crystalline residue was washed with water, filtered on a Büchner funnel, washed with ethyl alcohol and dried in air. The yield of iodoform was 375 g., or 95%; m. p. 119°.

Summary

Carbon tetraiodide, iodoform and bromoform are prepared readily and in good yield by redistribution reactions between carbon tetrachloride and methyl iodide, chloroform and methyl iodide, and chloroform and ethyl bromide, respectively.

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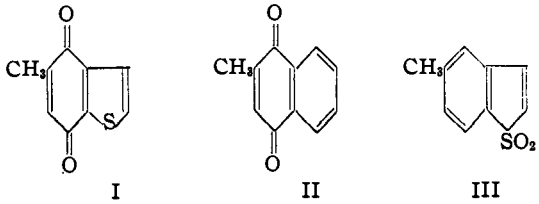
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF ARTS AND SCIENCES, AND DEPARTMENT OF BIOCHEMISTRY, SCHOOL OF MEDICINE, UNIVERSITY OF ROCHESTER]

The Synthesis and Antihemorrhagic Activity of 5-Methyl-4,7-thionaphthenequinone

BY D. S. TARBELL, D. K. FUKUSHIMA AND H. DAM

It is well known that the chemical and physiological properties of thiophene compounds are frequently very similar to those of the analogous benzene derivatives. A good deal of attention has been devoted to the synthesis and study of compounds differing from a vitamin or other physiologically active substance by having a sulfur atom instead of a vinyl group, or the converse.[1]

The present paper deals with the synthesis and testing of 5-methyl-4,7-thionaphthenequinone I, which is an isostere of 2-methyl-1,4-naphthoquinone II. It was of special interest to study

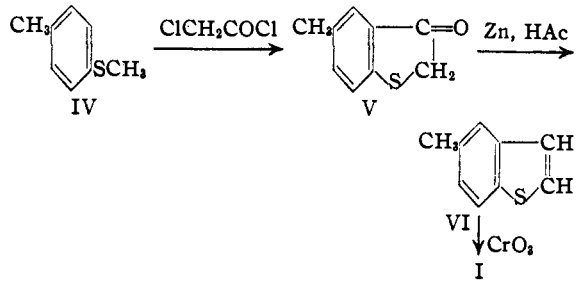


I II III

compound I, since in most other cases in the vitamin K series any substitution in the benzenoid ring of II usually caused an almost complete loss of activity.[2]

It was found that the thionaphthenequinone I could be obtained in 10% yield by oxidation of 5-methylthionaphthene with chromic acid in acetic acid solution.[3] When the oxidation was attempted using hydrogen peroxide in acetic acid,[4] which is a useful method of obtaining quinones in some cases, a product was obtained having the composition of the sulfone III.

The 5-methylthionaphthene was obtained by reduction of the corresponding keto compound (V) with zinc and acid[5]; the latter was prepared from methyl *p*-tolyl sulfide, chloroacetyl chloride



and aluminum chloride.[6] In this process, a by-product was isolated in small amount, which was not obtained by Auwers and Arndt.[6]

The structure of compound I was evident from the fact that it formed a diacetate on reductive acetylation, and gave a positive Craven's test[7] for an α-quinone. The ultraviolet absorption spectrum, as shown in the accompanying curves, is similar to that of 2-methyl-1,4-naphthoquinone II, but contains an additional peak at short wave lengths which is usually associated with the presence of sulfur.[8]

The vitamin K activity of compound I was determined in the usual manner,[9] and was found to be approximately 3% of that of 2-methyl-1,4-naphthoquinone, as a result of several runs.

