Other Reactions.—None of the three esters would react with *p*-acetaminobenzenesulfonyl chloride when treated with that reagent in acetone, in pyridine at 100°, or in quinaldine at 175°. The major part of the ester was recovered in every case.

α-2-Amino-4-thiazylcaprylic acid did not react with *p*-acetaminobenzenesulfonyl chloride in aqueous sodium hydroxide. 2-Amino-4-*n*-heptylthiazole was recovered from this reaction.

With 2-amino-4-*n*-heptylthiazole, 2-amino-4-*n*-amylthiazole and 2-amino-4-*n*-propylthiazole, *p*-acetaminobenzenesulfonyl chloride reacts normally giving products melting at 166–167°, 163–164° and 182–183° (cor.), respectively.

Anal. Calcd. for $C_{18}H_{25}O_3N_3S_2$: N, 10.7. Found: N, 10.5. Calcd. for $C_{16}H_{21}O_3N_3S_2$: N, 11.4. Found: N, 11.2. Calcd. for $C_{14}H_{17}O_3NS$: N, 12.4. Found: N, 12.4.

Summary

The preparation of some new ethyl α-alkyl-2-amino-thiazyl-4-acetates has been reported.

A method for the conversion of these esters to 2-amino-4-alkythiazoles has been described.

PHILADELPHIA, PENNSYLVANIA RECEIVED APRIL 18, 1941

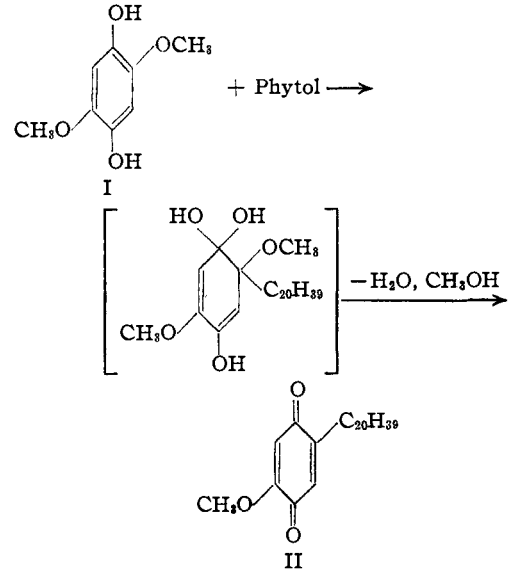
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Condensation of Allylic Alcohols with Hydroxyhydroquinones

BY LOUIS F. FIESER AND MARSHALL D. GATES, JR.

The starting point of this work was an attempt to investigate by synthesis the structure of maesaquinone, a pigment which Hiramoto[1] isolated from the fruit of a Japanese tree and which he characterized as a derivative of 2,5-dihydroxybenzoquinone with an alkenyl side chain of the composition $C_{20}H_{39}$. Since this is the composition of the phytyl radical, and since proof is still lacking of Hiramoto's reasonable postulate that the side chain is normal and not branched, 2,5-dihydroxy-3-phytylquinone would represent at least a possible structure for the pigment.

An attempted synthesis of the phytyl compound by the condensation method developed for the synthesis of vitamin K_1[2] took an unexpected course. The readily oxidizable 1,2,4,5-tetrahydroxybenzene proved to be a less promising starting material than 2,5-dimethoxyhydroquinone (I). When the latter compound was heated with phytol and oxalic acid in dioxane solution, it afforded an evident mixture of substances, but by fractional adsorption of the material in the oxidized condition on magnesium sulfate a chromatographically homogeneous product was isolated as an orange oil. This gives a positive (reddish purple) Dam–Karrer color test with alcoholic alkali, indicative of a β-alkenyl quinone, and it is convertible into a hydroquinone diacetate (liquid). Carbon-hydrogen and methoxyl determinations of the substance as such and in the form of the product of reductive acetylation clearly indicate the formula $C_{26}H_{41}O_2(OCH_3)$, rather than the expected $C_{26}H_{40}O_2(OCH_3)_2$, and therefore one methoxyl group has been eliminated. A plausible interpretation is that the reaction takes a course parallel to the formation, in the vitamin K_1 synthesis, of a by-product in which the phytyl group has affixed itself to a nuclear position already carrying a methyl substituent.[3] Thus a transient addition product or equivalent intermediate may be produced which not only can lose water from the *gem*-diol group, as in the formation of the K_1 by-product, but also suffer elimination of methanol to afford the quinone II.



