[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthesis of 4-Hydroxyquinolines. VI. Synthesis of 3-*n*-Heptyl-7-methoxy-2-methyl-4-quinolinol[1]

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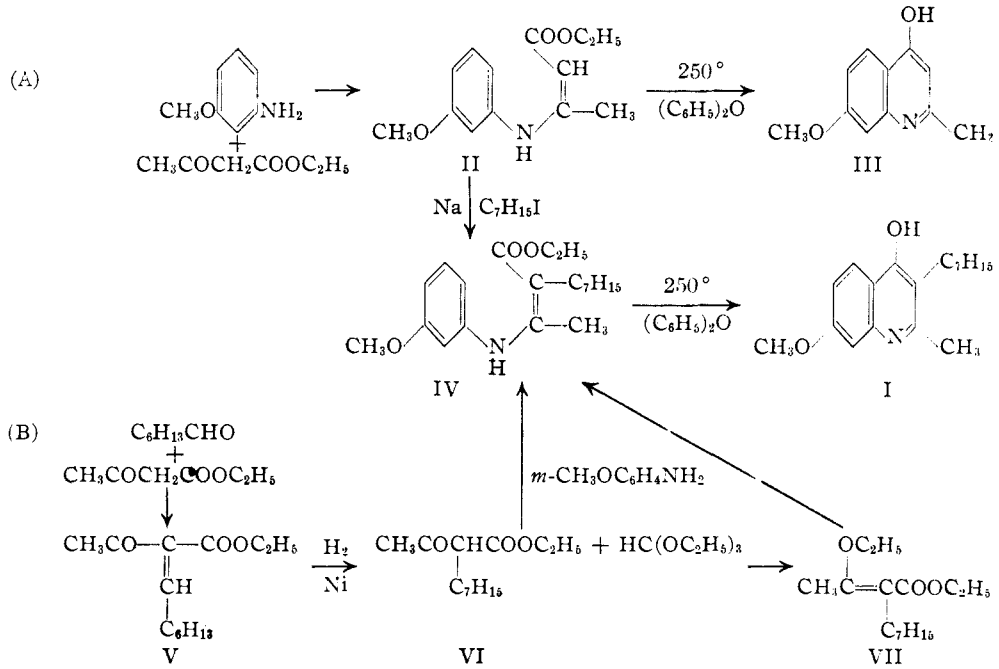
Interest in 3-*n*-heptyl-7-methoxy-2-methylquinolinol (I) (SN-13,421) as a potential antimalarial drug was evoked when intelligence investigators in Germany reported that this substance, known as Endochin, had been found to exhibit prophylactic and trophozoiticidal activity in infected canaries and gametocidal activity in finches infected with Hemoproteus. Two methods of synthesis were developed without the benefit of any detailed account of the German experience. One of these methods (B) is similar in part to the synthesis of Endochin first carried out by Andersag and Salzer in 1940. Their work was not published at the time and has been made available through Department of Commerce reports[1a] since the completion of the work reported herein.

Endochin was obtained in an over-all yield of 40% from *m*-anisidine by Method A, and in an over-all yield of 31% from *m*-anisidine by Method B.



For the first synthesis, *m*-anisidine, obtained by the catalytic reduction of *m*-nitroanisole, was caused to condense with an equimolar quantity of acetoacetic ester in the presence of an acid catalyst to give ethyl β-*m*-methoxyanilinocrotonate (II).[2] It was proposed to alkylate II with heptyl bromide and sodium ethoxide in ethanol according to the method of Gillis, Lions and Ritchie.[3] After such an attempted condensation from which the theoretical amount of sodium bromide separated, the crotonate was subjected to thermal cyclization.[4] However, only the unalkylated quinoline, 7-methoxy-2-methyl-4-quinolinol (III) was obtained. This compound had been prepared previously by Späth and Brunner.[5] Successful alkylation of ethyl β-*m*-methoxyanilinocrotonate was carried out with heptyl iodide[6] and the sodium salt of the crotonate in refluxing xylene to give ethyl α-*n*-heptyl-β-*m*-methoxy anilinocrotonate (IV). Cyclization of the alkylated crotonate was effected in diphenyl ether at 250° in a concentration of about 0.1 mole in 250 ml. of ether. Endochin, SN-13,421[7] obtained as

