen) the rearrangement product separated as a crystalline paste. It was collected, washed well with petroleum ether in which it is sparingly soluble, and obtained as completely colorless plates, m. p. 107–108.5°; yield 4.9 g. (88%). The substance is moderately soluble in ligroin (b. p. 70–90°) and crystallizes from this solvent in clusters of microcrystals, m. p. 108–109°. The solution turns slightly yellow in the air and the crystals acquire a pale tan color.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.30; H, 7.49. Found: C, 79.36; H, 7.78.

Oxidation (E. M. F.).—This was conducted in stages as above, first using 4.35 g. of the dihydronaphthohydroquinone in 25 cc. of acetic acid and 4.3 g. of chromic anhydride and warming to 50° to start the reaction. The initial reaction was controlled to 70° and after heating to 100°, cooling and diluting, the oily intermediate product was extracted with ether. Seed was obtained by cooling in alcohol to −78° and the product then crystallized from alcohol in bright yellow, rectangular tablets, m. p. 19.5–21° (previous sintering).

Anal. Calcd. for $(C_{16}H_{16}O_2)_x$: C, 80.31; H, 6.32. Found: C, 80.11; H, 6.30.

Further oxidation of 3.2 g. of the intermediate in 10 cc. of solvent was conducted with 1 g. of chromic anhydride at 60–90°, and the collected product (2 g.), being part liquid and part solid, was oxidized again as before, when an exothermic reaction was noted at 80–90°. The material recovered by ether extraction as a yellow oil crystallized readily from alcohol after obtaining seed and formed long, rectangular, bright yellow plates, m. p. 28–29.5°, identical with the sample described above.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.53; H, 6.02.

Summary

Details are given of observations summarized in two recent Communications. The chemical properties and absorption spectra of synthetic model compounds and the marked antihemorrhagic activity of at least one of these substances (2,3-dimethyl-1,4-naphthoquinone, assayed by the Almquist procedure) lends support to the formulation of vitamin K_1 as 2-methyl- (or ethyl)-3-phytyl-1,4-naphthoquinone and of vitamin K_2 as 2,3-difarnesyl-1,4-naphthoquinone.

A theoretical interpretation is given of the purple-blue color reaction of β-unsaturated alkyl naphthoquinones with sodium ethylate and it is shown that the reaction involves the replacement of the unsaturated side chain by hydroxyl. This accounts for the formation of a phthiocol-like pigment as the end-product of the color reaction with vitamin K concentrates, and the pigment probably is phthiocol or the ethyl homolog. The phthiocol isolated from human tubercle bacilli may have arisen from the alkaline cleavage of a K-type vitamin.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED JULY 8, 1939

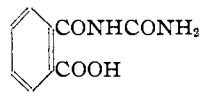
[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, COLLEGE OF MEDICINE THE OHIO STATE UNIVERSITY]

A Study of Some Derivatives of Phthalyl Urea

BY CLAYTON S. SMITH AND CHESTER J. CAVALLITO

Many types of derivatives of urea have been prepared, most of them in the search for compounds possessing hypnotic activity. A large number of substituted ureas possess some degree of hypnotic activity.[1] The most active hypnotics are found among the cyclic ureas, especially the ureides of substituted malonic acid.

The object of the present work was to synthesize derivatives of phthalyl urea, the cyclic ureide of phthalic acid, and to study them for hypnotic activity.

Phthalyl urea was first described by A. Piutti.[2] He prepared the compound by heating equimolecular quantities of phthalic anhydride and urea to 120–125°, forming first the intermediate acyclic ureide of phthalic acid,  , which when treated with phosphorus oxychloride yielded the closed ring structure.

In the present work, the general method of Piutti was used for the synthesis.

(1) A. Hjort, E. J. de Beer and co-workers, *J. Pharmacol.*, **52**, 211 (1934), to *ibid.*, **61**, 175 (1937).

(2) A. Piutti, *Ann.*, **214**, 17 (1882); *Gazz. chim. ital.*, **12**, 169 (1882).

Experimental Procedure

Preparation of Phthalyl Urea and Phthalyl Thiourea.—Equimolecular quantities of phthalic anhydride and urea were ground together in a mortar, then transferred to a round-bottomed flask. The mixture was heated at about 124° on a sulfuric acid bath until the reaction mixture became pasty and finally solidified to a hard mass. The melt should not be heated to such a temperature as to cause the evolution of gas bubbles. The product was pulverized, washed several times with cold water and ether, then recrystallized from hot water (about 35% yield).

Ring closure was brought about by treating the acyclic ureide with enough phosphorus oxychloride to form a thin paste and warming slowly on a water-bath. The reaction was considered complete when hydrogen chloride fumes were no longer liberated. Ether was then added to the reaction mixture, and the product filtered, washed with ether, and recrystallized from hot water.

Phthalyl urea decomposes at 185 to 190° leaving a residue which melts partly at about 230°, and completely above 300° with decomposition. Phthalimide and cyanuric acid $(CONH)_3$ are present as decomposition products.[2]

Phthalyl thiourea was prepared by the same general procedure as described above. The intermediate acyclic ureide did not form as rapidly in the case of thiourea as with urea.

Attempts to prepare the cyclic ureides by treating phthalic anhydride and urea directly with phosphorus oxychloride were unsuccessful. It appears necessary first to bring about the combination