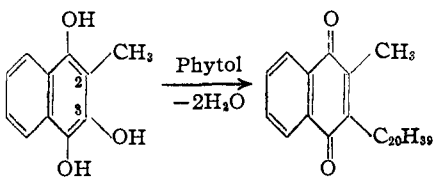
The reaction may have proceeded in other directions as well, but the properties and analyses of the only substance isolated from the mixture find adequate representation in formula II.

(1) Hiramoto, *Proc. Imp. Acad.* (Tokyo), **15**, 220 (1939).

(2) Fieser, THIS JOURNAL, **61**, 3467 (1939).

(3) Tishler, Fieser and Wendler, *ibid.*, **62**, 1982 (1940).

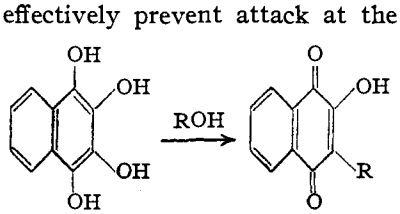
The apparent replacement of methoxyl by the phytyl group in this instance suggested other possible applications which should provide a means of testing the hypothesis. Thus the condensation of phytol with phthiocol hydroquinone (III) might result in the affixment of the phytyl radical to either the 2- or 3-position, but only the latter



III IV (Vitamin K_1)

reaction could yield a quinonoid product. The condensation was tried and found to afford a yellow oil identified as 2-methyl-3-phytyl-1,4-naphthoquinone (IV) by analysis and by direct comparison of the crystalline hydroquinone diacetate with the known derivative from IV. This constitutes a new synthesis of vitamin K_1; the yield is lower than in the synthesis from 2-methyl-1,4-naphthohydroquinone, and it is probable that some condensation takes place at the alternate 2-position. In a further trial, the condensation of cinnamyl alcohol with phthiocol hydroquinone in the presence of oxalic acid was found to yield the known[4] 2-methyl-3-cinnamyl-1,4-naphthoquinone, and it is evident that a nuclear hydroxyl or methoxyl substituent of a hydroquinone is indeed capable of being replaced by the phytyl residue with the formation of a quinonoid product.

In order to explore the synthetic possibilities of the new reaction, we investigated the condensation of phytol, farnesol, and geraniol with leucoisonaphthazarin (V), which should offer a particularly favorable case because of the equivalence of the 2- and 3-positions and because the introduction of a large alkenyl group at one position should effectively prevent attack at the other.[5]



V

VI, R = $C_{20}H_{39}$ (phytyl)
VII, R = $C_{15}H_{25}$ (farnesyl)
VIII, R = $C_{10}H_{17}$ (geranyl)

The reactions proceeded as expected, affording the isoprenologs of lapachol VI–VIII. The phytyl and geranyl derivatives were obtained as crystalline yellow solids, m. p. 57° and 112°, and further characterizated by the preparation of the hydroquinone diacetates and by cyclization with sulfuric acid. 2-Hydroxy-3-phytyl-1,4-naphthoquinone has been tested for antihemorrhagic activity by W. L. Sampson of the Merck Institute for Therapeutic Research and found to be remarkably potent (effective chick dose about 50 γ, final results to be reported later); the geranyl derivative exhibits considerable potency, and both substances contrast sharply with phthiocol and lapachol, which show little or no vitamin K activity.[6] The difference may well be associated with the more lipoidal character of the substances with long side chains. While phthiocol and lapachol form water-soluble, ether-insoluble sodium salts, the bright red salt of the hydroxy-phytyl compound when shaken with a water–ether mixture passes completely into the ether layer.

The farnesyl compound (VII) was isolated as an analytically pure yellow oil by a lengthy process involving various extractions, chromatographic fractionations, and high vacuum distillation, but it failed to solidify except when cooled well below room temperature. A determination of the absorption spectrum kindly made by Dr. R. N. Jones (Fig. 1) adequately establishes the essential