(1) The work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

(1a) Blanchard, "Work on Antimalarials, I. G. Farbenindustrie, Elberfeld," Report No. 246, Office of the Publication Board, Department of Commerce, Washington, D. C. Kleiderer, Rice and Conquest, "Pharmaceuticals at the I. G. Farbenindustrie Plant, Elberfeld, Germany," Report No. 248, Office of the Publication Board, Department of Commerce, Washington, D. C.

(2) Coffey, Thomson and Wilson, *J. Chem. Soc.*, 856 (1936).

(3) Gillis, Lions and Ritchie, *J. Proc. Roy. Soc., N. S. Wales*, **73**, 258 (1940).

(4) Conrad and Limpach, *Ber.*, **20**, 944 (1887); Conrad and Epstein, *ibid.*, **20**, 3055 (1887); Conrad and Limpach, *ibid.*, **24**, 2990 (1891).

(5) Späth and Brunner, *ibid.*, **57B**, 1247 (1924).

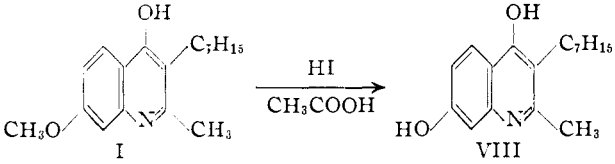
(6) Vogel, *J. Chem. Soc.*, 636 (1943).

(7) The Survey Number, designated SN-, refers to the number assigned a drug by the Survey of Antimalarial Drugs. The activities of these compounds will be tabulated in a forthcoming monograph.

white needles, m.p. 218.5–219.5° (cor.) from aqueous ethanol, was identical with an authentic German sample. It was soluble in alcohol and acetic acid, and completely insoluble in water.

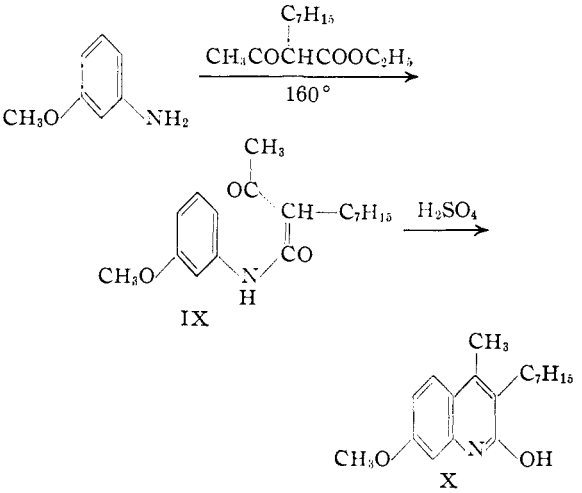
For the preparation of endochin by Method B, ethyl *n*-heptylacetoacetate (VI) was synthesized, in about 60% yield, by condensation of heptaldehyde with acetoacetic ester in the presence of piperidine[8] and reduction of the resulting heptylideneacetoacetic ester (V) with hydrogen over Raney nickel.[9] The formation of ethyl α-*n*-heptyl-β-*m*-methoxyanilinocrotonate (IV) from ethyl *n*-heptylacetoacetate and *m*-anisidine was attempted under various conditions. The optimum yield was realized when IV was formed by heating the reactants at 100° under vacuum for fifteen hours. The yield was not improved by increasing the time of heating or by using an acid catalyst. Compound IV was never isolated in the pure state but was obtained as an uncrystallizable oil which was cyclized directly to Endochin in refluxing diphenyl ether. In an effort to improve the yield obtained by Method B, ethyl α-*n*-heptyl-β-ethoxycrotonate (VII) was used as an intermediate for condensation with *m*-anisidine. Ethyl α-*n*-heptyl-β-ethoxycrotonate was prepared from ethyl *n*-heptylacetoacetate by the action of ethyl orthoformate and a ferric chloride catalyst.[10] A mixture of *m*-anisidine and VII was allowed to stand four days. The yield of Endochin obtained on cyclization of the liquid arylaminocrotonate was not improved by this variation, but remained 31% over-all based upon *m*-anisidine.

