[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ALBERTA]

The Synthesis of 5-Methyl-4,7-thionaphthenequinone and Related Compounds

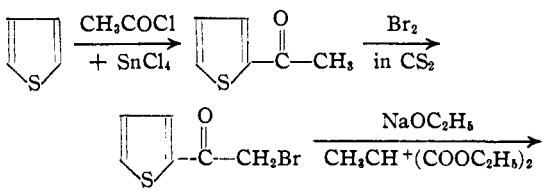
BY ROSS KITCHEN[1] AND REUBEN B. SANDIN

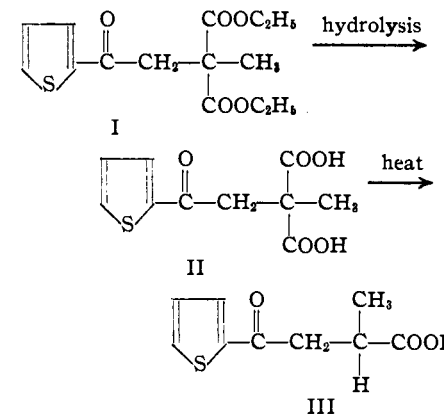
In 1939 vitamin K_1 was obtained in pure form and identified as 2-methyl-3-phytyl-1,4-naphthoquinone.[2] Since then numerous compounds have been shown to possess vitamin K_1 activity. One of the potent compounds is 2-methyl-1,4-naphthoquinone.[3] Of about half the potency of the latter compound and approximately as active as vitamin K_1 are 2-methyl-1-tetralone, 3-methyl-1-tetralone, 2-methyl-1-naphthol and 3-methyl-1-naphthol.[4]

We considered it useful to prepare thiophene isologs of some of the above compounds in order to determine the effect on vitamin K_1 activity of the replacement of a benzene ring by the less aromatic thiophene ring. The problem seemed of interest because of the observation of Fieser and Kennelly[5] that quinones with a thiophene ring in place of the benzene ring are about 75 mv. higher in reduction potential than the corresponding naphthoquinones. Furthermore, Burger and co-workers[6] have compared such compounds as dibenzothiophene and phenanthrene; and Sandin and Fieser[7] synthesized an isolog of 9,10-dimethyl-1,2-benzanthracene containing a terminal thiophene nucleus that proved to be very nearly as potent a carcinogen as the hydrocarbon.

5-Methyl-4,7-thionaphthenequinone was synthesized from thiophene and methylsuccinic anhydride by a process based on that applied by Fieser and Kennelly[5,8] for the synthesis of the parent quinone. The yields in some of the steps were disappointing, for the reactions do not proceed as well with methylsuccinic anhydride as with succinic anhydride.

A proof for the structure of α-methyl-β-(α'-thenoyl)-propionic acid was afforded by the following sequence of reactions





The formation of this isomer as a result of the Friedel–Crafts and Grignard reactions fits in with the data obtained by such workers as Weizmann, Blum-Bergmann and Bergmann.[9]

Experimental[10]

Methylsuccinic acid was prepared from ethyl crotonate according to Higginbotham and Lapworth.[11] One typical experiment produced 228 g. of the acid from 250 g. of ethyl crotonate. Methylsuccinic acid anhydride was prepared by refluxing the acid with acetic anhydride. The yield was 70%, after two fractional distillations. Methylsuccinic acid was also prepared by the method of Linstead, Noble and Wright[12] and the yield was excellent.

Preparation of α-Methyl-β-(α'-thenoyl)-propionic Acid (III). Method A.—The Grignard reagent from 25 g. of 2-iodothiophene,[13] 3.0 g. of magnesium, and 100 cc. of ether was filtered under nitrogen pressure and forced all at once into a well-stirred solution of 14 g. of methylsuccinic anhydride in 200 cc. of dry thiophene-free benzene. The mixture was refluxed for two hours, cooled, treated with dilute hydrochloric acid, and the benzene layer was separated and extracted thoroughly with sodium carbonate. Acidification of the combined soda extracts afforded the crude keto acid which after three crystallizations from water gave 6.6 g. (27%) of colorless needles, m. p. 110–111°.

