components containing a benzohydroquinone nucleus, although such substances are less reactive than the compounds of the naphthalene series and the yields are lower. 5,8-Dihydrovitamin $K_1$ and 2,3,5-trimethyl-6-phytyl-1,4-benzoquinone have been prepared by the standard synthesis and the latter substance has been utilized in a new synthesis of $\alpha$-tocopherol.

CAMBRIDGE, MASSACHUSETTS
RAHWAY, NEW JERSEY RECEIVED AUGUST 10, 1940

---

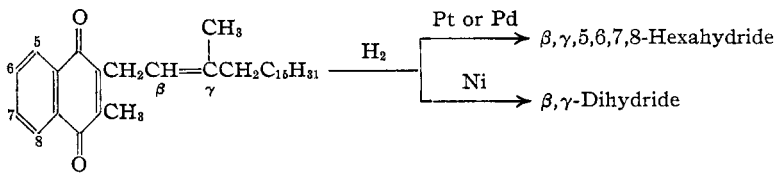
[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK AND CO., INC., AND THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

# Hydro, Oxido and Other Derivatives of Vitamin $K_1$ and Related Compounds

BY MAX TISHLER, LOUIS F. FIESER AND NORMAN L. WENDLER

This paper presents the details of preparative work which has been reported briefly in part in recent Communications.[1] The more significant findings concerning the biological activities of the compounds have been indicated in these preliminary reports and the complete assay data will be presented later.

One series of experiments was concerned with the preparation of various hydro derivatives. Doisy and co-workers[2] found that on hydrogenation of vitamin $K_1$ in a mixture of acetic acid and *n*-butyl ether in the presence of platinum catalyst the reaction proceeds readily to the stage of absorption of four moles of hydrogen. In the present work trial hydrogenations were conducted in various solvents with platinum and palladium catalysts in the search for conditions under which the reaction would stop after reduction of the quinone to the hydroquinone and the saturation of the double bond in the side chain, but the absorption of gas proceeded without noticeable break to the four-mole stage. The hydroquinone produced as the end-product of the reaction was separated, as in the vitamin $K_1$ synthesis, by virtue of its sparing solubility in petroleum ether




Vitamin $K_1$

and oxidized to $\beta,\gamma,5,6,7,8$-hexahydro-vitamin $K_1$, which was obtained as a yellow oil giving a negative Dam–Karrer color test and affording a crystalline hydroquinone diacetate. The preparation of the quinone by a similar method has been described also by Fernholz, MacPhillamy and Ansbacher.[3] When Raney nickel was used as catalyst in combination with methanol as solvent there was a sharp drop in the rate of hydrogenation after the absorption of two moles of gas. Purification was again accomplished through the solid hydroquinone produced, and after oxidation with silver oxide there was obtained a yellow oil which appears to be pure $\beta,\gamma$-dihydrovitamin $K_1$, or 2-methyl-3-dihydrophytyl-1,4-naphthoquinone. In contrast to the isomeric 5,8-dihydrovitamin $K_1$,[4] the quinone gives no blue color with alcoholic alkali in the presence of air. The preparation of the $\beta,\gamma$-dihydride by a longer synthesis has been reported by Karrer and Epprecht,[5] who isolated the material from a reaction mixture by chromatographic adsorption. The method of hydrogenation in the presence of Raney nickel and purification of the product in the hydroquinone form has been applied also to the conversion of 2-phytyl-1,4-naphthoquinone into the 2-dihydrophytyl compound. In the case of 2-methyl-3-cinnamyl-1,4-naphthoquinone hydrogenation in the presence of nickel failed to proceed beyond saturation of the quinone grouping, but the $\beta,\gamma$-dihydride was obtained satisfactorily using palladium chloride.

The biologically interesting oxido derivatives of several naphthoquinones possessing antihemorrhagic activity were prepared easily in almost quantitative yield by treatment of the quinone in alcohol or dioxane

(1) Fieser, Tishler and Sampson, THIS JOURNAL, **62**, 996, 1628 (1940); Tishler, Fieser and Sampson, *ibid.*, **62**, 1881 (1940).

