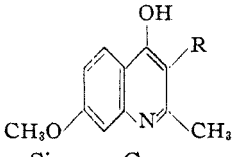
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthesis of 4-Hydroxyquinolines. VII. 3-(Di-*n*-butylaminomethyl)-7-methoxy-2-methyl-4-quinolinol[1]

BY CHARLES C. PRICE[2] AND WILLIAM G. JACKSON[3]

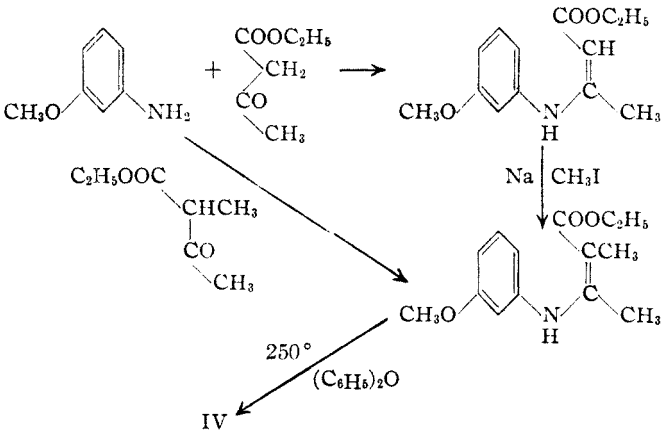
A survey of German progress in the field of antimalarial drugs has disclosed the discovery that 3-*n*-heptyl-7-methoxy-2-methyl-4-quinolinol, Endochin,[4] (I) appears to be a potent antimalarial drug when assayed in parasitized canaries. Since Endochin is extremely insoluble in water, the 3-di-*n*-butylaminomethyl analog (II) has been prepared, in the hope that the somewhat more hydrophilic side chain might aid in absorption in the body.

The synthesis was accomplished readily and in excellent yield by a Mannich reaction of 7-methoxy-2-methyl-4-quinolinol[5] (III) with formaldehyde and di-*n*-butylamine.



I, R = *n*-C_7H_{15}
II, R = $CH_2N(n\text{-}C_4H_9)_2$ (SN-14,171)[6]
III, R = H
IV, R = CH_3

Since a German patent[7] claims that the Mannich reaction on 2-methyl-4-quinolinol involves the methyl group rather than the active 3-position,



it was considered necessary to establish the structure of II. This was accomplished by hydrogenolysis of II to IV. The latter was identical with specimens prepared by two independent syntheses leaving no doubt as to its structure.

(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.

(2) Present address: University of Notre Dame, Notre Dame, Indiana.

(3) Present address: The Upjohn Company, Kalamazoo, Michigan.

(4) Leonard, Herbrandson and Van Heyningen, THIS JOURNAL, **68**, 1279 (1946).

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

(6) 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.

(7) German Patent, 597,907; *Frdl.*, **16**, 2669 (1931).

Experimental[8]

3-Dibutylamino-7-methoxy-2-methyl-4-quinolinol.—7-Methoxy-2-methyl-4-quinolinol[5] was prepared by allowing *m*-anisidine to condense with acetoacetic ester for several days at room temperature with a trace of hydrochloric acid catalyst followed by cyclization of the resulting oily crotonate by thirty minutes of boiling in Dowtherm (4 liters/mole). On cooling, a 50% yield of the product separated from solution.

To 36.3 g. (187 mM.) of crude 7-methoxy-2-methyl-4-quinolinol (m. p. 230–240°) dissolved in 165 ml. of hot 95% ethanol was added 17 ml. (226 mM.) of 40% formalin and 44 ml. (216 mM.) of dibutylamine. After an hour of reflux, during which no precipitation had occurred, a few grains of the desired product was dusted into the black boiling mixture. Precipitation was immediate and complete, leaving a clear light yellow mother liquor. After an additional fifteen minutes of reflux, the mixture was allowed to cool and, after six hours, the product was collected, washed well with ethanol and air-dried to 42.5 g. (69%) of a nearly white crystalline material, m. p. 188–189°. Crystallization of this product from 95% ethanol afforded 70% recovery of pure white material, m. p. 188–189° (192–193°, cor.).