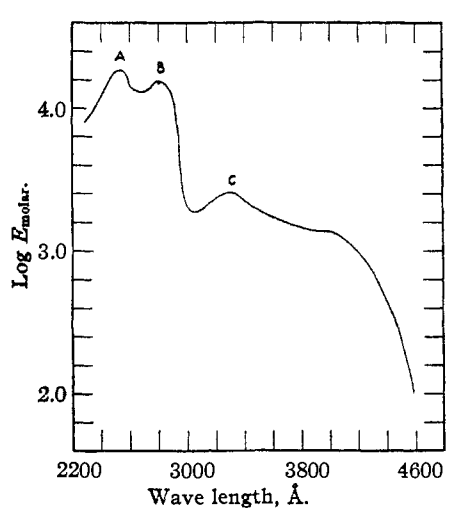


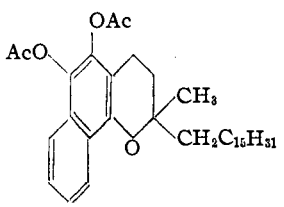
Fig. 1.—2-Hydroxy-3-farnesyl-1,4-naphthoquinone (in ethanol).

		A	B	C
Lapachol	Solvent not stated[7]	2515 (4.38)	2780 (4.28)	3310 (3.43)
Phthiocol		2500 (4.38)	2810 (4.18)	3310 (3.44)
Lomatiol		2515 (4.38)	2795 (4.17)	3310 (3.45)
2-Hydroxyl-3-farnesyl-1,4-naphthoquinone		2520 (4.26)	2800 (4.19)	3310 (3.41)

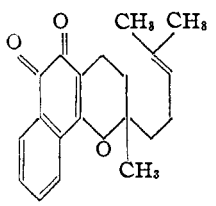
(4) Fieser, Campbell, Fry and Gates, THIS JOURNAL 61, 3216 (1939).
(5) Fieser, Tishler and Wendler, *ibid.*, 62, 2861 (1940).
(6) Fieser, Tishler and Sampson, *J. Biol. Chem.*, 137, 659 (1941).

homogeneity and nature of the material, for the characteristic absorption bands correspond closely in position and intensity with those observed[7] for phthiocol, lapachol, and lomatiol.

Treatment of the three hydroxy-alkenyl naphthoquinones with cold concentrated sulfuric acid gave red or orange isomeric products which form colorless bisulfite addition products and which therefore are of the β-lapachone type. In the phytyl series the cyclized product was a liquid and gave a liquid hydroquinone diacetate (IX). Since this "β-phytolapachone" in the reduced form bears some resemblance to naphthotocopherol,[8] the diacetyl derivative IX is being tested for vitamin E activity.



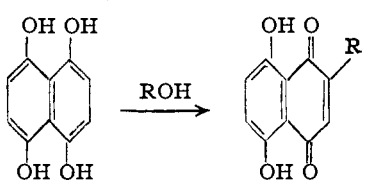
IX



X

Cyclization of 2-hydroxy-3-geranyl-1,4-naphthoquinone gave a beautifully crystalline orange isomer melting at 234°. The very high melting point suggests that this "β-geraniolapachone" may not have the structure X, with an intact double bond, but that a further cyclization of the side chain may have occurred. 2-Hydroxy-3-farnesyl-1,4-naphthoquinone on treatment with concentrated sulfuric acid gave a liquid product of variable composition which appears from the analyses to have been partially hydrated at the multiple double bonds.

A further expansion of the list of hydroxy quinones with isoprenoid side chains was made by the condensation of leuconaphthazarin (XI) with phytol and geraniol. This afforded the quinones XII and XIII as brilliant crimson oils which, like other members of the naphthazarin series, give clear cornflower blue solutions in alcoholic alkali. The sodium salt of XII is much more soluble in ether than in water, while that of XIII is distributed about equally between these two solvents. The placing of the substituent in the quinonoid rather than the benzenoid ring in the formula is based upon considerations outlined for the case of naphthopurpurin.[8]



XI

XII, R = $C_{20}H_{39}$ (phytyl)
XIII, R = $C_{15}H_{17}$ (geranyl)

(7) Cooke, Macbeth and Winzor, *J. Chem. Soc.*, 878 (1939).

Experimental Part[9]

2-Methoxy-5-phytyl-1,4-benzoquinone.—Initial experiments employing samples of 1,2,4,5-tetrahydroxybenzene, prepared in small batches immediately before use by the reduction of 2,5-dihydroxybenzoquinone[10] with stannous chloride according to Nietzki and Schmidt,[11] indicated that considerable condensation takes place, but no homogeneous reaction products could be isolated. After a number of orienting experiments with 2,5-dimethoxyhydroquinone (m. p. 171–172.5°), prepared by reduction of the quinone[10] with hydrosulfite, the methoxy-phytyl compound was prepared as follows.

