β-3-hydroxy-bisnorcholenic acid, and a C_6 aldehyde are obtained. The empirical formula of brassicasterol is therefore $C_{28}H_{46}O$.

The C_6 aldehyde appears to be a partially racemized 1-methylisopropyl-acetaldehyde, which is a degradation product of ergosterol.

The structural formula of 7,8-dihydroergosterol is proposed for brassicasterol.

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

The Vitamin K Activity of Naphthoquinones

BY ERHARD FERNHOLZ, S. ANSBACHER AND H. B. MACPHILLAMY

Soon after McKee, *et al.*,[1] reported that vitamins K_1 and K_2 have a quinoid structure, publications from various laboratories appeared on the vitamin K activity of naphthoquinones. Because of its outstanding potency 2-methyl-1,4-naphthoquinone and its derivatives have been investigated most thoroughly. A discussion of the pertinent literature concerning this compound has been presented in a foregoing publication.[2] A suggestion also has been made to use 2-methyl-1,4-naphthoquinone as a basic standard for the assay of vitamin K;[3] under the conditions used in our laboratory one milligram contains 2000 units.

The following summarizes our assay results with other naphthoquinones: inactive, 1,2-naphthoquinone; weakly active in a dose of one milligram, 2,6-dimethyl, 2-allyl-, 2,3-diallyl-, 2-*n*-hexadecyl-,2-*n*-octadecyl-1,4-naphthoquinone; one unit per milligram, 1,4-naphthoquinone, 2-ethyl-, 2-propyl-, and 2-methyl-3-*n*-octadecyl-1,4-naphthoquinone; 20 units per milligram, 2,3-dimethyl-1,4-naphthoquinone; 70 units per milligram, 2-methyl-3-phytyl-1,4-naphthoquinone(vitamin K_1).

Thayer, *et al.*,[4] reported that 1,2-naphthoquinone is inactive whereas 1,4-naphthoquinone is active in a dose of 1 mg.; our results confirm this report. Almquist and Klose,[5] however, stated that they had obtained entirely negative results with the latter compound. The interesting contrast between the comparatively active 2,3-dimethyl-1,4-naphthoquinone and the rather weakly active 2,6-dimethyl-1,4-naphthoquinone[6] has been reported also by Tishler and Sampson.[7] There is some uncertainty concerning the activity of 2-ethyl-1,4-naphthoquinone. Thayer, *et al.*,[4] state that it is fully active at a level of 125 γ, and according to Tishler and Sampson it shows activity above 200 γ. In our experience the compound is not nearly as active as reported by Thayer, *et al.*, since 1 mg. was found to be necessary to give a unit response. The propyl derivative has been assayed and found inactive at a level of 0.4 mg.;[7] we found it active in a dose of 1 mg. Fieser, *et al.*,[8] originally reported that 2-allyl-1,4-naphthoquinone is very active but Thayer, *et al.*,[4] stated in the same issue of THIS JOURNAL that the compound was inactive in a dose of 2 mg. In a later paper Fieser, *et al.*,[9] agreed with Thayer. We also found that 2-allyl-1,4-naphthoquinone and 2,3-diallyl-1,4-naphthoquinone have little, if any, activity at a level of 1 mg. We have prepared and assayed the *n*-hexadecyl, *n*-octadecyl, and 2-methyl-3-octadecyl-1,4-naphthoquinones. These compounds have shown rather low potencies.[10] The last of the three, containing the methyl group in the 2-position, is definitely more active than the two others.

The long-chain naphthoquinones were prepared by chromic acid oxidation of the corresponding hydrocarbons. With the exception of the *n*-octadecyl compound, substitution of the naphthalene nucleus in the β-position was ensured by using the method of Barbot[11] for the production of β-substituted tetralin ketones. The ketones were reduced by the Clemmensen

(1) McKee, Binkley, MacCorquodale, Thayer and Doisy, THIS JOURNAL, **61**, 1295 (1939).

(2) Ansbacher, Fernholz and Dolliver, THIS JOURNAL, **62**, 155 (1940).