Experimental[10]

Methyl *p*-tolyl sulfide (IV) was prepared in 94% yield by the action of methyl sulfate and alkali on *p*-thiocresol; b. p. 94–95° (13 mm.).[11]

5-Methyl-3-keto-1,2-dihydrothionaphthene (V).—To a cold solution of 10 g. of methyl *p*-tolyl sulfide and 8.5 g. of chloroacetyl chloride in 100 g. of carbon disulfide was added in small portions 12 g. of anhydrous aluminum chloride. After addition of the aluminum chloride, the reaction mixture was slowly brought to refluxing and the bath maintained at 60–65° for five hours. The solvent was re-

(1) For examples of such "isosteric" compounds, see Erlenmeyer, Berger and Leo, *Helv. Chim. Acta*, **16**, 733 (1933); Tracy and Elderfield, *J. Org. Chem.*, **6**, 54 (1941); Woolley and White, *J. Biol. Chem.*, **149**, 285 (1943); Blicke and Tsao, THIS JOURNAL, **66**, 1645 (1944); English, Clapp, Cole, Halverstadt, Lampen and Roblin, *ibid.*, **67**, 295 (1945).

(2) Doisy, Binkley and Thayer, *Chem. Rev.*, **28**, 501 (1941).

(3) A second method of synthesizing I is described in the accompanying paper by Kitchen and Sandin.

(4) Arnold and Larson, *J. Org. Chem.*, **5**, 250 (1940).

(5) Auwers, *Ann.*, **408**, 282 (1915); according to Auwers and Thies (*Ber.*, **53**, 2285 (1920)) the 3-hydroxythianaphthenes exist principally in the keto form.

(6) Auwers and Arndt, *Ber.*, **42**, 537 (1909).

(7) Craven, *J. Chem. Soc.*, 1605 (1931).

(8) Landolt-Börnstein, "Tabellen," 5 Aufl., Eg. IIb, p. 706, Eg. IIIb, p. 1419. The absorption curve of 2-methyl-1,4-naphthoquinone as previously reported by Ewing, Vandenbelt and Kamm, *J. Biol. Chem.*, **131**, 345 (1939), agrees closely with the curve as we observed it. Our curves were obtained with a Beckman ultraviolet spectrophotometer.

(9) Tarbell, Fukushima and Dam, THIS JOURNAL, **67**, 197 (1945).

(10) All melting points corrected; microanalyses by Dr. Carl Tiedcke, New York City.

(11) The reported value[6] is 94° (31 mm.); the figure of 31 mm. is probably a misprint.

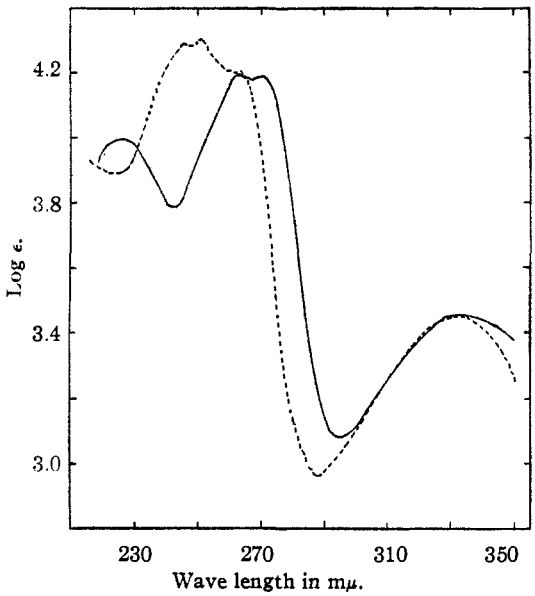


Fig. 1.—Absorption spectra of 5-methyl-4,7-thionaphthene-quinone (————) and 2-methyl-1,4-naphthoquinone (- - - -).

moved, the addition complex decomposed with ice and concentrated hydrochloric acid, and the mixture steam distilled. The distillate, on filtration, yielded 4.9 g. (41%) of crude product of m. p. 101–103°. Recrystallization from petroleum ether (b. p. 40–60°) yielded soft, white needles, m. p. 101.5–102.5°. The reported value[6] is 102°.

The dark residue from the above steam distillation when dissolved in methanol and decolorized with charcoal, yielded 0.75 g. (5%) of a compound, m. p. 128–130°. Recrystallizations from methanol yielded pale yellow crystals, m. p. 131.5–132.5°. The analysis corresponds to the composition of a bis-chloroacetyl derivative but, due to the small amount of the material, its structure was not investigated further.