A mixture of 2.00 g. of 2,5-dimethoxyhydroquinone, 1.48 g. of phytol, 1.09 g. of anhydrous oxalic acid, and 10 cc. of purified dioxane was heated under a positive pressure of nitrogen for thirty-seven hours in a boiling alcohol-bath. The solution was poured into water containing hydrosulfite and extracted with ether–petroleum ether (1:1) and the extract was filtered from some undissolved starting material and its quinone, washed six times with water containing hydrosulfite and then with brine, dried and evaporated in vacuum to a fairly mobile, light oil. To ensure complete reduction, a solution of the oil in alcohol was shaken with hydrosulfite solution for ten minutes and the diluted mixture was then extracted with ether–petroleum ether (1:1). With the use of nitrogen-flushed separatory funnels, the solution was extracted twice with Claisen's alkali[12] and the combined and washed bright orange-yellow extracts were diluted with water, treated with 20 cc. of glacial acetic acid and extracted with ether. (In earlier trials it had been ascertained that the reduced material could not be caused to separate as a solid from 30–60° petroleum ether even in a salt-ice-bath.) The ethereal solution was washed with water and with brine, filtered through sodium sulfate, and evaporated in vacuum. The oil was taken up in cold methanol, which left an undissolved residue consisting of crystalline sulfur, and the filtered solution was shaken with mercury to remove the last traces of sulfur. After standing overnight over the mercury the solution, when filtered and concentrated, afforded 632 mg. of dark red-orange oil. As a result of the extensive processing the material seemed to be largely in the oxidized form. With alcoholic alkali it gave first a brown and then a deep purple coloration. The analysis (Found: C, 77.03; H, 10.44) indicates that this material consisted largely of the methoxyphytylquinone in an impure condition.

After a test sample (27 mg.) had shown suitable adsorption characteristics, 587 mg. of the oil was chromatographed in petroleum ether (20–40°) on anhydrous mag-

(8) Fieser, THIS JOURNAL, 50, 439 (1928).

(9) All melting points are corrected.

(10) Knoevenagel and Bückel, *Ber.*, 34, 3994 (1901).

(11) Nietzki and Schmidt, *ibid.*, 21, 2377 (1888).

(12) From 35 g. of potassium hydroxide dissolved in 25 cc. of water and diluted to 100 cc. with methanol.

nesium sulfate. On development with petroleum ether, a weakly adsorbed yellow band passed through the column rapidly to give a light yellow filtrate (Fraction I). On further development with acetone–petroleum ether, an orange band moved slowly down the column and was collected in a second filtrate (Fraction II); this, after readsorption and elution, gave 130 mg. of an orange oil which did not appear to be homogeneous (Found: C, 76.95; H, 10.83). Fraction I, when concentrated under diminished pressure and thoroughly pumped out, gave 311 mg. of 2-methoxy-5-phytylquinone as a viscous orange oil.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.85; H, 10.65; OCH_3, 7.45. Found: C, 77.76; H, 10.88; OCH_3, 7.53 ($C_{28}H_{46}O_4$ requires: C, 75.28; H, 10.38; OCH_3, 13.89).

When treated in alcohol with alcoholic alkali the substance gives a reddish-brown color rapidly changing to deep purple. With antimony trichloride in acetic acid solution it gives a rich cherry-red color even in the cold.[13]

The **hydroquinone diacetate** was prepared from 76 mg. of the quinone, 0.3 cc. of acetic anhydride, 0.1 g. of zinc dust, and 3 drops of pyridine, mixed and manipulated at 0°, then allowed to stand at 25° for twenty minutes. After filtering the solution and washing the zinc with acetic acid and ether, the filtrate was treated with a small amount of water and allowed to stand for one hour, diluted further, and the ether layer separated and washed in turn with bicarbonate, dilute hydrochloric acid, and brine, dried and evaporated. There was obtained 94 mg. (theor. 92) of a very pale yellow, viscous oil.

Anal. Calcd. for $C_{31}H_{50}O_3$: C, 74.06; H, 10.03; OCH_3, 6.17. Found: C, 73.81; H, 9.93; OCH_3, 6.02.

Vitamin K_1 (L. F. F.).—Phthiocol (2.5 g.) was reduced by shaking it in a funnel with ether (40 cc.) and a solution of sodium hydrosulfite (4 g.) in water (20 cc.), washing the resulting nearly colorless ether layer with brine–hydrosulfite, filtering it through magnesium sulfate and concentrating the solution until crystallization began (10–15 cc.). After cooling in ice and adding petroleum ether, the pure white, fibrous product was collected; yield 2.1–2.3 g.