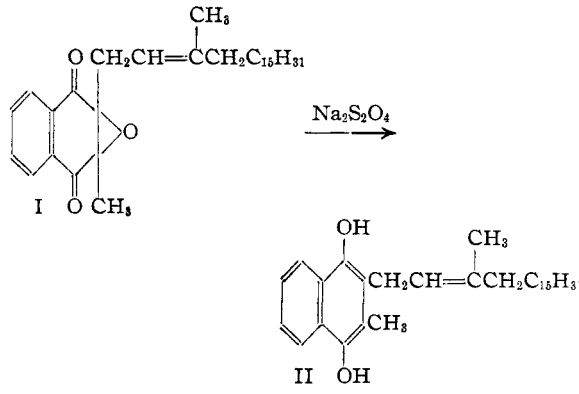
(2) Binkley, MacCorquodale, Thayer and Doisy, *J. Biol. Chem.*, **130**, 219 (1939).

(3) Fernholz, MacPhillamy and Ansbacher, THIS JOURNAL, **62**, 1619 (1940).

(4) Fieser, Tishler and Wendler, *ibid.*, **62**, 2861 (1940).

(5) Karrer and Epprecht, *Helv. Chim. Acta*, **23**, 272 (1940).

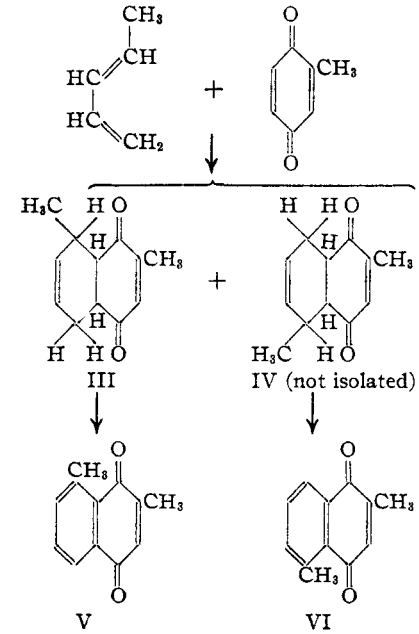
with hydrogen peroxide and aqueous sodium carbonate solution.[6] The method is applicable to both the 2-substituted and 2,3-disubstituted naphthoquinones, and in the case of compounds of high molecular weight where the oxide is an oil, a pure product is obtained merely by extraction with ether and evaporation of the solvent. Vitamin $K_1$ oxide (I) is a nearly colorless oil which does not




show the light sensitivity characteristic of the vitamin and which is not altered by being heated with aqueous dioxane at 150°. The absorption spectrum, kindly determined by Dr. T. J. Webb in 95% alcohol, showed narrow absorption bands at 259 and 305 mμ (log *EM* 3.79 and 3.31). 2,3-Dimethyl-1,4-naphthoquinone oxide gave a similar curve with a shoulder at about 259 mμ (3.8) and a narrow band at 303 mμ (3.25).

The oxide I can be reduced smoothly to vitamin $K_1$ hydroquinone (II) with sodium hydrosulfite in an alcohol–water medium at room temperature, and a similar reduction was observed with 2-methyl-1,4-naphthoquinone oxide. While the latter oxide can be converted almost quantitatively into phthiocol with concentrated sulfuric acid,[7] alkaline cleavage of this and other monoalkyl derivatives does not proceed in one direction. Thus 2-farnesyl-1,4-naphthoquinone oxide on treatment with alcoholic alkali in the cold was converted in part into 2-hydroxy-1,4-naphthoquinone and in part into a substance which was not isolated in a pure condition but which had the properties of a hydroxyalkenylnaphthoquinone.

The Experimental Part includes a description of the preparation of various other substances required in our investigation of the relationship between vitamin K activity and structure, as outlined for the most part in previous communications.[1] For completion of the series of monomethyl derivatives of the potent 2-methyl-1,4-naphthoquinone it was desired to obtain 2,8- and 2,5-dimethyl-1,4-naphthoquinone. These quinones have been prepared previously by the oxidation of 1,7-[8] and 1,6-[9]dimethylnaphthalene, respectively, and are described as melting at 136 and 95°. Only the second of these hydrocarbons is available commercially, and on oxidation of a sample of supposedly homogeneous material which gave a picrate of the recorded melting point[9] there was obtained an evident mixture of steam-volatile quinones. On careful fractional crystallization two dimethylnaphthoquinones (analysis) were isolated which corresponded in melting point with the 2,8- and 2,5-isomers, which evidently possessed a substituent at the 2-position, as indicated by their failure to react with acetic anhydride–sulfuric acid, and which were different from the known 2,3-, 2,6- and 2,7-isomers. This observation suggested that the sample of 1,6-dimethylnaphthalene may have been contaminated with some of the 1,7-isomer, but in the absence of a supply of the latter hydrocarbon or of a sample of the quinone for comparison, an independent synthesis was undertaken starting with the addition of piperylene to toluquinone.