From cyclizations in diphenyl ether at concentrations at about 0.08 mole of ethyl α-*n*-heptyl-β-*m*-methoxyanilinocrotonate in 100 ml. of diphenyl ether, two products were obtained. One was the expected Endochin, $C_{18}H_{25}NO_2$, the other was a compound A, m. p. 218–218.5° (cor.), which crystallized from ethanol as light yellow plates and which strongly depressed the melting point of Endochin. It was less soluble than Endochin in acetic acid and ethanol, and analysis corresponded to $C_{17}H_{23}NO_2$, indicating one methylene group less than Endochin. The possibility that demethylation of IV might have occurred was considered, and 3-*n*-heptyl-2-methyl-4,7-quinolinediol (VIII)



was prepared for comparison. This compound, obtained by cleaving Endochin with hydriodic acid, was isolated as silky, white needles, m. p. 232–234.5° (cor.), not identical with compound A. Since further analysis of compound A indicated the absence of a methoxyl group and the presence of two active hydrogens (Zerewitinoff determination indicated one active hydrogen in Endochin), it is therefore concluded that A is 3-*n*-heptyl-2-methyl-4,5-quinolinediol, the isomer of VIII.

For comparison with compound A and Endochin, 3-*n*-heptyl-7-methoxy-4-methyl-2-quinolinol (X) was synthesized after the manner of Knorr.[11] Ethyl *n*-heptylacetoacetate and *m*-anisidine were heated under reflux[12] and the resulting mixture was warmed gently with concentrated sulfuric acid.[13] The expected product X, which was isolated in a 50% yield, melted at 146–147°.



Experimental[14]

Method A

Ethyl β-*m*-Methoxyanilinocrotonate (II).—To a solution of 26 g. (0.2 mole) of distilled acetoacetic ester and 24.6 g. (0.2 mole) of *m*-anisidine at room temperature, a catalyst of four drops of dilute hydrochloric acid was added. Within the first ten minutes water began to separate and a small amount of heat was generated. The mixture was allowed to stand overnight, the water was separated, and the product was dried with magnesium sulfate before use in the next reaction.

7-Methoxy-2-methyl-4-quinolinol (III).—The crude ethyl β-*m*-methoxyanilinocrotonate obtained from 9.8 g. (0.08 mole) of *m*-anisidine and 10.4 g. (0.08 mole) of acetoacetic ester was taken up in dry ether and added to a solution of 1.8 g. (0.08 mole) of sodium in 100 ml. of dry ethanol. To this solution 14.5 g. (0.08 mole) of *n*-heptyl bromide was added, the ether was distilled out, and the solution was heated for thirteen hours under reflux. The sodium bromide (7.9 g., 98% of theoretical) was removed by filtration, and the filtrate was added over a period of one-half hour to 100 ml. of refluxing diphenyl ether. Refluxing was continued for one-half hour, after which the mixture was cooled and the solid was separated by filtration. After washing with petroleum ether and recrystallization from water, the product melted at 253–254° (cor.).[15]

(8) Ceuterich, *Bull. soc. chim. Belg.*, **45**, 545 (1936).

(9) Adkins and Wojcik, THIS JOURNAL, **56**, 2424 (1934).

(10) Michael, *ibid.*, **57**, 159 (1935).

(11) Knorr, *Ann.*, **245**, 358 (1889).

(12) Limpach, *Ber.*, **64**, 970 (1931).

(13) Mikhailov, *J. Gen. Chem.* (U.S.S.R.), **6**, 511 (1936).

(14) The authors are indebted to Miss Theta Spoor and Mr. Howard Clark for the microanalytical determinations and to Mr. James L. Johnson for the Zerewitinoff active hydrogen determinations reported in this paper.

