able from commercial ethyl sodioethoxalylacetate.

2. The yield of the intermediate 2-carbethoxy-4-quinolinol is not appreciably raised by use of pure oxalacetic ester.

3. Variations in yield due to different methods of decarboxylating the 2-quinolinecarboxylic acids are noted.

EVANSTON, ILLINOIS RECEIVED AUGUST 22, 1946

[JOINT CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE NATIONAL ANILINE DIVISION OF THE ALLIED CHEMICAL AND DYE CORPORATION, AND FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthesis of 7-Chloro-4-hydroxyquinoline Derivatives Employing Oxalacetic Ester[1]

BY GEORGE F. LISK AND GARDNER W. STACY[2]

Andersag, Breitner and Jung[3] prepared a number of 2-carbethoxy-4-hydroxyquinoline derivatives by thermal cyclization of β-carbethoxy-β'-anilinoacrylates, which themselves were obtained by the reaction of aromatic amines with oxalacetic ester. After removal of the carbethoxy group by hydrolysis and decarboxylation the 4-hydroxyquinolines were converted to 4-chloroquinolines which then could be condensed with basic side-chains yielding 4-dialkylaminoalkylaminoquinoline derivatives. Recently several workers[4] have elaborated on this synthesis and have prepared a number of substituted quinolines.

This synthesis is usually satisfactory; however, when cyclization of acrylates prepared from *meta*-substituted anilines is attempted, a mixture of 5- and 7-substituted quinolines results. For example, cyclization of β-carbethoxy-β-(*m*-chloroanilino)-acrylate yields both possible isomeric quinoline derivatives in about equal amounts. Since only the 7-isomer is desired in the preparation of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline, chloroquine, it seemed advisable to investigate the synthesis with the hope of finding conditions under which the tendency toward formation of the 5-isomer would be reduced. Therefore, a study was made of the variation of the ratio of isomers formed with the amount of diluent used in cyclization. The results of this series of experiments revealed that when limited amounts of diluent were employed, virtually all 5-isomer was obtained. When large amounts (thirty parts of diluent to one part of acrylate) were used, about 40% of the 5-isomer resulted. This trend is illustrated in Fig. 1. At the same time, however, the yields of combined dichloroquinolines, based on *m*-chloroaniline, varied from 17% at 2:1 (two parts of diluent to one part of acrylate) to 28% at 30:1, reaching a maximum of 32% at 15:1.

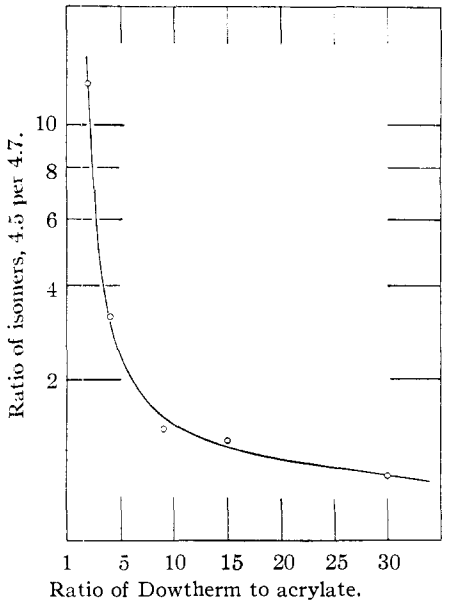
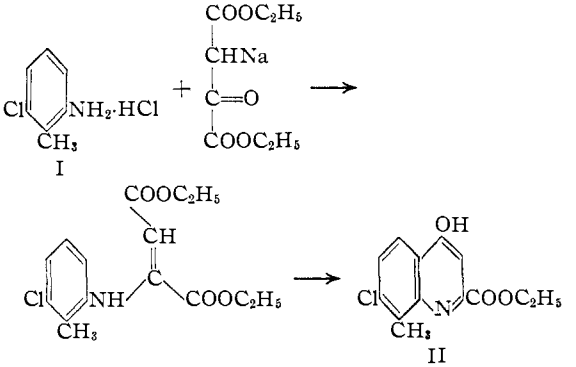


Fig. 1.—Curve showing changes in the composition of a mixture of isomeric dichloroquinolines, obtained by thermal cyclization of β-carbethoxy-β-(*m*-chloroanilino)-acrylate in varying amounts of Dowtherm. The melting points corresponding to the ratio of isomers indicated were: 2:1, 59.5–62.1°; 4:1, 58.8–64.2°; 8:1, 59.4–70.2°; 15:1, 59.4–71.0°; 30:1, 59.6–74.3°.

