[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE GEORGIA SCHOOL OF TECHNOLOGY]

# The Synthesis of Quinolines by the Pfitzinger Reaction

BY J. A. KNIGHT, JR.,[1] H. K. PORTER[1] AND PAUL K. CALAWAY

We have been interested for some time in the utilization of the Pfitzinger reaction[2] for the preparation of substituted quinoline acids which might have value as therapeutic agents.

In a previous paper[3] it has been shown that the product of the condensation of isatin with aryloxyketones has been the 3-aryloxy-4-quinaldinecarboxylic acid rather than the 2-aryloxymethylcinchoninic acid, and similar results have been obtained in the work reported in this paper.

We have studied the condensation of isatin with 1-phenylmercapto-2-propanone, and the condensation of 5-methylisatin with 1-phenylmercapto-2-propanone and phenoxyacetone, respectively. Two of the substituted cinchoninic acids obtained have been decarboxylated to yield the corresponding quinaldines, and derivatives of the latter have been prepared.

## Experimental

**Preparation of 1-Phenylmercapto-2-propanone.**[4]—A mixture of 45 g. of thiophenol (0.5 mole) and 300 cc. of benzene was introduced into a one-liter, three-neck, round-bottom flask equipped with an efficient mercury-sealed, mechanical stirrer, a dropping funnel and a condenser. The stirrer was started and 11 g. of finely divided sodium was added over a period of several hours. After several days all of the sodium dissolved and the sodium thiophenolate separated out as a white solid. After cooling, 46.3 g. of chloracetone (0.5 mole) was dropped in and the reaction mixture again heated to complete the reaction. The sodium chloride was removed by filtration and the benzene by distillation under diminished pressure. The residual liquid was fractionated and 56.5 g. of 1-phenylmercapto-2-propanone (68% yield) was obtained as a pale yellow oil boiling over the range 168–171° (35–38 mm.). The oil solidified on cooling and was recrystallized from alcohol. The melting point was 34°, agreeing closely with the literature.

**Preparation of Phenoxyacetone.**[3]—This compound was prepared similarly to 1-phenylmercapto-2-propanone, but was obtained in lower yield (50%) as a colorless oil boiling at 115° (12 mm.).

**Preparation of 5-Methylisatin.**[5]—Isonitrosoaceto-*p*-toluidine was prepared by the interaction of *p*-toluidine with chloral hydrate and hydroxylamine hydrochloride; treatment of the product with concentrated sulfuric acid resulted in the formation of crude 5-methylisatin (80% yield).

**Preparation of 3-Phenylmercapto-4-quinaldinecarboxylic Acid.**—Twenty-eight and seven-tenths grams of isatin (0.195 mole) was dissolved in 175 cc. of 33% aqueous potassium hydroxide solution, and 32.4 g. of 1-phenylmercapto-2-propanone (0.195 mole) was added. The mixture was heated under reflux on a steam-bath for twenty hours, diluted with an equal volume of water, boiled with Norite and filtered. The clarified solution was cooled in ice and made barely acid by the addition of dilute acetic acid. The white solid separating was recrystallized from ethyl alcohol and dried in an oven. The yield was 62% of the theoretical. The 3-phenylmercapto-4-quinaldinecarboxylic acid melted at 285–286° (cor.) (dec.).

*Anal.* Calcd. for $C_{17}H_{13}NO_2S$: neut. equiv., 295.3; C, 69.13; H, 4.44; N, 4.74; S, 10.85. Found: neut. equiv., 291.2; C, 68.89; H, 4.32; N, 4.90; S, 10.60.

**Preparation of 6-Methyl-3-phenylmercapto-4-quinaldinecarboxylic Acid.**—Sixteen and one-tenth grams of 5-methylisatin (0.1 mole) was dissolved in 150 cc. of 30% aqueous potassium hydroxide solution and placed in a 500-cc. three-neck, round bottom flask equipped with a mechanical stirrer, and a reflux condenser. Sixteen and six-tenths grams of 1-phenylmercapto-2-propanone (0.1 mole) was added with rapid stirring, and the mixture was heated on the steam-bath for thirty hours. The resulting dark brown solution was treated with Norite and filtered. The clarified solution was poured into an equal volume of ice water and a slight excess of acetic acid was added. The cream-colored solid which separated was filtered, washed with water, and dried over calcium chloride. After recrystallization from alcohol the purified 6-methyl-3-phenylmercapto-4-quinaldinecarboxylic acid was obtained as a colorless solid which melted at 290.8° (cor.) (dec.). The yield was 60% of the theoretical.