(15) Späth and Brunner[5] reported a m. p. 252–253° for 7-methoxy-2-methyl-4-quinolinol and a m. p. 269° for its hydrochloride.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86. Found: C, 69.12; H, 5.97.

The **hydrochloride** crystallized from hot, dilute hydrochloric acid as long, white needles, m. p. 266–267.5° (dec.).[15]

Ethyl α-*n*-Heptyl-β-*m*-methoxyanilinocrotonate (IV).—Two hundred milliliters of dry xylene was added to 0.2 mole of crude ethyl β-*m*-methoxyanilinocrotonate and about 100 ml. of xylene was distilled off *in vacuo* to complete the drying of II. The flask was fitted with a stirrer and a condenser, and during external cooling 4.6 g. (0.2 mole) of sodium shot was added. The sodium salt first separated as a flocculent precipitate, but after about half of the sodium had reacted, the solution became clear. Stirring was continued for about eight hours, when 45.2 g. (0.2 mole) of *n*-heptyl iodide was added and the solution was brought to the reflux temperature. After seven hours the solution was still alkaline and a further 10 ml. of *n*-heptyl iodide was added. Refluxing was discontinued when the mixture became neutral in another hour. The sodium iodide was removed by filtration and washed well with ether. Compound IV was not separated from the combined filtrates but was cyclized directly.

3-*n*-Heptyl-7-methoxy-2-methyl-4-quinolinol (Endochin) (I).—A solution of 130 ml. of xylene containing theoretically 0.1 mole of crude ethyl α-*n*-heptyl-β-*m*-methoxyanilinocrotonate was added over a period of twenty minutes to 250 ml. of refluxing diphenyl ether. The reflux period was continued for an additional twenty minutes. 3-*n*-Heptyl-7-methoxy-2-methyl-4-quinolinol separated from the cooled solution. After washing with petroleum ether (b. p. 90–110°) and drying, the yield was 11.4 g. (40% from the *m*-anisidine and acetoacetic ester). It crystallized from aqueous ethanol as glistening white needles, m. p. 218.5–219° (cor.). The mixed melting point with an authentic sample of German Endochin, m. p. 217–218° (cor.), was 218–219°.

Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.26; H, 8.82; N, 5.04.

The **picrate,** m. p. 172–172.5°, was obtained from 95% ethanol as a fine yellow powder.

From the attempted cyclization of 0.08 mole of ethyl α-*n*-heptyl-β-*m*-methoxyanilinocrotonate in 100 ml. of diphenyl ether, 11.2 g. of solid, m. p. 155–175°, was obtained. This could be separated by recrystallization from dilute acetic acid into two fractions: 6.3 g. of Endochin, and 1.5 g. of a compound A which was less soluble in this solvent but which also melted at 218–218.5° (cor.). Compound A crystallized from ethanol as light yellow plates and depressed the melting point of Endochin below 180°. The Zerewitinoff determination showed the presence of two active hydrogens.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12; moles CH_4, 2.00. Found: C, 74.34, 74.58; H, 8.48, 8.53; N, 5.21, 5.34; OCH_3, 0.0; moles CH_4, 2.04.

3-*n*-Heptyl-2-methyl-4,7-quinolinediol (VIII).—A solution of 5.0 g. of 3-*n*-heptyl-7-methoxy-2-methyl-4-quinolinol in 50 ml. of hydriodic acid (sp. gr. 1.50) and 15 ml. of glacial acetic acid was refluxed for twelve and one-half hours. Twenty milliliters additional of hydriodic acid was added after the first seven hours. An oil separated when the solution was cooled. The mixture was made strongly alkaline with sodium hydroxide, and sodium salt which separated was removed by filtration through hardened filter paper. A solution of the sodium salt in water was neutralized with acetic acid to yield the free quinolinediol. After filtration it was recrystallized from aqueous ethanol as silky white needles which melted at 234–234.5° (cor.). The compound depressed the melting point of Endochin to 175–190°.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.75; H, 8.65; N, 5.24.

