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.

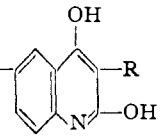
(2) P. Baumgarten and W. Kurgl, *Ber.*, **60**, 832 (1927).

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

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

TABLE I

SUBSTITUTED 3-ALKYL-2,4-QUINOLINEDIOLS



R	X	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Cyclohexyl	H	300–305	$C_{15}H_{17}NO_2$	74.0	74.9	6.98	7.33
Cyclohexyl	6-Methoxy	233–234	$C_{16}H_{19}NO_3$	70.4	69.9	6.96	7.19
Cyclohexyl	6-Dimethylamino	[a]	$C_{17}H_{22}N_2O_2$	71.3	70.9	7.67	8.19
3-Cyclohexylpropyl	H	188–189	$C_{18}H_{23}NO_2$	75.9	75.9	8.08	8.24
3-Cyclohexylpropyl	6-Methoxy	197–198	$C_{19}H_{25}NO_3$	72.4	72.3	7.96	8.12
3-Cyclohexylpropyl	6-Dimethylamino	[b]	$C_{20}H_{28}N_2O_2$	73.2	72.9	8.54	8.76

[a] Starts to decompose at 234–235°. [b] Starts to decompose at 250–255°.

Diethyl 3-Cyclohexylpropylmalonate.—3-Cyclohexylpropanol was prepared in 70% yield by hydrogenation of cinnamyl alcohol at 200° and 5000 lb. initial pressure of hydrogen using Raney nickel catalyst. This was converted to the bromide and reacted with sodiomalonic ester.[5]

Diethyl 3-Diethylaminopropylmalonate.—This was prepared in 63% yield from sodiomalonic ester and 3-diethylaminopropyl chloride.[6]

Diethyl Allylmalonate.—This was prepared from allyl bromide and sodiomalonic ester.[7]

3-Cyclohexyl-2,4-quinolinediols.—A solution of 0.11 mole of the malonic ester and 0.10 mole of the aniline in 50 ml. of diphenyl ether was heated under reflux for one hour. The solution was cooled, the product was collected by filtration and washed with hexane. The yield was 95–98% of the theoretical. The 3-cyclohexyl-2,4-quinolinediols were white crystalline solids, slightly soluble in ethanol but very soluble in pyridine, and were recrystallized from pyridine–alcohol solutions. No reaction occurred with malonic ester and *o*-nitroaniline under these conditions.

3-(3-Cyclohexylpropyl)-2,4-quinolinediols.—A solution of 0.11 mole of diethyl 3-cyclohexylpropylmalonate and 0.10 mole of the aniline in 25 ml. of diphenyl ether was heated under reflux for thirty minutes. After cooling, the product was precipitated by adding two volumes of hexane, collected by filtration, and washed with hexane. The 3-(3-cyclohexylpropyl)-2,4-quinolinediols were white crystalline compounds, very soluble in ethanol and were crystallized from an ethanol–water solution. No reaction occurred with 3-cyclohexylpropylmalonic ester and *o*-nitroaniline under these conditions.

Attempted Preparation of 3-(3-Diethylaminopropyl)-2,4-quinolinediols.—No quinolinediol was obtained when diethyl 3-diethylaminopropylmalonate was heated with aniline in diphenyl ether, diamyl ether, mineral oil heated to 250°, or heating in absence of a solvent *in vacuo*. Only intractable tars were obtained from the reaction along with a small amount of 3-diethylaminopropylmalonic acid dianilide, m. p. 163–164°.

Anal. Calcd. for $C_{22}H_{29}N_3O_2$:. N, 11.43. Found: N, 11.73.

Attempted Preparation of 3-Allyl-2,4-quinolinediol.—No crystalline material could be obtained from the reaction of allylmalonic ester with aniline in refluxing diphenyl ether, refluxing diamyl ether, or in mineral oil heated at 250°, 200°, or 180°, nor by heating in absence of a solvent *in vacuo*.

(5) R. Adams and G. Hiers, THIS JOURNAL, **48**, 2385 (1926).

(6) O. Magidson and I. Strukov, *Arch. Pharm. Ber. dtsch. pharmaz. Ges.*, **271**, 569 (1933); *Chem. Zentr.*, **105**, I, 2286 (1934).

(7) M. Conrad and C. Bischoff, *Ann.*, **204**, 168 (1880).

Summary

1. The syntheses of 3-cyclohexyl- and 3-(3-cyclohexylpropyl)-2,4-quinolinediols and their 6-methoxy and 6-dimethylamino derivatives have been described.

2. The diethyl ester and the dianilide of 3-cyclohexylpropylmalonic acid are also described.

EVANSTON, ILLINOIS RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Antimalarials. The Synthesis of 2,4,7-Trichloroquinoline[1]

BY ROBERT E. LUTZ, GILBERT ASHBURN, JAMES A. FREEK, ROBERT H. JORDAN,[2] NORMAN H. LEAKE, TELLIS A. MARTIN, RUSSELL J. ROWLETT, JR.,[3] AND JAMES W. WILSON, III

2,4,7-Trichloroquinoline (VII) was required and made in quantity as an intermediate in the synthesis of several types of dialkylaminoalkylaminoquinolines which were desired for testing against malaria. This compound was expected to be (and is) a versatile one because of the reactive 2- and 4-chlorine-atoms, and it was hoped that the difference in the reactivities of these two (chlorine atoms) would be sufficient to permit selective displacement.[4]

In the synthesis of this compound the use of *m*-chloroaniline and malonic ester in a quinoline ring closure according to the procedure of Baumgarten and Kärgel,[5] who used aniline itself, seemed certain to lead to mixtures of the isomeric 5- and 7-

(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 the University of Virginia.

(2) At present, Ensign, U. S. Navy.

(3) Present location, Jackson Laboratory, E. I. du Pont de Nemours and Co., Wilmington, Del.

(4) *Cf.* the 2,4-dichloroquinolines of Buchmann and Hamilton, THIS JOURNAL, **64**, 1357 (1942).

(5) Baumgarten and Kärgel, *Ber.*, **60B**, 832 (1927).