A mixture of 1.78–2.40 g. of phthiocol hydroquinone with 1.48 g. of phytol, 1 g. of oxalic acid and 10 cc. of dioxane was heated in the dark for four hours at 93° or for forty hours at 81°. The mixture was processed exactly as in the previously described syntheses.[2] The purified solid hydroquinone on oxidation gave 0.22–0.25 g. of 2-methyl-3-phytyl-1,4-naphthoquinone as a yellow oil giving the Dam–Karrer color test.

Anal.[14] Calcd. for $C_{31}H_{46}O_2$: C, 82.61; H, 10.29. Found: C, 82.70; H, 9.94.

The **hydroquinone diacetate** crystallized from alcohol in colorless needles, m. p. 60–61.5°; a mixture with the sample previously described[2] melted at 60.5–62.0°.

2-Methyl-3-cinnamyl-1,4-naphthoquinone (L. F. F.).—A similar condensation of 2.23 g. of phthiocol hydroquinone with 1 g. of cinnamyl alcohol was conducted at 95° for twenty-one hours. A washed ethereal solution of the reaction mixture was extracted with sodium carbonate solution, which removed 0.84 g. of phthiocol, and the solution remaining was reduced with hydrosulfite and extracted with 2–10% potassium hydroxide-hydrosulfite. After acidification of the yellow vat liquor the hydroquinone was extracted with ether and oxidized with silver oxide, giving 0.55 g. (26%) of once crystallized quinone, m. p. 123–125°. After successive recrystallizations from alcohol, ligroin, and methanol, the substance formed yellow blades melting at 126.5–127.5° and gave no depression when mixed with the prevous sample.[4]

Preparation of Isonaphthazarin (L. F. F., M. D. G.).—A suspension of 10 g. of the sodium salt of 2-hydroxy-1,4-naphthoquinone in 500 cc. of water was treated at room temperature with 20 cc. of 30% hydrogen peroxide. The liquor slowly turned from red to brown, the remaining salt went into solution, and after twenty-four hours a crop of red, leaf-like blades which had separated was collected and dried (2.03 g.). The filtrate was treated with 20 cc. of 30% hydrogen peroxide followed, after one hour, with 20 cc. of 5% acetic acid. After standing overnight a further crop of fine red crystals was collected; weight 1.53 g. The crude material from two runs was crystallized from dioxane, which dissolves the substance readily and deposits it in beautiful laminated leaves of orange-red needles which crumble on air drying to a deep red powder of the unsolvated material: yield, 5.5 g. from 20 g. of salt (27%).

2-Hydroxy-3-phytyl-1,4-naphthoquinone.—Isonaphthazarin (2.00 g.) was reduced with hydrosulfite as above, the ethereal solution of the leuco compound was evaporated to dryness, and the nearly colorless residue was heated under nitrogen in the dark with 2.00 g. of phytol, 1.25 g. of oxalic acid and 10 cc. of dioxane at 91° for twenty-six hours. The ethereal extract of the reaction mixture was washed with successive portions of water containing hydrosulfite; the combined washes on standing in the air slowly deposited crystals of isonaphthazarin (recrystallized, 620 mg.), along with some sulfur. The last traces of starting material were removed by repeated extraction with 1.5% alkali containing hydrosulfite and the ether layer was diluted with an equal volume of alcohol and shaken with aqueous hydrosulfite until the color changed from dark greenish brown to pale lemon-yellow. The