The melting point of a mixture of 3-*n*-heptyl-2-methyl-4,7-quinolinediol and compound A was 232–234.5°, but they were not dimorphs since their interconversion was impossible.

Method B

Ethyl *n*-Heptylacetoacetate (VI).—This compound was prepared by the method of Adkins and Wojcik.[10] Condensation of heptaldehyde (b. p. 150–155°, $n^{20}D$ 1.4140) with acetoacetic ester (distilled over a two-degree range at reduced pressure) catalyzed with piperidine gave ethyl heptylideneacetoacetate, b. p. 110–112.5° (3 mm.), $n^{20}D$ 1.4560. Reduction in ether solution with Raney nickel at room temperature and a pressure of 700 lb. of hydrogen gave ethyl *n*-heptylacetoacetate in an over-all yield of 60% based on acetoacetic ester. It distilled at 107–108° (3 mm.), $n^{20}D$ 1.4362.

Ethyl α-*n*-Heptyl-β-ethoxycrotonate (VII).—To 10 g. (0.0675 mole) of ethyl orthoformate and 15.4 g. (0.0675 mole) of ethyl *n*-heptylacetoacetate in 10 g. of absolute ethanol there was added 0.2 g. of ferric chloride. This mixture was allowed to stand at room temperature for fifty-one hours. The ethyl formate and ethanol were removed under mild vacuum and the remaining liquid was then distilled at 16 mm. The fraction distilling at 113° (1 mm.) ($n^{20}D$ 1.4520) weighed 11.3 g. (0.044 mole) and represented a 65% yield of ethyl α-*n*-heptyl-β-ethoxycrotonate.

Anal. Calcd. for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 69.51; H, 11.20. (Calcd. for $C_{17}H_{34}O_4$: C, 67.51; H, 11.33).

Endochin (I).—The synthesis of Endochin involved first the formation of ethyl α-*n*-heptyl-β-*m*-methoxyanilinocrotonate and then thermal cyclization as above. The intermediate was produced by two methods but was not isolated.

1. From ethyl *n*-heptylacetoacetate and *m*-anisidine: Equimolar quantities of these two reagents were mixed and heated at 100° under 20 mm. vacuum for fifteen hours, after which the product was cyclized to give Endochin in 31% over-all yield.

2. From ethyl α-*n*-heptyl-β-ethoxycrotonate and *m*-anisidine: Equimolar quantities of these two reagents were mixed and stored in a shallow dish over phosphorus pentoxide within a vacuum desiccator for four days. Cyclization in refluxing diphenyl ether during one hour and forty minutes provided Endochin in 31% over-all yield. The product obtained in both cases was identical with the Endochin obtained by Method A.

3-*n*-Heptyl-7-methoxy-4-methyl-2-quinolinol (X).—The method of Limpach[12] was used to prepare heptylacetoacet-*m*-anisidide (IX). Three grams (0.025 mole) of *m*-anisidine and 23.0 g. (0.097 mole) of ethyl *n*-heptylacetoacetate were heated to 160–165° for one-half hour. Excess ester was then removed from the mixture by distillation at a pressure of 20 mm.

For cyclization, the amide (IX) was mixed with 12 ml. of concentrated sulfuric acid and after the initial evolution of heat had subsided, the mixture was heated in an oil-bath at 95° for twenty minutes, then cooled to 60° and poured into 750 ml. of water also at 60°. The solid which separated when the solution was cooled was removed by filtration. Recrystallization from aqueous methanol, with decolorization, gave 3.5 g. (50% yield) of long, white needles, m. p. 146–147°.

Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.60; H, 8.95; N, 4.94.

Summary

Endochin, 3-*n*-heptyl-7-methoxy-2-methyl-4-quinolinol, has been prepared by two methods of synthesis which are applications of the Conrad–Limpach reaction. 3-*n*-Heptyl-2-methyl-4,7-quinolinediol and 3-*n*-heptyl-7-methoxy-4-methyl-2-quinolinol have also been synthesized for comparison.

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