[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Diene Synthesis of 2,3-Dialkyl-1,4-naphthoquinones Related to Vitamin K

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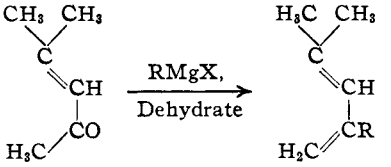
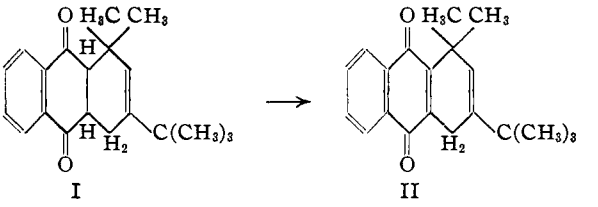
This research was undertaken with the idea of utilizing the reaction of α-naphthoquinone with dienes as a means of synthesizing compounds sharing with vitamins K_1 and K_2 the structural feature of a 1,4-naphthoquinone nucleus with alkyl substituents at the 2 and 3 positions. It soon became apparent from other observations in this Laboratory[2] that in the series of 2,3-dialkyl-1,4-naphthoquinones which have been assayed the antihemorrhagic activity of the first member (dimethyl) of the group is rather anomalous and that among the remaining compounds vitamin K activity begins to appear only when the alkyl side chains include a total of about ten carbon atoms. Preference was therefore given in the present work to the use of dienes of reasonably high molecular weight.

One scheme was to add a 1,1-dialkyl derivative of butadiene to α-naphthoquinone and convert the product to a 2,3-disubstituted naphthoquinone by isomerization and oxidation, for the presence of the *gem*-dialkyl group would counteract the normal tendency of the terminal ring to become aromatized with the formation of an anthraquinone. A satisfactory route to dienes of the desired type consists in the addition of a Grignard reagent to mesityl oxide and dehydration of the resulting carbinol.



The diene resulting from the use of the methyl Grignard reagent has already been added to α-naphthoquinone by Diels and Alder,[3] who converted the addition product as outlined above into 1,1,3-trimethyl-1,4-dihydroanthraquinone. On repeating their experiments a quinone was obtained of such widely different melting point as to suggest that a typographical error may have been made in their report. The substance was found by Dr. W. L. Sampson to be inactive in the chick assay at a dosage of 200 γ. A more promising case for present purposes consisted in the



introduction of a *t*-butyl group in the first step. The addition product I was obtained in a crystalline condition and easily isomerized and oxidized by treatment with alcoholic alkali and air and converted into the naphthoquinonoid substance II. A tertiary alkyl group has the advantage of preventing dehydration of the carbinol from occurring in more than one direction. This complication may have been involved in an experiment utilizing the carbinol[4] resulting from the reaction of mesityl oxide with ethylmagnesium bromide. The diene obtained on dehydration corresponded in boiling point with the material described by Abelmann[5] but gave no crystalline product when added to α-naphthoquinone.

A few attempts were made to employ 1,1,4,4-tetraalkylbutadienes in the synthesis without success. Suitable starting materials are available by the condensation of diethyl succinate with excess methyl[6] or ethyl[7] Grignard reagent and dehydration of the resulting glycols, as described for the first example by Faworsky.[8] The tetramethyl and tetraethyl compounds were both prepared but neither substance added readily to α-naphthoquinone and under forcing conditions extensive decomposition occurred.

A further scheme of synthesis is illustrated by the sequence of reactions starting with the addition of myrcene to α-naphthoquinone. The known addition product III[9] cannot be treated as above because of the ready conversion of the intermediate oxidation product into an anthraquinone under the conditions of its formation. The required partial dehydrogenation was accom-

(1) Department of Chemistry, Skidmore College.

(2) Fieser, Campbell and Fry, THIS JOURNAL, **61**, 2206 (1939); Fieser, Campbell, Fry and Gates, *ibid.*, **61**, 3216 (1939); Fieser, *ibid.*, **61**, 3467 (1939).