Since the ratio of isomers could not be altered



(1) The work described in this paper was done in part under contracts, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the National Aniline Division of the Allied Chemical and Dye Corporation and between the Office of Scientific Research and Development and the University of Illinois.

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(3) Andersag, Breitner and Jung, German Patent 683,692; *C. A.*, **36**, 4973 (1942); U. S. Patent 2,233,970; *C. A.*, **35**, 3771 (1941).

(4) (a) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946); (b) Steck, Hallock and Holland, *ibid.*, **68**, 132 (1946); (c) Steck, Hallock and Holland, *ibid.*, **68**, 380 (1946); (d) Surrey and Cutler, *ibid.*, **68**, 514 (1946).

favorably by modifying conditions of cyclization, another approach to the problem was initiated. The opportunity for the formation of the 5-isomer could be completely eliminated by use of a blocking group. Thus, by applying the synthesis to 6-chloro-*o*-toluidine (I), only one quinoline derivative could be obtained (II). Although the structure of chloroquine would be altered by the introduction of a methyl group in position eight of the quinoline nucleus, it was conceivable that the activity might not be changed unfavorably.

Therefore, 4,7-dichloro-8-methylquinoline was prepared as proposed and condensed with 4-amino-1-ethylpiperidine.[5] The resulting 7-chloro-4-(1-ethyl-4-piperidylamino)-8-methylquinoline was submitted for testing[6] as a potential antimalarial. It was interesting to note that introduction of the methyl group in the 8-position of the quinoline nucleus rendered the material inactive against *Plasmodium lophurae* in ducks.

Experimental[7]

A Study of the Cyclization of Ethyl β-Carbethoxy-β-(*m*-chloroanilino)-acrylate in the Presence of Varying Amounts of Diluent.—Ethyl β-carbethoxy-β-(*m*-chloroanilino)-acrylate used in this study was prepared according to Musajo,[8] wherein *m*-chloroaniline hydrochloride was allowed to react with sodio ethyl oxalacetate in absolute alcohol. The yields of acrylate were somewhat improved by the addition of a desiccant such as anhydrous sodium sulfate. An example of this procedure is subsequently outlined in connection with the synthesis of 4,7-dichloro-8-methylquinoline.

By addition to refluxing Dowtherm the acrylate obtained was cyclized to a mixture of isomeric 2-carbethoxy-4-hydroxyquinolines which was then transformed to a mixture of the corresponding dichloroquinolines in the usual manner. The relative amounts of isomers in the mixture were determined by melting point according to the thaw-melt method of Rheinboldt.[9] These melting points were compared with a melting point diagram for the system 4,5-dichloroquinoline-4,7-dichloroquinoline (Fig. 2) and the composition obtained by interpolation. The melting point diagram was constructed from data obtained from mixture melting points of samples of 4,5-dichloroquinoline (m. p. 62.5°) and 4,7-dichloroquinoline (m. p. 84°). The samples of the dichloroquinolines, totaling 0.400 g., were fused, so that a uniform mixture was ensured.

Ethyl β-Carbethoxy-β-(3-chloro-2-methylanilino)-acrylate.—Forty grams (0.225 mole) of 3-chloro-2-methylaniline hydrochloride, 50 g. (0.224 mole on the basis of 94.1% strength) of sodio ethyl oxalacetate and 50 g. of anhydrous sodium sulfate were suspended in 250 ml. of absolute ethanol. The reaction mixture was stirred for a period of twenty hours, placed in a separatory funnel and 1.5 liters of water added. The acrylate accumulated in the bottom of the separatory funnel as an oil. This was separated and the aqueous layer extracted twice with 250-ml. portions of ether. The ether extracts and the acrylate were combined and dried over anhydrous magnesium sulfate. The ether was removed by distillation. The residual acrylate amounted to 62.3 g. or 89% of the theoretical amount.