(6) Fieser, Campbell, Fry and Gates, THIS JOURNAL, **61**, 3216 (1939). Weitz, Schobbert and Seibert, *Ber.*, **68**, 1163 (1935), obtained α-naphthoquinone oxide in unspecified yield with the use of hydrogen peroxide in an alkali–methanol mixture, but this method does not appear applicable to the alkali-sensitive quinones of the vitamin K type.

(7) Fieser, *J. Biol. Chem.*, **133**, 391 (1940).

(8) Kruber and Schade, *Ber.*, **69**, 1722 (1936).

(9) Weissgerber and Kruber, *ibid.*, **52**, 346 (1919).

A crystalline and homogeneous reaction product was isolated easily, but in only 43% yield. This was isomerized with hydrochloric acid in the presence of stannous chloride and the resulting hydroquinone oxidized with chromic acid. The product was an easily purified substance identical with the higher melting dimethylnaphthoquinone obtained from the hydrocarbon. The non-crystalline residue from the diene addition reaction was put through a similar process and afforded, after steam distillation, a quinone mixture from which there was obtained on fractionation a pure substance identical with the dimethylnaphthoquinone of lower melting point. Since the synthesis could yield as end-products only the 2,8- and 2,5-isomers, it is safe to assume that the higher melting compound obtained from the crude hydrocarbon is indeed 2,8-dimethyl-1,4-naphthoquinone (V). The crystalline diene addition product is therefore *III*, but it is interesting to note that piperylene adds to toluquinone in both possible directions.

## Experimental Part[10]

**β,γ,5,6,7,8-Hexahydrovitamin $K_1$†.**—Trials were made of the hydrogenation of synthetic vitamin $K_1$ in methyl or ethyl alcohol, ethyl acetate or acetic acid in the presence of platinum or palladium oxide, platinum or palladium chloride, or platinum black, but in no case was there a sharp break in the reaction after the absorption of one mole of hydrogen and the hydrogenation proceeded at a rapid rate until four moles of gas had been taken up. In a typical experiment 1 g. of the quinone in 15 cc. of methanol in the presence of 100 mg. of Adams catalyst absorbed one mole of hydrogen in two minutes, when the hydrogen absorption fell off to about 6 cc. per minute and continued at this rate until 4 moles had been absorbed and then dropped to about 0.5 cc. per minute.

When the reaction was stopped at the four-mole stage, the filtered solution on dilution with water deposited hexahydrovitamin K hydroquinone as a solid. Since this tended to darken when collected by filtration, it was extracted with petroleum ether and the pale yellow solution was concentrated under nitrogen to a volume of 10 cc. and chilled. The hydroquinone separated readily and was washed twice with petroleum ether by centrifugation and oxidized in ether with silver oxide in the presence of magnesium sulfate. Evaporation of the filtered solution afforded 0.8 g. of the quinone as a golden-yellow oil. The substance gave an orange-red color when heated with alcoholic potassium hydroxide and the purple phase characteristic of vitamin $K_1$ was absent.

*Anal.* Calcd. for $C_{31}H_{52}O_2$: C, 81.59; H, 11.48. Found: C, 81.83; H, 11.51.

(10) The experiments indicated by the symbol † were carried out at the Merck Research Laboratories (M. T. and N. L. W.), with microanalyses by D. Hayman, W. Reiss and H. C. Clark; those designated * were conducted at Harvard (L. F. F.) with microanalyses by Lyon Southworth.

The **hydroquinone diacetate** was obtained by reductive acetylation with pyridine as catalyst and formed colorless crystals, m. p. 53°, from ethanol.

*Anal.* Calcd. for $C_{35}H_{58}O_4$: C, 77.43; H, 10.75. Found: C, 77.34; H, 10.73.