(3) Diels and Alder, *Ber.*, **62**, 2358 (1929).

(4) Jacquemoin, *Compt. rend.*, **198**, 483 (1934).

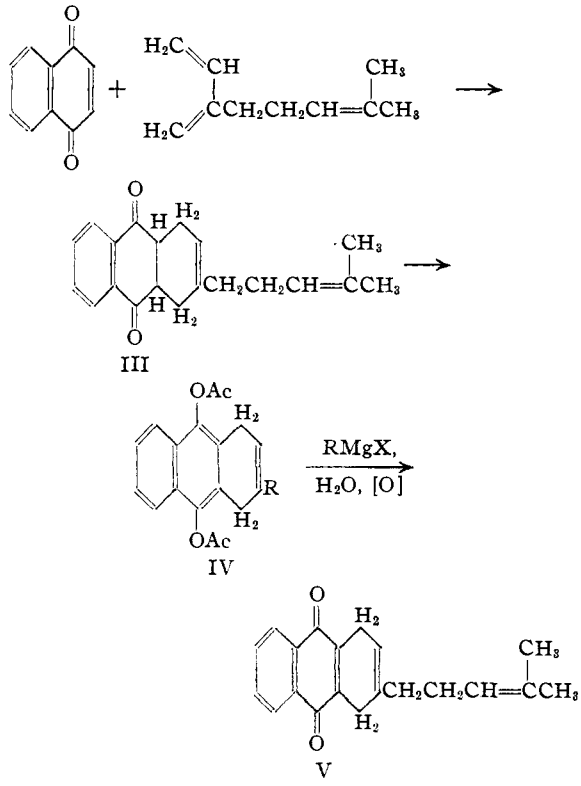
(5) Abelmann, *Ber.*, **43**, 1586 (1910).

(6) Harries, *Ann.*, **343**, 364 (1905).

(7) Valeur, *Compt. rend.*, **132**, 834 (1901).

(8) Faworsky, *J. prakt. Chem.*, **44**, 228 (1891).

(9) Arbusow and Abramow, *Ber.*, **67**, 1942 (1934).



plished successfully by conversion with acetic anhydride and pyridine into the diacetate IV, cleavage of this with methylmagnesium chloride, and oxidation of the liberated hydroquinone with silver oxide. 2-(∂-Methyl-γ-pentenyl)-1,4-dihydroanthraquinone (V) was thereby obtained in good yield as a crystalline yellow product.

Although 1,1-dimethyl-3-*t*-butyl-1,4-dihydroanthraquinone (II) and 2-(∂-methyl-γ-pentenyl)-1,4-dihydroanthraquinone (V) are comparable in molecular complexity with the antihemorrhagic 2-methyl-3-geranyl and 2-methyl-3-cinnamyl derivatives of α-naphthoquinone, neither substance showed vitamin K activity when assayed at 400 γ and 50 γ, respectively (W. L. Sampson).

Experimental Part[10]

1,1,3 - Trimethyl - 1,4 - dihydroanthraquinone.—1,1,3-Trimethylbutadiene was prepared essentially as described by Fellenberg.[11] From 50 g. of mesityl oxide and the reagent from 18 g. of magnesium and excess methyl chloride, refluxing in ether for one hour, there was obtained after two distillations 50 g. (86%) of the carbinol, b. p. 46° (14 mm.). This was dehydrated by distillation from 10 g. of potassium bisulfate at about 80–88°. The twice distilled diene boiled at 93°; yield, 27.5 g. (65%).