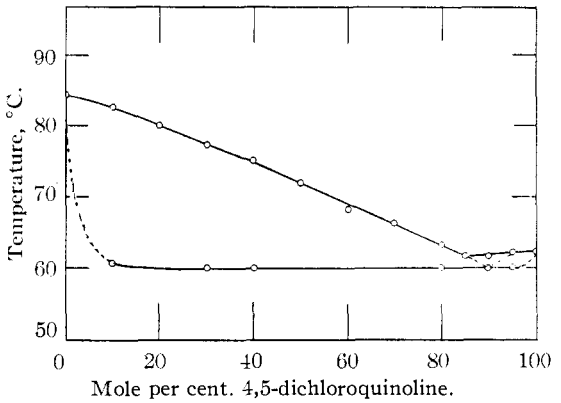


Fig. 2.—Melting point curve for the system: 4,5-dichloroquinoline–4,7-dichloroquinoline.

Since it had been indicated that these acrylates decompose on attempted distillation (recently, however, Surrey and Cutler[4] have managed to distil acrylates at a pressure of 0.2 mm.), a sample was purified for analysis in the following manner: An ether solution of the acrylate was washed several times with dilute hydrochloric acid and then with water. The ether solution was then dried over anhydrous magnesium sulfate, filtered and the solvent removed by distillation.

Anal. Calcd. for $C_{15}H_{18}ClNO_4$: C, 57.79; H, 5.82. Found: C, 57.66; H, 5.59.

2-Carbethoxy-7-chloro-4-hydroxy-8-methylquinoline.—To 500 ml. of Dowtherm preheated to 255° was added 62.3 g. (0.200 mole) of acrylate over a period of five minutes. After the reaction mixture had cooled, the crystalline precipitate was removed by filtration and washed several times with petroleum ether. Yield of crude product was 33.4 g. or 62.8%.

After recrystallization from Cellosolve a sample melted at 207–208°.

Anal. Calcd. for $C_{13}H_{12}ClNO_3$: C, 58.76; H, 4.55; N, 5.27. Found: C, 58.77; H, 4.47; N, 5.12.

3-Carboxy-7-chloro-4-hydroxy-8-methylquinoline.—Hydrolysis of the ester group was accomplished by heating 28 g. (0.106 mole) of the 2-carbethoxyquinoline derivative with 170 ml. of 10% sodium hydroxide under reflux for one-half hour. The alkaline solution was made acid with 47 ml. of concentrated hydrochloric acid, the carboxyquinoline collected, washed and dried. The yield of crude material was 31.2 g.

A sample was prepared for analysis by recrystallization from Cellosolve, m. p. 250–252°.

Anal. Calcd for $C_{11}H_8ClNO_3$: C, 55.59; H, 3.39; N, 5.90. Found: C, 55.91; H, 3.17; N, 5.89.

7-Chloro-4-hydroxy-8-methylquinoline.—To 150 ml. of Dowtherm at 230–240° was added 20.5 g. (0.0864 mole) of the carboxyquinoline in portions. Heating at this temperature was continued for fifteen minutes, the reaction mixture cooled, and the product washed with Skellysolve C. The crude material amounted to 14.1 g. or 84.5% of the theoretical amount.

To purify this compound it was recrystallized several times from Cellosolve, m. p. 317°.

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.02; H, 4.17; N, 7.23. Found: C, 62.26; H, 4.35; N, 7.42.

4,7-Dichloro-8-methylquinoline.—To 11.6 g. (0.06 mole) of 7-chloro-4-hydroxy-8-methylquinoline was added 22 ml. (0.24 mole) of phosphorus oxychloride. The reaction mixture was heated under reflux for one hour. After it had cooled, it was added to 75 ml. of water with

(5) Fuson, Parham and Reed, THIS JOURNAL, **68**, 1239 (1946).

(6) The authors wish to express their appreciation to the Eli Lilly Co. for conducting the pharmacological tests pertinent to this investigation.

