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.

URBANA, ILL. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

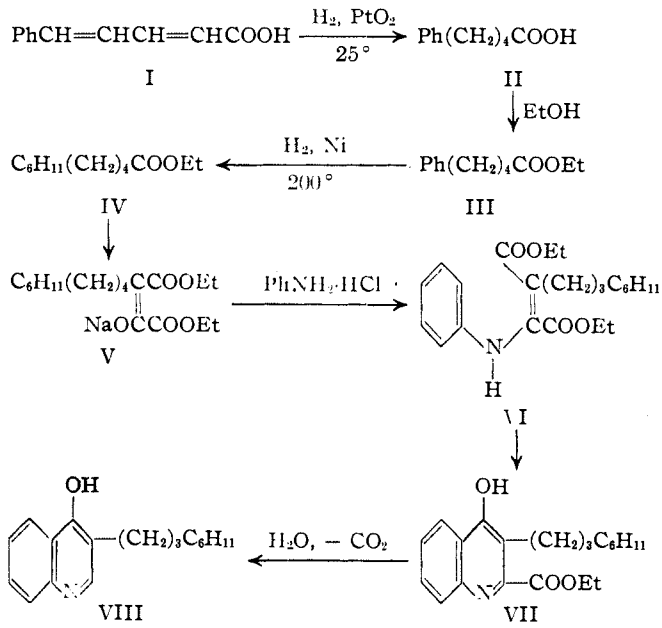
The Synthesis of 3-(3-Cyclohexylpropyl)-4-quinolinol[1]

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, THC 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).

Experimental[6]

Ethyl δ-Cyclohexylvalerate.—Cinnamylideneacetic acid[5] was converted into δ-phenylvaleric acid by low pressure hydrogenation in acetic acid suspension using Adams catalyst. When a 17% suspension is employed, the acid goes into solution with the absorption of the first mole of hydrogen within ten minutes, and the reduction is complete in forty minutes. After removal of the catalyst and solvent, the acid was esterified with ethyl alcohol and sulfuric acid to produce ethyl δ-phenylvalerate, b. p., 157–160° at 18 mm.[7] This ester was then dissolved in alcohol and hydrogenated over Raney nickel at 210° and an initial pressure of 120 atmospheres. The product, ethyl δ-cyclohexylvalerate, IV, b. p. 148–153° at 19 mm.,[8] was produced in 75% yield based on the cinnamylideneacetic acid.

2-Carbethoxy-3-(3-cyclohexylpropyl)-4-quinolinol, VII.—The sodium salt of ethyl α-ethoxalyl-δ-cyclohexylvalerate, V, was prepared by the condensation of ethyl oxalate and ethyl δ-cyclohexylvalerate with sodium ethoxide in dry ether according to the directions given for the preparation of a similar compound in "Organic Syntheses".[9] The ether was distilled under vacuum from the sodium salt leaving a thick, light red oil. This oil was used directly in the next step without purification.

The sodium salt, V, prepared from 10 g. (0.047 mole) of ethyl δ-cyclohexylvalerate, was suspended in 50 ml. of water. To this was added a solution of 6.10 g. (0.047 mole) of aniline hydrochloride in 25 ml. of water. The mixture was thoroughly shaken, then allowed to stand at room temperature with occasional shaking for four hours. The resulting anilino compound, VI, was separated from the water by means of a small separatory funnel.

Cyclization was effected by the addition of the crude, moist anilino compound to 200 ml. of mineral oil, preheated to 250°, and stirred rapidly. The temperature of the resulting solution was held at 250–260° for five minutes after the addition was complete; the solution was then allowed to cool with stirring. When cold, the crystalline product separated from the oil. The mineral oil was then diluted with 200 ml. of cold Skellysolve A (petroleum ether, b. p., 28–38°) and the product filtered with suction and washed with Skellysolve A. The yield of 2-carbethoxy-3-(3-cyclohexylpropyl)-4-quinolinol was 7.90 g., 49% from the ethyl δ-cyclohexylvalerate used. After one crystallization from benzene and Skellysolve C (b. p. 86–100°) the compound melted at 166–167°.[10]

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.85; H, 7.97. Found: C, 73.61; H, 8.13.