(13) The following test for vitamin K_1 and certain related quinones is a modification of one described to me by Dr. Allan M. Butler ($SbCl_5$–$CHCl_3$). A solution of the vitamin in 0.3–0.4 cc. of acetic acid is treated with an equal volume of a solution prepared by dissolving 8 g. of antimony trichloride in 10 cc. of acetic acid. This produces an intensification of any discernible yellow color due to the vitamin alone and gives a clear yellow solution which undergoes no apparent alteration at 25° in the course of several hours. In the present test, however, the mixture is heated directly in a boiling water-bath for five minutes. With a test solution containing 10 mg. of vitamin K_1 per cc. the yellow color bleaches within one-half minute and the solution then becomes rich pink (1 min.) and finally deep cherry-red (2 min.). With 1 mg. of K_1 per cc. the final color is rich pink, and a test solution of 0.1 mg. per cc. gives a faint but distinct pink. No alterations were detected when the solutions had stood for twenty-four hours. Tests with other 1,4-naphthoquinones (about 1 mg. per cc.) were considered negative if the initial color either persisted or deepened, and positive if the yellow faded completely in the course of the heating and gave place to another color. The test was negative with the 2-methyl, 2,3-dimethyl and 2-methyl-3-benzyl derivatives (yellow persists); also with 1,1,3-trimethyl- and 1,1-dimethyl-3-*t*-butyl-1,4-dihydroanthraquinone (deeper yellow). Typical 1,4-naphthoquinones giving positive tests are: 2-methyl-3-geranyl (cherry red), 2-methyl-3-cinnamyl (orange-pink), lapachol methyl ether (rich orange), 2-methyl-3-trimethylallyl (intense purple), 2-allyl and 2-phytyl (deep orange-brown), 2,3-diallyl (faint olive-green). The test appears to be specific for quinones having in the quinonoid ring one or more β-alkenyl groups not present as part of a side ring.—L. F. F.

(14) Microanalysis by Lyon Southwoath.

hydrosulfite-washed ether layer was diluted with an equal volume of petroleum ether (30–60°) and extracted repeatedly with Claisen's alkali–hydrosulfite and the hydroquinone was liberated from the yellow vat liquor with dilute acetic acid and extracted with ether as in the above example. After aspiration of air through the ether solution for two hours, the collected material was shaken with mercury in methanol to remove sulfur and recovered by evaporation of the filtered solution as a viscous brown resin. When this was chromatographed in petroleum ether (20–40°) on freshly ignited magnesium sulfate the colored impurities were retained in an upper, grayish-brown zone and a weakly adsorbed bright yellow band readily passed into the filtrate and, on concentration under diminished pressure, afforded 468 mg. of a light yellow, waxy solid. After two crystallizations from methanol containing ether the substance formed yellow nodules, m. p. 48–54° (170 mg.), and recrystallization from methanol–ether, effected by allowing the solution to stand over sulfuric acid in the cold room, gave 89 mg., m. p. 56–57.4°. Reworking of the mother liquors afforded 81 mg., m. p. 56–57.6°; total yield 170 mg. An earlier sample recrystallized three times from slightly diluted methanol formed nodular clusters of close-packed needles, m. p. 56.5–57.7°. A solution of the substance in methanol turns bright scarlet red on the addition of alkali, and when the solution is diluted with water and shaken with ether the scarlet color passes completely into the ether layer; acidification restores the original yellow color.

Anal.[14] Calcd. for $C_{30}H_{44}O_3$: C, 79.59; H, 9.80. Found: C, 79.29; H, 9.91.

The **hydroquinone triacetate** was obtained as a nearly colorless, viscous oil (63 mg. from 45 mg. of the quinone) by the procedure illustrated above. It is miscible with petroleum ether (20–40°) at 0°, soluble in methanol at 25° but sparingly soluble at 0°, and could not be induced to crystallize.

Anal. Calcd. for $C_{36}H_{52}O_6$: C, 74.45; H, 9.02. Found: C, 74.07; H, 9.03.

β-Phytolapachone.—2-Hydroxy-3-phytyl-1,4-naphthoquinone (30 mg.) was dissolved in 0.3 cc. of concentrated sulfuric acid in the cold and the bright orange-red solution was diluted with 10 cc. of water. The orange oil which precipitated was collected by ether extraction and the product was chromatographed in petroleum ether on magnesium sulfate. On development with benzene a light, narrow band passed into the filtrate and was discarded; a narrow, dark orange band appeared at the top, and the chief reaction product was adsorbed in a broad intermediate salmon-red band; this when sectioned and eluted with ether afforded 21 mg. of the cyclized product as a bright red oil.

Anal. Calcd. for $C_{30}H_{44}O_3$: C, 79.59; H, 9.80. Found: C, 79.01; H, 10.33.

The analysis indicates that the sample was not quite pure. However, it no longer gave the red color with alkali characteristic of the hydroxy compound and when rubbed with alcohol and bisulfite solution it dissolved to a completely colorless solution which soon deposited a flocculent white precipitate. Reductive acetylation of another sample, prepared and chromatographed in the same way from 40 mg. of the hydroxy compound, gave 43 mg. of the **hydroquinone diacetate IX** as a nearly colorless oil.