Anal. Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.68; H, 9.15. Found: C, 72.77; H, 9.33.

2,3-Dimethyl-7-methoxy-4-quinolinol. (a) **By Hydrogenolysis.**—A mixture of 8.3 g. (25 mM.) of 3-dibutylaminomethyl-7-methoxy-2-methyl-4-quinolinol, 150 ml. of absolute ethanol, and 5 g. of copper chromite was placed in a bomb, hydrogen was added, and the mixture was shaken at room temperature to an equilibrium pressure of 2225 lb. The temperature was then raised in fifty-seven minutes to 175° (3200 lb.) and shaking was continued at this temperature for one hundred minutes until the calculated loss (125 lb.) of hydrogen was incurred. The bomb was allowed to cool to room temperature, the reaction mixture was filtered from the catalyst, concentrated until solid began to form, then cooled in ice. There was thus obtained 1.9 g. of a white crystalline product (m. p. 265–271°). Two crystallizations of the crude material from ethanol raised the melting point to 293–295° (dec.).

(b) **By Alkylation.**—A 47-g. sample (0.2 mole) of ethyl β-*m*-methoxyanilinocrotonate[9] was dissolved in 200 ml. of anhydrous benzene and treated immediately with small pieces of sodium totalling 4.6 g. (0.2 mole). After four hours, 14 ml. (21% mM.) of methyl iodide was added without visible reaction. The light red-brown solution deposited a quantity of sodium iodide upon standing overnight. The mixture was heated to boiling for a few moments, cooled, washed with water, and extracted with ether. The combined ether–benzene extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a sirupy residue of ethyl α-methyl-β-*m*-methoxyanilinocrotonate.

Cyclization of the crotonic ester was accomplished by adding it to 800 ml. (4 liters/mole) of boiling Dowtherm, and boiling for an additional thirty minutes. After four hours, a quantity of tar had precipitated, a portion of which was removed, partially crystallized by rubbing with various solvents, and replaced in the cyclization mixture along with about 100 ml. of ligroin. After a day, some flocculent precipitate was visible in addition to more tar. The mixture was filtered, an attempt being made to leave

(8) Micro-analyses by Miss Theta Spoor and Mr. Howard Clark.

the tar in the flask while the flocculent material was collected on the filter. This product was washed with ligroin and dried to a weight of 7 g. (17%), m. p. 240–250°. Several crystallizations from ethanol and acetic acid (used alternately) raised the melting point to 293–295° (dec.).

(c) **By Cyclization.**—Equimolar quantities of *m*-anisidine and freshly distilled α-methylacetoacetic ester were condensed by standing for several days at room temperature with a trace of hydrochloric acid catalyst. Condensation was much slower than for the unsubstituted acetoacetic ester. The cyclization was accomplished as before with a dilution of 4 liters/mole and a boiling period of thirty-five minutes. One preparation (0.22 mole) was allowed to condense for four days before cyclization and a 20% yield of product was isolated. A second preparation was allowed to condense for eighteen days before cyclization and yielded 27.5% of the desired product. Several crystallizations from ethanol and from acetic acid raised the melting point from 220–240° to 293–295° (dec.).

The three products above melting at 293–295° (304–306°, cor.) were shown to be identical by mixed melting point.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45. Found: C, 70.83; H, 6.60.