(3) Thayer, Binkley, MacCorquodale, Doisy, Emmet, Brown and Bird, *ibid.*, **61**, 2563 (1939).

(4) Thayer, Cheney, Binkley, MacCorquodale and Doisy, THIS JOURNAL, **61**, 1932 (1939).

(5) *Ibid.*, **61**, 2557 (1939).

(6) We are indebted to Professor Fieser for sending us samples of these two substances as well as of allyl-naphthoquinone and diallyl-naphthoquinone.

(7) *Ibid.*, **61**, 2563 (1939).

(8) Fieser, Bowen, Campbell, Fry and Gates, *ibid.*, **61**, 1926 (1939).

(9) Fieser, Campbell and Fry, THIS JOURNAL, **61**, 2206 (1939).

(10) After this paper had been submitted a paper by Fieser [THIS JOURNAL, **61**, 3467 (1939)] appeared wherein it is postulated that vitamin K activity begins to appear as the alkyl groups are increased in size. Obviously our results do not support this idea.

(11) Barbot, *Bull. soc. chim.*, [4] **47**, 1314 (1930).

method and the resulting hydrocarbons dehydrogenated with sulfur to give the desired alkylnaphthalenes. In the case of the *n*-octadecyl derivative, naphthalene was substituted directly and the mixture of α- and β-naphthalene ketones separated according to the directions of Seidel and Engelfried.[12]

The starting material used in the preparation of the 2-methyl-3-octadecyl derivative was prepared by the catalytic hydrogenation of 2-methylnaphthalene to the corresponding tetralin derivative. That the product thus obtained is 2-methyl-5,6,7,8-tetrahydronaphthalene has been shown by Schroeter[13] and by Fieser and Jones.[14] Since condensation of this substance with stearyl chloride would lead to substitution only in the 3-position, experiments to prove the structure of this compound were not carried out.

We reported recently[15] that the minimum effective dose of vitamin K_1 depends much more on the assay period than does that of 2-methyl-1,4-naphthoquinone or of alfalfa concentrates prepared and investigated by us. While 15 γ of vitamin K_1 is required in our six-hour assay, only 1γ is needed if the test period is prolonged to eighteen hours. In similar fashion it is possible, therefore, that the activity of the long-chain naphthoquinones may be greater if an eighteen hour or longer test period is used. Although the number of naphthoquinones which could be tested for vitamin K activity could be greatly increased, from the present investigation it does not appear likely that the preparation of such compounds would lead to the discovery of a substance surpassing in activity 2-methyl-1,4-naphthoquinone.

Experimental Part

2-*n*-Pentadecyl-5,6,7,8-tetrahydronaphthyl Ketone.—The acid chloride[16] from 15 g. of palmitic acid was decanted into 100 cc. of carbon disulfide containing 8 g. of tetralin. Gradually 8 g. of anhydrous aluminum chloride was added and the reaction mixture allowed to stand overnight. After evaporating the carbon disulfide, the residue was decomposed with ice water and extracted with ether. The ether extract was washed with dilute alkali and dried over anhydrous sodium sulfate. The ether was removed and the remaining oil was distilled at 130–140° (about 1 mm.). The distillate solidified on cooling and was recrystallized from acetone. The yield was 12 g. (56%) of white crystals melting at 44–45°.

Anal. Calculated for $C_{26}H_{42}O$: C, 84.3; H, 11.4. Found: C, 84.2; H, 11.2.

2-*n*-Hexadecyl-5,6,7,8-tetrahydronaphthalene.—Ten grams of the above ketone was reduced according to the modification of the Clemmensen method described by Mikeska, *et al.*[16] The final product was distilled at 210–215° (about 1 mm.), yield 6 g. (63%) of hydrocarbon.

Anal. Calculated for $C_{26}H_{44}$: C, 87.6; H, 12.4. Found: C, 88.0; H, 12.1.