A mixture of 6 g. of the diene and 2 g. of α-naphthoquinone was refluxed for eight hours and the excess diene removed in vacuum. The residual yellow oil solidified on cooling, and two crystallizations from alcohol (Norite) gave 2 g. (62%) of colorless addition product, m. p. 119°, as reported by Diels and Alder.[2] This was dissolved in 10 cc. of hot alcohol and after adding one drop of 10% alcoholic potassium hydroxide, air was bubbled through the solution until the color changed from green to red to orange (ten minutes). The quinone separated in yellow plates and on recrystallization from alcohol formed yellow plates, m. p. 129–129.5°; yield 1.2 g. (60.5%). The melting point remained unchanged on recrystallization, and several preparations were made with the same results. Since Diels and Alder[3] report a very different m. p. (162°), the sample was analyzed. A cold alcoholic solution of the quinone acquires an intense greenish blue color on adding 10% alcoholic potassium hydroxide; the color fades slowly on standing, or rapidly on shaking with air, to a light orange.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.12; H, 6.58.

1,1 - Dimethyl - 3 - *t* - butyl - 1,4 - dihydroanthraquinone (II).—In the first step, conducted essentially as described by Stevens,[12] the reagent prepared under nitrogen from 18 g. of magnesium, 70 g. of *t*-butyl chloride, and 600 cc. of ether was added with stirring to 40 g. of mesityl oxide in 300 cc. of ether and after refluxing for one hour the complex was decomposed with dilute acetic acid. The ether layer was washed neutral, washed with sodium chloride solution, dried with sodium sulfate, and evaporated. In the first distillation of the carbinol a 36-g. fraction, b. p. 85–105° (40 mm.), was collected; redistillation gave 23.4 g. (37%) of material, b. p. 94–95° (40 mm.). This fraction was distilled from 5 g. of potassium bisulfate and the cloudy distillate dried over sodium sulfate and distilled. There was obtained 13.3 g. (64%) of **1,1-dimethyl-3-*t*-butylbutadiene,** b. p. 58–59° (32 mm.).

For preparation of the addition product 12 g. of the diene was first heated with 4 g. of α-naphthoquinone without solvent at 100–110° for twenty-four hours. Some product crystallized on cooling, but the reaction was evidently incomplete and some decomposition had occurred (dark melt), and consequently 10 cc. of dioxane was added and heating continued for twenty-four hours longer. After evaporation in vacuum the viscous brown residue was triturated with 3 cc. of alcohol and the dark crystalline product obtained was recrystallized three times from alcohol using Norite, when glistening, colorless needles of the **addition product I** were obtained. The substance melts at 142–143°; yield 1 g. (13%).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.97; H, 8.09.

For isomerization and oxidation, 1 g. of the addition product was dissolved in 5 cc. of hot alcohol, a drop of 10% alcoholic potassium hydroxide was added, and air was bubbled through until the sequence of color changes reached an orange end-stage. The quinone crystallized on rubbing and the material, purified by two further crystallizations, formed yellow needles, m. p. 102–103°. The

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

(11) Fellenberg, *Ber.*, **37**, 3578 (1904).

(12) Stevens, THIS JOURNAL, **57**, 1116 (1935).

yield of satisfactory material was 0.35 g. (35%). In the test with alcoholic potassium hydroxide in the cold, the quinone gives an intense blue changing slowly to yellow.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53. Found: C, 81.60; H, 7.62.

2 - (∂ - Methyl - γ - pentenyl) - 1,4 - dihydroanthraquinone (V).—The myrcene employed was obtained from a commercial terpene fraction of bay oil. About half of this distilled at 64–69° (20 mm., 1-m. column), and on redistillation of 250 cc. of this material the myrcene collected chiefly in a fraction boiling at 64.5–66° (20 mm.) and weighing 120 g. Semmler[13] reports the b. p. 67–68° at 20 mm. For identification a sample was converted into the maleic anhydride addition product, which corresponded in b. p. (188° at 8 mm.) and m. p. (34–35°) with the material described in the literature.[9,14]

The reaction between myrcene (30 cc.) and α-naphthoquinone (10 g.) was conducted by refluxing in dioxane (30 cc.) for twelve hours. After evaporation in vacuum the oily product was taken up in petroleum ether (b. p. 30–60°) and the solution was chilled and seeded with crystals obtained by cooling a dilute solution in petroleum ether to −70°. There was obtained 15.4 g. (83%) of cream colored crystalline product, m. p. 60–61°. Two crystallizations gave colorless crystals, m. p. 61–61.3°; yield 12 g. (64%). Arbusow and Abramow[9] found the m. p. 58–58.5°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53. Found: C, 81.70; H, 7.66.