Anal. Calcd. for $C_{34}H_{50}O_5$: C, 75.79; H, 9.36. Found: C, 75.42; H, 9.70.

2-Hydroxy-3-geranyl-1,4-naphthoquinone.—The condensation of the leuco compound from 2 g. of isonaphthazarin with 4 g. of geraniol was conducted as above at 91° for twenty-seven hours. The processing of the reaction mixture included these steps: extraction of unchanged leuco compound with aqueous hydrosulfite (380 mg. of isonaphthazarin recovered), hydrosulfite reduction in water–alcohol, extraction from ether–petroleum ether with Claisen's alkali, removal of sulfur with mercury in methanol, aeration, and adsorption on magnesium sulfate from petroleum ether (20–40°). Elution with this solvent gave first a yellow filtrate, which was set aside and combined with similar material obtained by systematic readsorptions of the eluate from a second, brown band. Evaporation of the solvent left a semisolid residue which after three crystallizations from ether–petroleum ether gave 68 mg. of small, bright yellow plates, m. p. 109–112°; a further crystallization gave 56 mg. of material, m. p. 111.4–112.6° (analytical sample). The material from the mother liquors was shaken in 50% ether–petroleum ether with 10% soda solution containing a little methanol, when both phases became somewhat red. The black-red sodium salt is sparingly soluble in soda solution and largely separated at the interface. After drawing off the soda, the salt could be extracted satisfactorily with water. After acidification of the red extract and collection of the product by ether extraction, two crystallizations from ether–petroleum ether gave 68 mg. of bright yellow plates, m. p. 110–111.5° (total yield 124 mg.).

Anal.[14] Calcd. for $C_{20}H_{22}O_3$: C, 77.38; H, 7.15. Found: C, 77.47; H, 7.21.

When a sample in methanol is tested with alkali, followed by the addition of water and ether, a pink color is imparted to the ether but the major portion of the color remains in the aqueous phase.

The **hydroquinone triacetate,** obtained crystalline by allowing a solution in methanol–ether to evaporate over sulfuric acid at 5°, melted at 109–112.5° (24 mg. from 31 mg. of quinone). Recrystallization in the same way gave 16 mg. of large flat blades with a slight pinkish cast, m. p. 111–112.8°. The substance is sparingly soluble in petroleum ether, fairly soluble in methanol, and readily soluble in ether.

Anal. Calcd. for $C_{26}H_{30}O_6$: C, 71.21; H, 6.90. Found: C, 70.76; H, 7.13.

β-Geranolapachone (X?).—The deep scarlet solution of 43 mg. of the hydroxy quinone in 0.3 cc. of sulfuric acid was allowed to stand for one minute and diluted with 6 cc. of water. The curdy orange precipitate did not crystallize satisfactorily and was chromatographed from benzene–hexane on magnesium sulfate. A broad reddish-pink zone appearing between a weakly adsorbed light yellow band and a brown band at the top was sectioned, eluted with ether–benzene, and afforded a solid residue which when crystallized from acetone gave 20 mg. of beautiful clusters of orange prismatic needles, m. p. 232–234°, with slight softening at 230°. The substance is very sparingly soluble

in petroleum ether, rather sparingly soluble in ether, and readily soluble in hot acetone. It gives a colorless bisulfite addition product.

Anal.[14] Calcd. for $C_{20}H_{22}O_3$: C, 77.38; H, 7.15. Found: C, 77.21; H, 7.30.

2-Hydroxy-3-farnesyl-1,4-naphthoquinone.—The leuco compound from 1.85 g. of isonaphthazarin was condensed with 2 cc. of farnesol (fifty-one hours at 91°) and the mixture processed exactly as indicated for the preparation of the geranyl derivative (477 mg. of isonaphthazarin recovered). The bright yellow petroleum ether eluate on evaporation gave a golden-orange oil which could be caused to solidify at low temperatures in petroleum ether but which melted below room temperature. This was then extracted from petroleum ether with a mixture of 8 cc. of 10% sodium carbonate solution, 27 cc. of water, and 65 cc. of methanol. Two such extractions removed all material giving a red alkali salt, and after washing the red liquor twice with petroleum ether, the carbonate solution was diluted with water, some brine was added, and the solution was extracted four times with ether, giving a bright red ethereal solution of the sodium salt. This was washed with brine, treated with just enough acetic acid to change the color to bright yellow, washed thoroughly with water, dried and evaporated. The residue consisted of 234 mg. of a clear, golden oil. Analyses indicated that this material was not entirely pure, but distillation at 0.002 mm. (bath 110–120°) gave a product of satisfactory purity, as judged by the analysis and absorption spectrum.