2-*n*-Hexadecylnaphthalene.—The above hydrocarbon was subjected to sulfur dehydrogenation according to the directions of Barbot.[11] Five grams of the tetralin derivative and 3 g. of sulfur were heated to 200–210° for five hours. The product was extracted with ether and the ethereal solution washed with dilute alkali. On evaporation of the dried solution an oil remained which distilled *in vacuo* at about 200° (1 mm.). The distillate solidified on cooling and was recrystallized from ether–methanol mixture giving about 1 g. (20%) of material melting at 45–46°.

Anal. Calculated for $C_{26}H_{40}$: C, 88.56; H, 11.44. Found: C, 88.24; H, 11.68.

2-*n*-Hexadecyl-1,4-naphthoquinone.—A solution of 1.5 g. of chromic acid in 3 cc. of 50% acetic acid was added dropwise to a suspension of 0.5 g. of 2-*n*-hexadecylnaphthalene in 10 cc. of glacial acetic acid. The reaction mixture was stirred rapidly during the addition. The temperature was then raised to 60° and the agitation continued for 1.5 hours at this temperature. The reaction mixture was then diluted with water and extracted with ether. The ethereal solution was washed with dilute alkali and dried over anhydrous sodium sulfate. After removal of the ether the solid yellow residue was crystallized from a small amount of ether yielding 0.2 g. (37%) of quinone melting at 80–81°.

Anal. Calculated for $C_{26}H_{38}O_2$: C, 81.6; H, 10.0. Found: C, 81.6; H, 10.3.

2-*n*-Octadecyl-1,4-naphthoquinone.—The compound was prepared as described for the above quinone. Four grams of 2-*n*-octadecylnaphthalene[16] (m. p. 58–59°) upon oxidation with 10 g. of chromic acid gave 1 g. (23%) of quinone melting at 84–85°.

Anal. Calculated for $C_{28}H_{42}O_2$: C, 81.9; H, 10.3. Found: C, 81.7; H, 10.4.

Methyl-3-*n*-heptadecyl-5,6,7,8-tetrahydronaphthyl Ketone.—This substance was prepared from 2-methyl-5,6,7,8-tetralin and stearyl chloride as described in the preparation of 2-pentadecyl tetrahydronaphthyl ketone. A yield of 5.0 g. (36%) of the ketone was obtained from 2.5 g. of 2-methyl tetralin and 5 g. of stearic acid. The material was crystallized from acetone, m. p. 64–65°.

Anal. Calculated for $C_{29}H_{48}O$: C, 84.4; H, 11.7. Found: C, 84.6; H, 11.6.

2-Methyl-3-*n*-octadecyl-5,6,7,8-tetrahydronaphthalene.—The above ketone was reduced as described for the preparation of 2-octadecylnaphthalene; 3.5 g. of ketone yielded 2.5 g. (72%) of hydrocarbon. The final product after recrystallization from ether–methanol mixture melted at 60–61°.

Anal. Calculated for $C_{29}H_{50}$: C, 87.4; H, 12.6. Found: C, 87.3; H, 12.8.

(12) Seidel and Engelfried, *Ber.*, **69**, 2584 (1936).
(13) Schroeter, *Ber.*, **54**, 2247 (1921).
(14) Fieser and Jones, THIS JOURNAL, **60**, 1940 (1938).
(15) Ansbacher, Fernholz and MacPhillamy, *Proc. Soc. Exp. Biol. Med.*, **42**, 655 (1939).
(16) Mikeska, Smith and Lieber, *J. Org. Chem.*, **2**, 449 (1938).

2-Methyl-3-*n*-octadecylnaphthalene.—Two grams of the above hydrocarbon was subjected to sulfur dehydrogenation as already described for the preparation of 2-hexadecylnaphthalene. After crystallization from acetone 0.7 g. (35%) of a product was obtained melting at 47–48°.

Anal. Calculated for $C_{29}H_{46}$: C, 88.25; H, 11.75. Found: C, 88.60; H, 11.30.