Anal.[14] Calcd. for $C_9H_{10}O_3S$: S, 16.17. Found: S, 16.26, 16.28.

The m. p. of this compound was sharp and remained constant after repeated crystallizations, indicating that it was not a mixture of the two possible isomers.

Method B.—From 45 g. of methylsuccinic anhydride, 32 g. of thiophene and aluminum chloride (115 g.) in 350 cc. of nitrobenzene, there was obtained only 5.0 g. of compound, m. p. 110–111°. Tar formation was extensive. A mixture of this preparation and the one above showed no depression of the melting point. Because the Grignard synthesis proved more economical, it was used in all the later runs, the average yield being 28%.

(1) Present address: Shawinigan Chemicals, Ltd., Shawinigan Falls, Quebec.

(2) For the fascinating story of vitamin K, see Doisy, Binkley and Thayer, *Chem. Rev.*, **28**, 477 (1941).

(3) Ansbacher and Fernholz, THIS JOURNAL, **61**, 1924 (1939).

(4) Tishler, Fieser and Sampson, *ibid.*, **62**, 1881 (1940).

(5) Fieser and Kennelly, *ibid.*, **57**, 1611 (1935).

(6) (a) Burger, Wartman and Lutz, *ibid.*, **60**, 2628 (1938); (b) Burger and Bryant, *J. Org. Chem.*, **4**, 119 (1939); (c) Burger and Bryant, THIS JOURNAL, **63**, 1054 (1941).

(7) Sandin and Fieser, *ibid.*, **62**, 3098 (1940).

(8) The synthesis of this compound by a different method is described in the accompanying paper by Tarbell, Fukushima and Dam.

(9) Weizmann, Blum-Bergmann and Bergmann, *J. Chem. Soc.*, 1370 (1935).

(10) All melting points are corrected.

(11) Higginbotham and Lapworth, *J. Chem. Soc.*, **121**, 49 (1922).

(12) Linstead, Noble and Wright, *ibid.*, 911 (1937).

(13) Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 357.

(14) Macroanalysis by R. K.

Method C and Proof of Structure.—A solution of 2-acetothienone[15] in carbon bisulfide was brominated according to Brunswig[16] and afforded a good yield of α-bromo-2-acetothienone. The latter compound was condensed with sodium methylmalonic ester and the reaction mixture was worked up according to the regular procedure. Attempts to purify the resulting diethyl methyl-α-thenoylmethylmalonate (I) by vacuum distillation resulted in considerable decomposition. The ester (35 g.) was therefore hydrolyzed and the resulting acid (II) (10 g.) was crystallized from water. It was obtained as white crystals; m. p. 165–166° (dec.).

Anal.[17] Calcd. for $C_{10}H_{20}O_5S$: S, 13.22. Found: S, 13.30, 13.36.

The dicarboxylic acid was readily decarboxylated in good yield to α-methyl-β-(α'-thenoyl)-propionic acid, m. p. 110–111°. A mixture of this compound and the compound obtained by method B showed no depression of the melting point.

α-Methyl-γ-(α'-thienyl)-butyric Acid.—Reduction of the above keto acid was carried out using amalgamated zinc and 1:1 hydrochloric acid at 25° according to the directions of Fieser and Kennelly[5] for the preparation of γ-(α-thienyl)-butyric acid. There was obtained an oily product (b. p. 130–135° at 15 mm.) which on cooling to 0° produced colorless crystals, m. p. 28–29°. The yield was 70%.

Anal.[14] Calcd. for $C_9H_{12}O_2S$: S, 17.40. Found: S, 17.53, 17.63.