The **hydroquinone diacetate IV** was prepared by heating the addition product (12 g.) in acetic anhydride (20 cc.) and pyridine (4 cc.) for one hour on the steam-bath. The solution was cooled and stirred with dilute hydrochloric acid; with the hydrolysis of the excess anhydride the diacetate separated as a tan colored solid. This was taken into ether and the solution was washed free of acid, dried, and the solvent evaporated in vacuum. Three crystallizations from alcohol gave 13 g. (84%) of colorless needles having a fluorescent greenish tinge and melting at 121–122°.

Anal. Calcd. for $C_{24}H_{26}O_4$: C, 76.16; H, 6.93. Found: C, 76.34; H, 6.98.

For conversion to the quinone, 13 g. of the diacetate was added in ether solution to the Grignard reagent prepared from 12 g. of magnesium, 400 cc. of ether, and the required amount of methyl chloride. After refluxing for forty-five minutes the ether was largely displaced with benzene and refluxing was continued for one-half hour longer. The mixture was decomposed with ammonium chloride and hydrochloric acid and the yellow organic layer was washed, dried, and shaken for one-half hour with 3 g. of silver oxide and 20 g. of sodium sulfate. The filtered solution was evaporated eventually under vacuum, leaving a residue of 7 g. (70%) of the quinone, m. p. 88–89°. Crystallized from alcohol, the substance formed glistening yellow plates, m. p. 89.8–90.8°. With alcoholic alkali the substance gives a red color changing rapidly on shaking with air to pale yellow.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.20; H, 6.89. Found: C, 82.25; H, 7.00.

Summary

As a route to 2,3-dialkyl-1,4-naphthoquinones of high molecular weight which might show vitamin K activity, a study has been made of the addition of suitable dienes to α-naphthoquinone and the partial dehydrogenation of the products. Two satisfactory syntheses were developed and applied to the preparation of C_{20}-quinones of the type desired. Neither of these substances shows activity.

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(13) Semmler, *Ber.*, **34**, 3126 (1901).
(14) Diels and Alder, *Ann.*, **470**, 65 (1929).

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

Vitamin K-Active Derivatives of 2-Methyl-1,4-naphthohydroquinone

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About six months ago we reported[2] that 2-methyl-1,4-naphthoquinone has a vitamin K potency of 1 unit[3] in about 0.5 γ. Simultaneously other investigators[4,5,6] published their work with this substance, and it is apparent that they then failed to observe the outstanding biological activity of this compound. However, the same authors,[7,8,9] and others[10,11] fully confirmed our results in more recent communications. Meanwhile we prepared and investigated several derivatives which are the object of the present report.

(1) Chemist at the Development Laboratory of E. R. Squibb & Sons, Brooklyn, N. Y.
(2) Ansbacher and Fernholz, THIS JOURNAL, **61**, 1924 (1939).
(3) Ansbacher, *J. Nutrition*, **17**, 303 (1939).
(4) Almquist and Klose, THIS JOURNAL, **61**, 1923 (1939).
(5) Fieser, Bowen, Campbell, Fry and Gates, Jr., *ibid.*, **61**, 1926 (1939).
(6) Thayer, Cheney, Binkley, MacCorquodale and Doisy, *ibid.*, **61**, 1932 (1939).
(7) Fieser, *ibid.*, **61**, 2559 (1939).
(8) Thayer, Binkley, MacCorquodale, Doisy, Emmett, Brown and Bird, *ibid.*, **61**, 2563 (1939).
(9) Almquist and Klose, *J. Biol. Chem.*, **130**, 787 (1939).
(10) Tishler and Sampson, THIS JOURNAL, **61**, 2563 (1939).
(11) Personal communication of September 25, 1939, from Dr. H. Dam of the University of Copenhagen, Denmark.