2-Methyl-3-*n*-octadecyl-1,4-naphthoquinone.—The oxidation of 0.5 g. of the above hydrocarbon with chromic acid gave 0.2 g. (37%) of quinone which melted at 95–97° after recrystallization from ether.

Anal. Calculated for $C_{29}H_{44}O_2$: C, 82.0; H, 10.4. Found: C, 81.7; H, 10.2.

Summary

The preparation and vitamin K activity of a number of naphthoquinones is described. None of these compounds surpasses or even approaches 2-methyl-1,4-naphthoquinone in activity.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

o-Halide Synthesis of 10-Methyl-1′,9-methylene-1,2-benzanthracene

BY LOUIS F. FIESER AND JAMES CASON[1]

Since attempts to introduce methyl or hydroxyl groups into the interesting and reactive 1′,9-methylene-1,2-benzanthracene[2] (XIII) by direct substitution offered little promise of success a second synthesis was investigated which affords a route not only to the parent hydrocarbon but to various 10-substituted derivatives. The method embodies the general scheme of synthesis of anthracene derivatives introduced by one of us and Seligman.[3] This involves the preparation, through a Grignard reaction and reduction, of a suitable *o*-halide of a diphenylmethane, conversion through the nitrile to the acid and ring closure. The halogen may be introduced in various sequences into either aromatic ring, giving considerable flexibility to the method.

For the present application of the *o*-halide synthesis 7-acenaphthenone (IV) was required as starting material, and as the ketone heretofore has been accessible only by quite laborious processes,[4] a new method was sought. Marquis[5] observed that the corresponding alcohol is produced in low yield in the form of the acetate by the oxidation of acenaphthene with lead dioxide in acetic acid, and in connection with a study of the action of lead tetraacetate on other hydrocarbons[6] Dr. E. B. Hershberg noted that 7-acenaphthenyl acetate can be obtained more smoothly with the use of this reagent.[7] M. E. Gross then worked out a practical procedure for conducting the oxidation and this was employed initially in the present investigation. The experience of treating quantities of red lead with acetic acid for the preparation of a reagent for use in this solvent suggested that the operation might be dispensed with, and indeed it was found that acenaphthene can be converted smoothly and easily into the 7-acetoxy compound with red lead and acetic acid. The yield is equal to that obtained with purified lead tetraacetate, and considerable time is saved. The acetate is a liquid and is not easily freed from traces of acenaphthene and acenaphthenone, but pure crystalline 7-acenaphthenol is readily obtained in good over-all yield on saponification. Under the most favorable conditions found, oxidation with chromic acid and steam distillation of the product gave the pure ketone in reasonably good yield, and by this sequence of reactions 7-acenaphthenone is obtainable in quantity from the hydrocarbon in 47% over-all yield.

The further stages of the synthesis are indicated in the chart. The carbinol (V) resulting from the action of *o*-chlorophenylmagnesium bromide on 7-acenaphthenone was obtained in a crystalline condition only with considerable loss; the dehydration of the crude reaction product with acetic acid proceeded smoothly enough but in rather low over-all yield. The unsaturated compound VI crystallizes in brilliant orange prisms, while its dihydride VII is a colorless solid of lower

(1) Research Fellow on funds from the National Cancer Institute.
(2) Fieser and Cason, THIS JOURNAL, **61**, 1740 (1939).
(3) Fieser and Seligman, *ibid.*, **61**, 136 (1939).
(4) Ewan and Cohen, *J. Chem. Soc.*, **55**, 580 (1889); Graebe and Gfeller, *Ann.*, **276**, 12 (1893); Graebe and Jequier, *ibid.*, **290**, 197 (1896); Badische Anilin u. Soda-Fabrik, German Patent 230,237 (1910); Ghigi, *Gazz. chim. ital.*, **68**, 184 (1938).
(5) Marquis, *Compt. rend.*, **182**, 1227 (1926).
(6) Fieser and Hershberg, THIS JOURNAL, **60**, 1893, 2542 (1938).
(7) Our results appear to be at variance with the observations reported by Monti, *C. A.*, **33**, 9316 (1939).