4-Keto-5-methyl-4,5,6,7-tetrahydrothionaphthene.—The acid chloride was prepared by boiling gently for five hours a solution of α-methyl-γ-(α'-thienyl)-butyric acid, thionyl chloride and pyridine in absolute ether. After removal of the solvent and excess reagent, and without distillation in vacuum, the acid chloride was cyclized in carbon bisulfide by means of anhydrous stannic chloride. The reaction mixture was worked up in the usual manner and then steam distilled. Following the elimination of the solvent the cyclic ketone came over in the distillate as an oil which solidified on cooling. The material was steam distilled a second time. It formed colorless crystals, m. p. 35–36°. The over-all yield from the acid was 35%.

Anal.[14] Calcd. for $C_9H_{10}OS$: S, 19.29. Found: S, 19.32, 19.36.

4-Hydroxy-5-methyl-thionaphthene.—The above ketone was dehydrogenated with sulfur. The reaction product was purified by distillation in vacuum, alkali extraction, and crystallization from ligroin. The substance has a phenolic odor and crystallizes from ligroin as fine colorless needles, m. p. 109–110°, yield 10–15%.

Anal.[14] Calcd. for C_9H_8OS: S, 19.52. Found: S, 19.65, 19.80.

5-Methyl-4,7-thionaphthenequinone.—Following the procedure of Fieser and Fieser,[18] the phenol was coupled with diazotized sulfanilic acid, the azo dye reduced with sodium hydrosulfite and the amine converted to the amine hydrochloride. Because of insufficient quantity the latter compound was not analyzed, but was converted directly into the quinone according to the directions of Fieser and Kennelly.[5] The quinone was purified by sublimation in vacuum (100° at 15 mm.). It formed yellow needles, m. p. 120–121°, over-all yield from the phenol 15%.

Anal.[19] Calcd. for $C_9H_6O_2S$: C, 60.65; H, 3.39. Found: C, 60.82; H, 3.63.

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Summary

5-Methyl-4,7-thionaphthenequinone and some related compounds have been prepared.

(15) Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 8.

(16) Brunswig, *Ber.*, **19**, 2890 (1886).

(17) Macroanalysis by J. C. Nichol.

(18) Fieser and Fieser, THIS JOURNAL, **57**, 491 (1935).

(19) Microanalysis by Eleanor Werble.

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[CONTRIBUTION FROM THE WILLIAM G. KERCKHOFF LABORATORIES OF THE BIOLOGICAL SCIENCES OF THE CALIFORNIA INSTITUTE OF TECHNOLOGY]

Chemical Studies of Pineapple (*Ananas sativus* Lindl). I. The Volatile Flavor and Odor Constituents of Pineapple[1]

BY A. J. HAAGEN-SMIT, JUSTUS G. KIRCHNER, ARTHUR N. PRATER[2] AND CLARA L. DEASY[3]

Our chemical knowledge of the flavors of the fleshy fruits is largely based on comparison with the smell of synthetically-obtained esters. Few investigations have been carried out with the object of isolating and identifying the substances actually present in the fruit and responsible for their flavor. The production of these substances is an expression of the metabolism going on during ripening and their accurate knowledge is of both scientific and technical value. A direct contribution is also made by substitution of the analytical chemical determination of these compounds for the subjective scale of grading used at present in the fruit industry. In this way, the effects of climatological factors, changes in agricultural methods, and the results of breeding experiments may be investigated.

The following investigations on pineapple (*Ananas sativus* Lindl) were carried out to determine the chemical nature of the volatile constituents and, if possible, to establish a correlation between flavor and these substances. It has been observed that the taste of pineapple varies with the season in which it is grown. Although there is a great variation in individual fruits, in general the fruit grown during the summer season has a much sweeter and more fruity flavor than that of the winter crop, and it was, there-

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(2) Present address: C. B. Gentry Co., Los Angeles, California.

(3) Present address: Temple University of Medicine, Philadelphia, Penn.