**β,γ-Dihydrovitamin $K_1$.†**—Attempts to obtain this compound by partial hydrogenation using platinum or palladium catalyst were unsuccessful, for even after the absorption of 3 moles of hydrogen the reaction mixture gave a strong Dam–Karrer test. With Raney nickel catalyst (1 g.), 3 g. of vitamin $K_1$ in 25 cc. of methanol absorbed the first mole of gas in five minutes and the absorption then dropped to 5 cc. per minute; after a second mole of hydrogen had been taken up the rate fell to about 1 cc. per minute. For the preparation of the dihydride the reaction was stopped after 2 moles of hydrogen had been absorbed and the solution was filtered and extracted with petroleum ether. The hydroquinone separated easily on slight cooling and was washed three times with fresh solvent; it seemed more crystalline and less soluble than vitamin $K_1$ hydroquinone. Oxidation with silver oxide gave a golden-yellow oil which showed no purple-blue phase in the Dam–Karrer test.

*Anal.* Calcd. for $C_{31}H_{48}O_2$: C, 82.29; H, 10.69. Found: C, 82.35; H, 10.71.

The **hydroquinone diacetate** melted at 57–58°.

*Anal.* Calcd. for $C_{35}H_{54}O_4$: C, 78.02; H, 10.09. Found: C, 78.02; H, 10.06.

**2-Dihydrophytyl-1,4-naphthoquinone.†**—On hydrogenation of phytylnaphthoquinone (1 g.) in methanol (15 cc.) using Raney nickel (1 g.) the absorption of two moles of gas was complete in one hour. The hydroquinone was obtained from chilled petroleum ether as a waxy solid, and was washed and oxidized as usual. The quinone was a golden-yellow oil giving a negative Dam–Karrer test and a positive Craven test.

*Anal.* Calcd. for $C_{30}H_{46}O_2$: C, 82.12; H, 10.57. Found: C, 82.18; H, 10.69.

**2-Methyl-3-hydrocinnamyl-1,4-naphthoquinone.†**—On shaking 1 g. of the cinnamyl compound, 0.1 g. of palladium chloride and 15 cc. of methanol with hydrogen, the calculated amount of hydrogen was taken up in about fifteen minutes and the reaction then stopped. (With Raney nickel the hydrogenation would not proceed beyond the hydroquinone stage.) The filtered solution was diluted with water and extracted with ether; the dried solution was then shaken with silver oxide and magnesium sulfate, filtered and concentrated to about 2 cc. On adding an equal volume of petroleum ether and chilling, the product separated as fine yellow needles, m. p. 42° (0.85 g.). The Dam–Karrer test was negative.

*Anal.* Calcd. for $C_{20}H_{18}O_2$: C, 82.75; H, 6.21. Found: C, 82.99; H, 6.14.

**2-Methyl-5,6,7,8-tetrahydro-1,4-naphthohydroquinone.†**—A solution of 8.55 g. of 2-methyl-1,4-naphthoquinone in 100 cc. of acetic acid was hydrogenated at 50° in the presence of 0.4 g. of palladium chloride. On diluting the filtered solution the hydroquinone separated as fluffy white needles, m. p. 165–167° (7.9 g.). A sample for analysis was recrystallized from ether.

*Anal.* Calcd. for $C_{11}H_{14}O_2$: C, 74.15; H, 7.87. Found: C, 74.08; H, 7.94.

Silver oxide oxidation gave **2-methyl-5,6,7,8-tetrahydro-1,4-naphthoquinone,**[8,11] m. p. 58° (found: C, 75.02; H, 6.94), and on reductive acetylation this yielded the **hydroquinone diacetate,**[11] m. p. 100–101° (found: C, 68.64; H, 7.08).

**2-Methyl-1,4-naphthohydroquinone Dimesitoate.***—On mixing 1 g. of the pure hydroquinone with 2.3 g. of mesitoyl chloride, the evolution of hydrogen chloride commenced almost at once, and on stirring a smooth reaction ensued without heat effect and the mixture soon solidified. The mixture was melted over a free flame to complete the reaction and after resolidification of the nearly colorless melt the product was crystallized from pyridine–water, giving colorless material, m. p. 204–205° (2.2 g.). Recrystallization from acetic acid (moderately soluble, heavy plates) or benzene (very soluble, clusters of prisms) did not raise the m. p. The ester is highly resistant to hydrolysis with alcoholic alkali (remains colorless) and contrasts in this respect with the dibenzoate (yellow coloration).

*Anal.* Calcd. for $C_{31}H_{36}O_4$: C, 79.80; H, 6.48. Found: C, 80.11; H, 6.70.