2-Carboxy-3-(3-cyclohexylpropyl)-4-quinolinol.—2-Carbethoxy-3-(3-cyclohexylpropyl)-4-quinolinol, VII, 42.1 g., was suspended in 600 ml. of a 10% solution of sodium hydroxide in 15% aqueous ethyl alcohol, and the suspension heated under reflux for three hours. The resulting solution was filtered hot, diluted with an equal volume of water and acidified with 6 *N* hydrochloric acid. The product was filtered with suction and dried at 55° in air to give a quantitative yield. After crystallization from 60% ethyl alcohol, the product melted at 214–214.5° with evolution of carbon dioxide.

Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40. Found: C, 73.12; H, 7.47.

3-(3-Cyclohexylpropyl)-4-quinolinol, VIII.—The acid, 41.3 g., was decarboxylated by heating it in a flask contained in a Glas-Col heating mantle at 220–225° for ten minutes. The glassy melt that resulted was dissolved in ethyl alcohol; the alcoholic solution was decolorized with 3 g. of Nuchar C and filtered. The hot alcoholic solution was then diluted with hot water until it became cloudy. On cooling, 24.0 g. of product crystallized from the solution, m. p. 168–169°. An additional 2.7 g. of material was recovered from the mother liquors, increasing the yield to 75%.

Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.24; H, 8.60. Found: C, 80.12; H, 8.42.

Summary

1. A synthesis of 3-(3-cyclohexylpropyl)-4-quinolinol has been described. The method used appears to be a generally applicable method for the preparation of 3-alkyl-4-quinolinols.

2. Convenient syntheses of ethyl δ-phenylvalerate and δ-cyclohexylvalerate are described.

(6) Microanalyses by Margaret Ledyard, Winifred Brandt and Rita Pivan.

(7) J. V. Braun and H. Deutsch, *Ber.*, **45**, 2171 (1912).

(8) M. M. Katsnel'son and B. M. Dubinin, *Compt. rend. acad. sci. (U. R. S. S.)*, [N. S.] **4**, 405 (1936).

(9) "Organic Syntheses," Coll. Vol. II, 194 (1943).

(10) All melting points were taken on a Fisher–Johns melting point apparatus.

EVANSTON, ILLINOIS RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Some 3-Alkyl-2,4-quinolinediols[1]

BY ROBERT H. BAKER, GERALD R. LAPPIN AND BYRON RIEGEL

In an attempt to find a new type of compound which might prove effective in the treatment of malaria, it was decided to prepare some 3-alkyl-2,4-quinolinediols. The condensation of alkylmalonic esters with anilines to give 3-alkylquinolinediols has been carried out by heating the reactants *in vacuo* to 300°,[2] and by heating in nitrobenzene as a solvent.[3] Neither of these methods proved satisfactory when applied to cyclohexylpropylmalonic ester with aniline or to *p*-dimethylaminoaniline with any alkylmalonic ester. However, when equimolar quantities of cyclohexylpropylmalonic ester or cyclohexylmalonic ester and an aniline were heated in refluxing diphenyl ether, a quantitative yield of the 3-alkyl-2,4-quinolinediol was obtained. This method was successful with *p*-dimethylaminoaniline but not with *o*-nitroaniline, allylmalonic ester, nor with 3-diethylaminopropylmalonic ester. The 3-alkyl-2,4-quinolinediols prepared are listed in Table I.

Experimental

Diethyl Cyclohexylmalonate.—This compound was prepared from cyclohexyl bromide and sodiomalonic ester.[4]

(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) P. Baumgarten and W. Kurgl, *Ber.*, **60**, 832 (1927).

(3) German Patent, 505,798; *Chem. Abs.*, **25**, 525 (1931).

(4) E. Hope and W. H. Perkin, Jr., *J. Chem. Soc.*, 1360 (1909).