*Anal.* Calcd. for $C_{18}H_{15}NO_2S$: neut. equiv., 309.4; N, 4.53; S, 10.36. Found: neut. equiv., 308.9; N, 4.61; S, 10.34.

**Preparation of 6-Methyl-3-phenoxy-4-quinaldinecarboxylic Acid.**—To 16.1 g. of 5-methylisatin (0.1 mole) dissolved in 100 cc. of 30% potassium hydroxide solution was added 15 g. of phenoxyacetone (0.1 mole) and the mixture was heated for thirty hours on the steam-bath. The reaction mixture was diluted with 200 cc. of water, boiled with Norite and filtered. The filtrate was cooled to 0° and made barely acid by the addition of acetic acid. After twelve hours the crude product was filtered and purified by washing with hot ethyl alcohol. The yield was 42% of the theoretical. The melting point of the white 6-methyl-3-phenoxy-4-quinaldinecarboxylic acid was 267.5° (cor.) (dec.).

*Anal.* Calcd. for $C_{18}H_{15}NO_3$: neut. equiv., 293.4; N, 4.77. Found: neut. equiv., 288.5; N, 4.74.

**Preparation of 3-Phenylmercaptoquinaldine.**—Ten grams of 3-phenylmercapto-4-quinaldinecarboxylic acid was heated in a Claisen distilling flask on an oil-bath at 285°. At this temperature the acid melted and carbon dioxide was liberated from the mass. After the effervescence had ceased the liquid was distilled under diminished pressure. The pale brown distillate was redistilled and the fraction boiling between 250 and 256° (40 mm.) was retained. The odor of thiophenol was evident and the liquid was washed with dilute sodium hydroxide solution. After three recrystallizations from alcohol the material was obtained as a white solid melting at 67.8° (cor.).

*Anal.* Calcd. for $C_{16}H_{13}NS$: N, 5.57; S, 12.73. Found: N, 6.10; S, 12.52.

**Preparation of the Picrate of 3-Phenylmercaptoquinaldine.**—A small amount of 3-phenylmercaptoquinaldine was dissolved in alcohol and added to an alcoholic solution of picric acid. The picrate was formed immediately and after recrystallization from alcohol showed a melting point of 201° (cor.).

**Preparation of the Hydrochloride of 3-Phenylmercaptoquinaldine.**—The hydrochloride of 3-phenylmercaptoquinaldine was prepared in good yield by passing dry

(1) From the theses submitted in partial fulfillment of the requirements for the Degree of Master of Science in Chemistry by J. A. Knight, Jr., June, 1944, and H. K. Porter, June, 1942.

(2) Pfitzinger, (a) *J. prakt. Chem.*, **33**, 100 (1886); (b) **38**, 582 (1888); (c) **56**, 283 (1897).

(3) Calaway and Henze, THIS JOURNAL, **61**, 1355 (1939).

(4) Otto and Rossing, *Ber.*, **23**, 756 (1890).

(5) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. 1: 1932, page 321.

hydrogen chloride through a benzene solution of the quinaldine. The hydrochloride separated from the benzene solution as a white solid. The melting point of the purified compound was 200.5° (cor.).

*Anal.* Calcd.: neut. equiv., 287.6. Found: neut. equiv., 288.

**Preparation of 6-Methyl-3-phenylmercaptoquinaldine.**—Three grams of 6-methyl-3-phenylmercapto-4-quinaldinecarboxylic acid was placed in a 25-cc. distilling flask attached to an air condenser, and the mass heated on an oil-bath to 290°. At this temperature the acid melted and carbon dioxide was evolved. After the effervescence had ceased the liquid was distilled under diminished pressure, and the fraction boiling at 280° (1–2 mm.) was collected as a heavy oil which solidified on cooling. After two recrystallizations from alcohol the white 6-methyl-3-phenylmercaptoquinaldine melted at 79.8° (cor.).

*Anal.* Calcd. for $C_{17}H_{15}NS$: N, 5.28. Found: N, 5.90.