**Alkylnaphthoquinone Oxides.**—Naphthoquinones of low molecular weight can be converted very rapidly and smoothly into the oxides by the procedure of Fieser, Campbell, Fry and Gates.[6] Thus on treating 0.5 g. of 2,3-dimethyl-1,4-naphthoquinone in 15 cc. of alcohol at 30° with 1 cc. of 30% hydrogen peroxide and 2 cc. of water containing 0.2 g. of sodium carbonate the yellow color was discharged at once and, after adding water and cooling, the oxide separated in a nearly pure condition, m. p. 103.5–104.5° (0.45 g.). With quinones of lower solubility the reaction may be a two-phase one and a longer time of contact or a higher temperature may be required. In preparing 2-farnesyl-1,4-naphthoquinone oxide a solution of the quinone in dioxane was mixed with hydrogen peroxide and aqueous soda solution and allowed to stand at room temperature for five days. Vitamin $K_1$ oxide was prepared by adding 1 cc. of 30% hydrogen peroxide and 2 cc. of water containing 1 g. of sodium carbonate to a warm (75°) solution of 1 g. of vitamin $K_1$ in 50 cc. of ethanol. The mixture was kept at 75° and stirred vigorously with a glass rod for about five minutes. The yellow color had faded by this time and a slight pink coloration had developed; the Dam–Karrer test was negative. The mixture was cooled, diluted with water, and extracted with ether. The solution was dried, treated with Norit, and the solvent evaporated, eventually with suction. The residue was a nearly colorless oil having the analysis reported in the table, yield 0.85 g.

TABLE I

2,3-OXIDES OF 1,4-NAPHTHOQUINONES

| Oxide of -1,4-naphthoquinone | Form | Properties M. p., °C. | Analyses, % Carbon Found | Carbon Calcd. | Hydrogen Found | Hydrogen Calcd. |
|---|---|---|---|---|---|---|
| 2,3-Dimethyl* | Needles | 104–104.5 | 71.26 | 71.27 | 5.09 | 4.99 |
| 2-Methyl-3-cinnamyl† | Needles | 85–86 | 78.94 | 78.94 | 5.47 | 5.26 |
| 2-Farnesyl* | Oil | | 78.88 | 79.33 | 8.16 | 7.99 |
| 2-Phytyl† | Oil | | 79.91 | 79.61 | 9.76 | 9.81 |
| 2-Methyl-3-phytyl (Vit. $K_1$)† | Oil | | 79.85 | 79.77 | 9.69 | 9.94 |

The reaction of the quinones with hydrogen peroxide in a weakly alkaline medium appears to be essentially quantitative, and the only impurities likely to be present in the oxides are those present in an imperfectly purified starting material. The crystalline oxides are easily obtained in a completely colorless condition, and the liquid substances listed in the table had at most a faint yellowish tinge. The oxides of the 2,3-disubstituted naphthoquinones do not give the Craven test, whereas the 2-methyl and 2-phytyl compounds when treated with alcoholic ammonia and cyanoacetic ester give, after a lag of several seconds and not as rapidly as the parent quinones, a blue color which rapidly deepens.

Vitamin $K_1$ oxide is much more stable to light than the vitamin itself and the oxidic ring apparently is not opened easily. Thus a slightly turbid solution of 1 g. of the oxide in 15 cc. of dioxane and 1.5 cc. of water was heated in a sealed tube at 140–150° for six hours and the product was recovered by ether extraction and found to be of unchanged composition (found: C, 79.53; H, 10.09) and to give the same reddish color test with alcoholic alkali.†

The following experiments illustrate the ease with which the oxide linkage is eliminated by reduction. A solution of 0.5 g. of 2-methyl-1,4-naphthoquinone oxide in 3 cc. of hot alcohol was treated with 2 g. of sodium hydrosulfite in 10 cc. of water, when the solution changed through a transient red to yellow.* This largely faded after heating for one-half hour on the steam-bath, when an oil had deposited and the solution had acquired a pinkish tinge. The color was discharged with the addition of a little more hydrosulfite and on cooling there was obtained 0.37 g. of colorless methylnaphthohydroquinone, dec. about 160°. This was identified by conversion to the diacetate (clusters of sparlike prisms, m. p. and mixed m. p. 112.5–113°) and the quinone (m. p. and mixed m. p. 105–106.5°). A mixture of 1 g. of vitamin $K_1$ oxide in 50 cc. of methanol and 1.5 g. of sodium hydrosulfite in 3 cc. of warm water was shaken mechanically for seventy-two hours at room temperature.† The mixture was then poured into a separatory funnel containing 150 cc. of water and 15 cc. of petroleum ether. On shaking, a waxy white solid appeared in the hydrocarbon layer. This was separated, chilled at −10°, and the product collected and washed by centrifugation. Silver oxide oxidation in the usual way gave 0.5 g. of vitamin $K_1$, identified by a positive Dam–Karrer test and by analysis.