Anal. Calcd. for $C_{25}H_{30}O_3$: C, 79.32; H, 7.99. Found: C, 79.04; H, 8.43.

The **hydroquinone triacetate** was obtained as a very pale lemon-yellow oil (42 mg. from 36 mg. of quinone).

Anal. Calcd. for $C_{31}H_{38}O_6$: C, 73.49; H, 7.56. Found: C, 73.31; H, 8.01.

In attempts to prepare β-farnesolapachone the hydroxy compound was treated with sulfuric acid and the mixture processed as described for β-geranolapachone. In one experiment the material eluted from the reddish-pink zone on the column was distilled at 0.002 mm. (bath 140°). The samples were bright orange oils dissolving in alcoholic-aqueous bisulfite solution with loss of the color, which was restored on the addition of soda. The composition (C, H: 76.73, 8.71; 77.77, 8.74) varied but was in a range intermediate between that of the expected compound (79.32, 7.99) and that of the product of its monohydration (76.73, 8.71).

2-Phytylnaphthazarin (XII).—The condensation of 753 mg. of leuconaphthazarin[15] with 1.00 g. of phytol was conducted in the usual way at 91° for fifty hours. The solution became dark red-brown almost immediately and at the end was poured into water containing hydrosulfite and extracted with ether. The solution was washed with aqueous hydrosulfite and then three times with 1.5% alkali containing hydrosulfite, the first wash being yellow and the third colorless. The material recovered from the ether layer was completely miscible with cold petroleum ether (20–40°), and hence it was submitted to the steps of hydrosulfite reduction in alcohol–water, extraction from petroleum ether with Claisen's alkali, recovery by acidification with acetic acid, extraction, and oxidation with silver oxide. The resulting bright crimson ethereal filtrate gave a deep crimson residue on evaporation, and this when chromatographed on magnesium sulfate from petroleum ether (20–40°) gave two narrow pink bands at the top and a broad red band, which was sectioned and eluted with ether. After evaporating the solution and pumping out the residue there was obtained 58 mg. of a bright crimson, viscous oil. A solution of the substance in methanol turns deep cornflower blue on the addition of alkali and on adding water and ether the blue sodium salt passes completely into the ether.

Anal. Calcd. for $C_{30}H_{44}O_4$: C, 76.87; H, 9.47. Found: C, 77.02; H, 9.62.

2-Geranylnaphthazarin (XIII).—The reaction mixture from 1.88 g. of leuconaphthazarin and 2 cc. of geraniol could not be processed exactly as in the foregoing example because after six or seven extractions with 1.5% alkali-hydrosulfite the persistence of a strong vat color indicated that some of the substituted hydroquinone was being extracted along with the starting material. The alkaline liquor was therefore acidified and extracted with ether and the solution was shaken with silver oxide and the latter, after filtration, was washed with hot acetone. The deep crimson solution was taken to dryness and the residue, consisting of the reaction product mixed with naphthazarin, was leached with several portions of warm petroleum ether (30–60°). On passing the extract through a column of magnesium sulfate a rose-red band passed readily into the filtrate and this material was combined with that obtained from the main body of the reaction mixture following the usual processes of reduction, Claisen's alkali extraction, oxidation with silver oxide, and removal of sulfur with methanol–mercury. Thrice repeated adsorption on magnesium sulfate (weakly adsorbed broad red band) then afforded 85 mg. of a clear, bright crimson oil.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.59; H, 6.80. Found: C, 73.90; H, 7.27.

Summary

The condensation of an allylic alcohol with a hydroxy (or methoxy) hydroquinone in the presence of oxalic acid results in the replacement of the hydroxyl group by a β-alkenyl group. Examples of the application of this reaction include a new synthesis of vitamin K_1 starting with phthiocol, and the synthesis of the 3-phytyl, farnesyl, and geranyl derivatives of 2-hydroxy-1,4-naphthoquinone. 2-Phytyl and 2-geranylnaphthazarin were synthesized by the older process from the alcohol and leuconaphthazarin.

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(15) Zincke and Schmidt, *Ann.*, **286**, 37 (1895).