Summary

3-Dibutylaminomethyl-7-methoxy-2-methyl-4-quinolinol has been prepared by the action of formaldehyde and dibutylamine upon 7-methoxy-2-methyl-4-quinolinol. Its structure follows from its hydrogenolysis to 2,3-dimethyl-7-methoxy-4-quinolinol, which was identical with samples prepared by two alternative methods.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

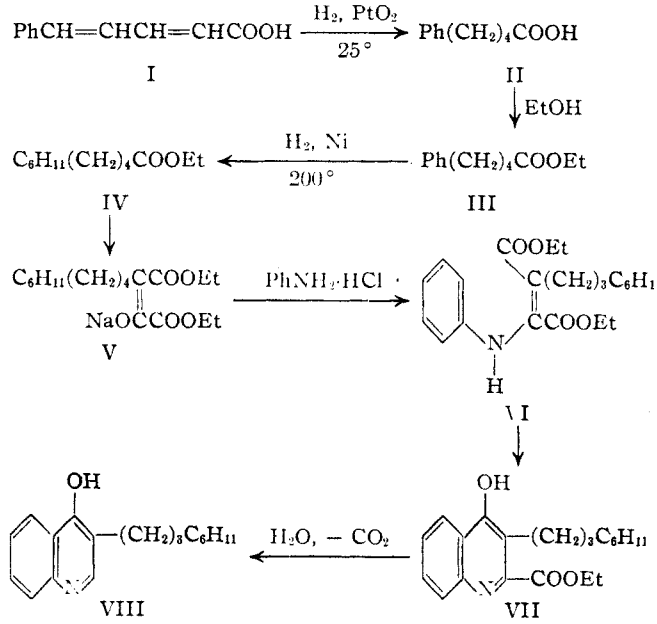
The Synthesis of 3-(3-Cyclohexylpropyl)-4-quinolinol[1]

BY ROBERT H. BAKER AND R. M. DODSON

This synthesis was undertaken in an effort to produce a compound superior in antimalarial activity to that reported for the German compound, Endochin, 2-methyl-3-heptyl-7-methoxy-4-quinolinol.[2] It was felt that the methyl group in position 2 of Endochin might be undesirable and that the side chain in position 3 should be made more resistant to biological oxidation. The literature revealed only one similar compound, 3-homoveratryl-4-quinolinol,[3] and its method of synthesis, from 4-keto-1,2,3,4-tetrahydroquinoline, was not suitable for this work.

The preparation of 3-(3-cyclohexyl)-4-quinolinol, VIII, was accomplished through the condensation of the sodium salt of ethyl α-ethoxalyl-δ-cyclohexylvalerate, V, with aniline hydrochloride.[4] The key compound in the series of reactions was ethyl δ-cyclohexylvalerate, IV, which was made in a 75% yield by a new series of reactions starting with the readily available cinnamylideneacetic acid.[5] Reduction of the side chain of this acid to δ-phenylvaleric acid, II, was easily carried out at low temperature and pressure with Adams catalyst. It was not practical to hydrogenate the phenyl group with platinum oxide in acetic acid solution even at high temperature and pressure but after conversion to the ethyl ester, III, reduction was accomplished over Raney nickel.

Condensation of the ester, IV, with oxalic ester and sodium ethoxide produced the sodium salt of the ketoester, V. This reacted with



aniline hydrochloride and the product, VI, was then heated in mineral oil to convert it into the quinoline ester, VII. The over-all yield of the three condensation reactions was 45–50%. Saponification of the ester, followed by decarboxylation of the resulting acid, produced the desired quinolinol, VIII, in 75% yield. Efforts to avoid the decarboxylation step by the use of ethyl α-formyl δ-cyclohexylvalerate were unpromising, but no detailed study of this method was made.

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

(2) Blanchard, TIIC Report No. 246, Department of Commerce.

(3) G. R. Clemo and H. J. Johnson, *J. Chem. Soc.*, 2133 (1930).

(4) Since the completion of this work the preparation of 3-methyl-4-quinolinols by essentially this procedure has been described by E. Steck, L. Hallock and A. Holland, THIS JOURNAL, **68**, 129, 132 (1946).

(5) E. Friedmann and H. Mai, *Helv. Chim. Acta*, **14**, 1213 (1931).