*Anal.* Calcd. for $C_{31}H_{46}O_2$: C, 82.61; H, 10.29. Found: C, 82.52; H, 10.35.

When treated with alcoholic alkali the oxides develop a pink or red coloration. The following experiment* partially indicates the nature of the changes, although the identification was not complete. On covering 0.22 g. of 2-farnesyl-1,4-naphthoquinone oxide with 3 cc. of 10% alcoholic potassium hydroxide the oil rapidly dissolved to a deep red solution and in a few minutes a bright red salt (of hydroxynaphthoquinone) separated. Water was added to dissolve the salt and the solution was acidified and extracted with ether. Extraction with aqueous sodium carbonate gave an orange–red solution from which there was recovered 0.08 g. of 2-hydroxy-1,4-naphthoquinone, m. p. 186–188°, dec., identified by mixed m. p. determination,

(11) Chuang and Han, *Ber.*, **68**, 876 (1935).

color tests, and conversion to the methyl ether, m. p. and mixed m. p. 183–184°. Evaporation of the washed and dried residual ethereal solution gave 0.13 g. of a rather dark yellow oil. When distributed between petroleum ether and Claisen's alkali a deep red alkaline layer was obtained, and on diluting this and extracting with ether the pigment passed into the ether layer in the form of a red potassium salt, for on adding acetic acid the ethereal solution became yellow. The substance thus has the properties of an alkenylhydroxynaphthoquinone, but it was not isolated in a pure condition.

**Oxidation of Commercial 1,6-Dimethylnaphthalene.***—Three lots of hydrocarbon obtained from the Gesellschaft für Teerverwertung were examined by the preparation of the picrate and in each case this melted initially at about 112–113° and after recrystallization from alcohol at 113–114° (compare 114° for the 1,6-isomer[9] and 121° for the 1,7-compound[9]). Two 15.6-g. batches of hydrocarbon when oxidized as described by Weissgerber and Kruber[9] gave, after steam distillation, 2.2 g. and 2.93 g. of total quinone. The material melted initially at about 85–110° and on crystallization from 20 cc. of methanol about one-third separated in a first crop, m. p. 120–127°. In one experiment three recrystallizations from methanol gave **2,8-dimethyl-1,4-naphthoquinone** of the constant m. p. 135–135.5°; in the second run comparable material was obtained from methanol after a preliminary treatment with acetic anhydride–sulfuric acid designed to remove any quinone present which did not carry a hindering methyl group at the 2-position. The purified quinone gave a 20° depression when mixed with 2,6-dimethyl-1,4-naphthoquinone, m. p. 138.5–139°.

*Anal.* Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.42; H, 5.64.

The initial mother liquor afforded low melting material (78–82°) which was not greatly improved by crystallization from methanol and which was not affected by treatment with acetic anhydride–sulfuric acid. Crystallization from ether–petroleum ether, however, gave radiating clusters of heavy, lemon-yellow needles melting at 92–93°, and a further crystallization gave pure **2,5-dimethyl-1,4-naphthoquinone,** m. p. 93.5–94.5°

*Anal.* Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.33; H, 5.67.

**Synthesis from Piperylene and Toluquinone.***—A solution of 8 g. of sublimed toluquinone and 8 cc. of piperylene (b. p. 42–42.5°) in 20 cc. of purified dioxane was heated in a capped bottle at 60–70° for forty hours and the still yellow solution was then diluted with water and the product extracted with ether. The washed and dried ether layer was evaporated to about 15 cc. and treated with petroleum ether until cloudy (*ca.* 50 cc.). On cooling there separated 4.48 g. of heavy, somewhat yellow prisms, m. p. 99°, and the mother liquor afforded 0.86 g. more, m. p. 98°. The processing of the residual oil is described below. The crystalline product, shown to be **2,8-dimethyl-1,4-diketotetrahydronaphthalene** (III), was crystallized several times from methanol (very soluble), methanol–water, and ligroin (readily soluble), when it formed faintly yellow, heavy, rectangular plates. The m. p. is like that of camphor, softening occurring at about 96° and the last crystal disappearing sharply at 101.5°.

*Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.79; H, 7.42. Found: C, 75.76; H, 7.59.

For isomerization to **2,8-dimethyl-5,8-dihydro-1,4-naphthohydroquinone,** 3.2 g. of III in 15 cc. of alcohol was warmed with 0.3 g. of stannous chloride and 1 cc. of concentrated hydrochloric acid in 3 cc. of water. The solution turned strongly yellow at first and then became colorless. On dilution with water a colorless oil separated, and in the course of several days this solidified, in part to well formed needles (1.86 g.). Purified by crystallization from ligroin (70–90°), the substance formed tufted clusters of colorless, rather stout needles, m. p. 91–91.5°.

*Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.79; H, 7.42. Found: C, 75.78; H, 7.62.

Oxidation of 1.71 g. of this substance in 10 cc. of acetic acid was accomplished with 2.5 g. of chromic anhydride in 2 cc. of water and 5 cc. of acetic acid. The temperature was kept at 60° (except for a brief temporary rise) during the addition and for one-half hour longer. The addition of water gave a bright yellow precipitate, and one crystallization from methanol produced 0.61 g. of **2,8-dimethyl-1,4-naphthoquinone** in the form of long yellow needles, m. p. 134–135.5°. The recrystallized material melted at 135–135.5° and gave no depression with the above sample.

The residual oil from the diene addition was isomerized as above except that more stannous chloride was required to discharge the color. The collected product, a viscous brown oil (5.32 g.) was oxidized at 60° and the product was extracted with ether and steam distilled, giving 2.08 g. of bright yellow quinone mixture. Crystallization from methanol gave low melting material (*e. g.* 78–82°) in all fractions, indicating the predominance of 2,5-dimethyl-1,4-naphthoquinone. This was isolated from a more soluble fraction by crystallization from ether–petroleum ether and obtained, after further purification, as yellow needles, m. p. and mixed m. p. 93.5–94°. A small amount of the 2,8-isomer was isolated from the top fraction by crystallization first from ether–petroleum ether and then from methanol; it melted at 133–134° and was identified by mixed m. p. determination.

**Preparation of Methylnaphthols and Methyltetralones.**—**4-Methyl-1-naphthol*** was prepared according to Elbs and Christ[12] and obtained from ligroin as colorless prisms, m. p. 83.5–84.5°. L. W. Newton prepared **3-methyl-2-naphthol,**[13] m. p. 160.9–161.5°, corr., by Wolff–Kishner reduction of the corresponding aldehyde; he prepared **9-methylperinaphthenone-7,** m. p. 156.5–157.2°, corr., according to Criegee.[14]

**3-Methyl-1-tetralone**† was prepared from γ-phenyl-β-methylbutyric acid by ring closure through the acid chloride by a procedure similar to that recently reported by Bachmann and Struve[15] and, better, by heating the acid with 7 volumes of 80% sulfuric acid on the steam-bath for two hours (75% yield). The product distilled at 140° at 13 mm. pressure. The **semicarbazone** crystallized from ethanol as prisms, m. p. 195–196°.

(12) Elbs and Christ, *J. prakt. Chem.*, **106,** 17 (1923).

(13) Veselý and Stursa, *Collection Czechoslov. Chem. Commun.*, **6,** 137 (1934).

(14) Criegee, *Ann.*, **507,** 176 (1933).

(15) Bachmann and Struve, THIS JOURNAL, **62,** 1618 (1940).

*Anal.* Calcd. for $C_{11}H_{12}ON_3$: C, 66.36; H, 6.92. Found: C, 66.40; H, 7.05.

**3-Methyl-1-naphthol,**† previously synthesized by Fittig,[16] was prepared by dehydrogenation of the methyltetralone. Heating with selenium at 310–330° for twenty hours or with sulfur at 250° for thirty minutes afforded the methylnaphthol in yields of 25 and 30%, respectively. By brominating the methyltetralone in carbon bisulfide, removing the solvent, and then boiling the oily residue with dimethylaniline, the methylnaphthol was obtained in a satisfactory condition in 65% yield. The substance crystallized from petroleum ether in fine needles which melted initially at 91–93.5°, solidified, and remelted at 93.5–94°. The **benzoate** melted at 75–76°.

*Anal.* Calcd. for $C_{18}H_{14}O_2$: C, 82.44; H, 5.34. Found: C, 82.22; H, 5.38.