Anal. Calcd. for $C_{16}H_{11}ClOS$ (chloroacetyl derivative of IV): C, 55.91; H, 5.16. Calcd. for $C_{12}H_{12}Cl_2O_2S$ (bis-chloroacetyl derivative of IV): C, 49.49; H, 4.16. Found: C, 49.16; H, 3.84.

5-Methylthionaphthene (VI).—To a solution of 5 g. of 5-methyl-3-keto-1,2-dihydrothionaphthene (V) in 60 cc. of glacial acetic acid was added 6 g. of zinc dust and 1 cc. of concentrated hydrochloric acid. The mixture was refluxed for six hours, and after being made strongly alkaline with solid sodium hydroxide, was steam distilled and the distillate extracted with ether. From the extracts was obtained 2.2 g. (49%) of colorless 5-methylthionaphthene, b. p. 105–110° (13 mm.), m. p. 20–22°. Auwers[5] reports a m. p. of 19–22°.

5-Methyl-4,7-thionaphthenequinone (I).[12]—To an ice-cold solution of 8 g. of chromic oxide in 15 cc. of 80% acetic acid was added dropwise a solution of 2 g. of 5-methylthionaphthene in 20 cc. of acetic acid. The reaction mixture was kept below 10° during the addition, then slowly brought to room temperature and allowed to stand for twelve hours. The mixture was diluted with water and the acetic acid partially neutralized with sodium bicarbonate; it was then steam distilled and the distillate neutralized with sodium bicarbonate. Upon standing, 0.08 g. (3%) of greenish-yellow needles, m. p. 119–120°, separated which, on crystallization from ethanol and decolorizing with charcoal, yielded soft, yellow needles, m. p. 120–121°, giving a positive Craven test. The aqueous filtrate from the first crop yielded, on ether extraction, 0.17 g. (7%) of green solid, m. p. 80–115°, which on purification from ethanol yielded yellow needles, m. p. 120–121°.

Anal. Calcd. for $C_9H_6O_2S$: C, 60.64; H, 3.4. Found: C, 60.68; H, 3.89.

5-Methyl-4,7-thionaphthenehydroquinone Diacetate.—A mixture of 0.02 g. of the quinone I, 0.03 g. of anhydrous sodium acetate, 0.04 g. of zinc dust, 0.05 cc. of glacial acetic acid and 1 cc. of acetic anhydride was refluxed for about an hour. The reaction mixture was then decanted and the residue washed with small portions of hot glacial acetic acid; the washings were combined with the reaction mixture, and the whole diluted with water. The white crystals which were obtained melted, after recrystallization from petroleum ether (b. p. 40–60°), at 116–117°.

Anal. Calcd. for $C_{13}H_{12}O_4S$: C, 59.06; H, 4.58. Found: C, 59.10; H, 4.62.

5-Methylthionaphthene Sulfone (III).—A solution of 1.2 g. of 5-methylthionaphthene, 4 cc. of Superoxol and 15 cc. of glacial acetic acid was kept at 80–85° for six hours. After the oxidation was complete, the mixture was diluted with water and partially neutralized with potassium carbonate, which precipitated 0.9 g. (63%) of cream-colored needles, m. p. 105–116°, giving a negative Craven test. Several recrystallizations from ethanol yielded soft, white needles of the dioxide, m. p. 125.5–126.5°; mixed with 5-methyl-4,7-thionaphthenequinone, the m. p. was 82–95°.

Anal. Calcd. for $C_9H_8O_2S$: C, 59.96; H, 4.48. Found: C, 59.97; H, 4.59.

Summary

5-Methyl-4,7-thionaphthenequinone, an isostere of 2-methyl-1,4-naphthoquinone, has been synthesized by the oxidation of 5-methylthionaphthene, and has been found to have about 3% of the vitamin K activity of 2-methyl-1,4-naphthoquinone. The absorption spectra of both compounds have been determined.

ROCHESTER, NEW YORK RECEIVED JUNE 18, 1945

(12) *Cf.* Anderson and Newman, *J. Biol. Chem.*, **103**, 405 (1933); Fieser, Campbell, Fry and Gates, THIS JOURNAL, **61**, 3218 (1939).