**Preparation of the Picrate of 6-Methyl-3-phenylmercaptoquinaldine.**—The picrate was prepared by dissolving the substituted quinaldine in hot alcohol and pouring into a saturated aqueous solution of picric acid. The picrate separated immediately and after recrystallization melted at 217.5° (cor.).

## Summary

1. Pfitzinger's method has been extended to include the utilization of thiophenoxyacetone in the synthesis of 3-phenylmercapto-4-quinaldinecarboxylic acid and 6-methyl-3-phenylmercapto-4-quinaldinecarboxylic acid from isatin and 5-methylisatin, respectively.

2. Phenoxyacetone has been condensed with 5-methylisatin to form 6-methyl-3-phenoxy-4-quinaldinecarboxylic acid.

3. The thio acids have been decarboxylated, and some derivatives of their quinaldines prepared.

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# The Oxidation of Thio-ethers by Unsaturated Fatty Acids

BY WILLIAM V. B. ROBERTSON, JONATHAN L. HARTWELL AND SYLVIA KORNBERG

In the course of a toxicological investigation of β,β′-dichloroethyl sulfide it was observed that 1% and 5% olive oil solutions of the sulfide gradually decreased in toxicity and after standing several weeks at room temperature deposited varying amounts of crystals. These were identified as β,β′-dichloroethyl sulfoxide by mixed melting point determination with an authentic specimen. Fresh olive oil solutions of the sulfide when kept under nitrogen did not deposit crystals, nor did the pure sulfide when exposed to oxygen for over one year. The possibility that bacterial or other enzymes caused the reaction was excluded since olive oil which had been heated at 150° for two hours under nitrogen was still able to effect the oxidation of the sulfide.

A review of the literature revealed only one brief note about such an oxidation. In 1925 Walker[1] reported the oxidation of β,β′-dichloroethyl sulfide, diphenylchloroarsine and diphenyl arsenious oxide by aged turpentine or rancid olive oil. Investigation of this reaction seems to have been dropped, since no other reports appeared. Destruction of carotene,[2] vitamin A,[3,4] biotin,[5] vitamin D,[6] vitamin E,[3] and of the carcinogenic azo dye *p*-dimethylaminoazobenzene[7] by rancid fats has been noted. Recently Burr and Barnes[8] have discussed the deterioration of dietary essentials caused by the presence of unsaturated fats in the diet. In view of these physiological implications a more detailed study of the oxidation of thio-ethers was undertaken. This paper presents the results of experiments dealing with the mechanism and specificity of the reaction.

Highly unsaturated linseed oil, when substituted for olive oil, was found to react even more rapidly, whereas mineral oil was completely inactive. Various other oils were then tested for the ability to mediate the oxidation of the β,β′-dichloroethyl sulfide. The oils were selected either because of general interest or for their content of specific fatty acids. The results, which are shown in Table I, indicated that all unsaturated oils tested, with the exception of those consisting mainly of glycerides of fatty acids with conjugated unsaturation (tung oil and oiticica oil), were able to oxidize the sulfide to sulfoxide. Neither the yield nor the time until appearance of sulfoxide crystals was related to the degree of unsaturation. The addition of driers was necessary in some cases in order to overcome the effect of naturally-occurring oxidation inhibitors; that the drier did not effect the oxidation in the absence of unsaturated oils is seen from the table in the results with liquid petrolatum and tricaprylin. The deposition of crystals was always preceded by oxygen consumption, as indicated by a strong vacuum within the reaction flask. Although both tung and oiticica oil absorbed oxygen, subsequent oxidation of the sulfide did not

(1) Walker, *J. Chem. Soc.*, **127**, 1491 (1925).
(2) Olcovich and Mattill, *J. Biol. Chem.*, **91**, 105 (1931).
(3) Mattill, *J. Am. Med. Assoc.*, **89**, 1505 (1927).
(4) Sumner, *J. Biol. Chem.*, **146**, 215 (1942).
(5) Pavcek and Shull, *ibid.*, **146**, 351 (1942).
(6) Fritz, Halpin, Hooper and Kramke, *Ind. Eng. Chem.*, **34**, 979 (1942).
(7) György, Tomarelli, Ostergard and Brown, *J. Exptl. Med.*, **76**, 413 (1942).
(8) Burr and Barnes, *Physiol. Rev.*, **23**, 256 (1943).