**2-Methyl-1-tetralone**† was prepared by cyclization of α-methyl-γ-phenylbutyryl chloride according to Schroeter, *et al.*,[17] and also, in 75% yield, by heating the acid with 80% sulfuric acid. The ketone boiled at 136–137° at 16 mm. pressure.

The **oxime** melts at 98–99°; the **semicarbazone** forms needles, m. p. 205–206°.

*Anal.* Calcd. for $C_{11}H_{12}ON_3$: C, 66.36; H, 6.92. Found: C, 66.49; H, 6.77.

**2-Methyl-1-naphthol**† was prepared from 2-methyl-1-tetralone by dehydrogenation with bromine (41% yield) and from 2-methyl-1-naphthylamine according to Lesser[18] (55% yield). The substance crystallized from petroleum ether as fluffy needles, m. p. 63–64°. The **benzoate** formed needles from ether–petroleum ether, m. p. 94–95°.

*Anal.* Calcd. for $C_{18}H_{14}O_2$: C, 82.44; H, 5.34. Found: C, 82.40; H, 5.69.

(16) Fittig, *Ann.*, **255**, 270 (1889); **314**, 73 (1901).
(17) Schroeter, Lichtenstadt and Irineu, *Ber.*, **51**, 1600 (1918).
(18) Lesser and Aczél, *Ann.*, **402**, 30 (1914).

The **acetate** separates from ether–petroleum ether as needles, m. p. 81–82°.

*Anal.* Calcd. for $C_{13}H_{12}O_2$: C, 78.00; H, 6.00. Found: C, 78.15; H, 5.93.

## Summary

By partial hydrogenation under suitable conditions vitamin $K_1$ and 2-methyl-3-cinnamyl-1,4-naphthoquinone can be converted into the corresponding β,γ-dihydrides. More drastic hydrogenation of the former compound affords the β,γ,5,6,7,8-hexahydride. The products are conveniently purified through their solid hydroquinones.

The 2,3-oxides of 2-substituted and 2,3-disubstituted 1,4-naphthoquonones having both saturated and β-unsaturated groups are easily prepared by the action of hydrogen peroxide and sodium carbonate. Vitamin $K_1$ oxide is a stable, colorless oil. The oxides of the 2-substituted series are easily cleaved by alkali, in part with elimination of the substituent group.

Piperylene adds to toluquinone in both possible directions, but one of the isomeric addition products is easily isolated and affords a ready source of 2,8-dimethyl-1,4-naphthoquinone.

Details are given of the preparation of the various methylnaphthols and methyltetralones assayed for antihemorrhagic activity.

RAHWAY, NEW JERSEY
CAMBRIDGE, MASSACHUSETTS RECEIVED AUGUST 10, 1940

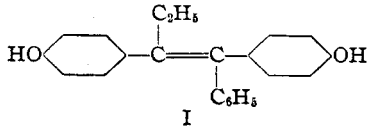
---

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

# Studies on the Preparation of Synthetic Sex Hormones. I. Hexoestrol

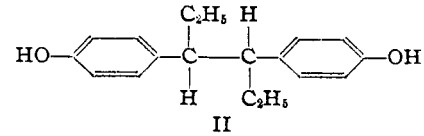
BY SEYMOUR BERNSTEIN AND EVERETT S. WALLIS

That relatively simple, synthetic organic compounds exhibit an oestrogenic activity is now well known. The number of oestrogens is amazingly large. Considerable interest has been centered upon diethylstilboestrol (I). The preparation of this highly interesting compound has been accomplished by Dodds, Robinson, *et al.*[1]



I

In 1938, Campbell, Dodds and Lawson reported the isolation, in poor yields, of a highly potent oestrogen from the products of the demethylation of anethole.[2] Later, it was shown that this compound was in reality *p,p'*-dihydroxydiphenylhexane (II) and was named *hexoestrol.*[1b,3]



II

It is evident that diethylstilboestrol, I, and

(1) E. C. Dodds, R. Robinson, *et al.*, (a) *Nature*, **141**, 247 (1938); (b) *Proc. Roy. Soc.* (London), **B127**, 140 (1939).

(2) N. R. Campbell, E. C. Dodds and W. Lawson, *Nature*, **142**, 1121 (1938).

(3) N. R. Campbell, E. C. Dodds and W. Lawson, *Proc. Roy. Soc.* (London), **B128**, 253 (1940).