(7) All melting points are uncorrected. Microanalyses were carried out by Mr. Howard S. Clark and Miss Theta Spoor. The assistance of Mr. Herbert Schwenke and Miss Dorothy Collins in carrying out a portion of the experimental work is herewith gratefully acknowledged.

(8) Musajo, *Gazz. chim. ital.*, **67**, 222 (1937).

(9) Rheinboldt, *J. prakt. Chem.*, **111**, 242 (1925).

caution. The solution was made alkaline by the addition of about 60 ml. of 12 *N* sodium hydroxide, the precipitate collected, washed with water, and dried. The yield of crude product, was 7.6 g. or 59.9% of the theoretical amount.

After several recrystallizations from alcohol the 4,7-dichloro-8-methylquinoline melted at 87–89°.

Anal. Calcd. for $C_{10}H_7Cl_2N$: C, 56.62; H, 3.33; N, 6.60; Cl, 33.36. Found: C, 56.53; H, 3.37; N, 6.44; Cl, 33.29.

7-Chloro-8-methyl-4-(1-ethyl-4-piperidylamino)-quinoline.—Fifteen grams (0.0707 mole) of 4,7-dichloro-8-methylquinoline, 9.1 g. (0.0708 mole) of 1-ethyl-4-aminopiperidine, and 6.65 g. (0.708 mole) of phenol were heated for one-half hour at 100–160° and for twelve hours at 160–165°. During this period of heating the reaction mixture was agitated by a stream of nitrogen.

After the reaction mixture had cooled, it was poured into a solution of 60 ml. of 4 *N* hydrochloric acid. The red-brown solution was treated with Darco and filtered. It was then made alkaline with sodium hydroxide solution (15 g. in 50 ml. of water).

A yellow oil was obtained, which after it had been stirred for about fifteen minutes, solidified to a white granular solid. The crude product was recrystallized from benzene and a white, microcrystalline solid (m. p. 200–202°) was obtained. The yield was 15.9 g. or 73.8% of the theoretical amount.

To purify a sample for analysis and pharmacological testing it was necessary to recrystallize the material several times from benzene and then to allow it to stand in ether for an extended period of time to ensure complete removal of benzene from the product.

Anal. Calcd. for $C_{17}H_{22}ClN_3$: C, 67.20; H, 7.30; N, 13.83. Found: C, 67.05; H, 7.30; N, 13.58.

Summary

When ethyl β-carbethoxy-β-(*m*-chloroanilino)-acrylate was subjected to thermal cyclization in limited amounts of diluent, virtually all 3-carbethoxy-5-chloro-4-hydroxyquinoline was formed. On the other hand, when larger amounts of diluent were employed, as much as sixty per cent. of the corresponding 7-isomer was obtained.

7-Chloro-(1-ethyl-4-piperidylamino)-8-methylquinoline has been synthesized and found to be inactive against *Plasmodium lophurae* in ducks.

URBANA, ILLINOIS RECEIVED OCTOBER 21, 1946

CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY No. 1041]

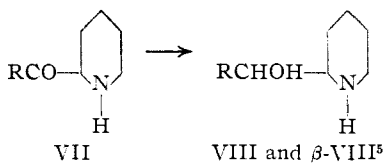
Potential Antimalarials. (6-Methoxyquinolyl-4)-α-piperidylcarbinols[1,2]

BY HERBERT SARGENT[3]

H. King and co-worker[4] have described the synthesis of (6-methoxyquinolyl-4)-α-piperidylcarbinol (VIII)[5] by the series of reactions shown in the chart. A reinvestigation of this synthesis, carried out under the supervision of Dr. E. R. Buchman, has resulted in substantial improvement (see Experimental).

$$RCOOC_2H_5^{6} + C_2H_5OOC(CH_2)_5NHCOC_6H_5 \longrightarrow$$
I II
$$RCOCH(CH_2)_4NHCOC_6H_5 \longrightarrow$$
$$COOC_2H_5$$
III

$$RCO(CH_2)_5NHCOC_6H_5 \longrightarrow RCO(CH_2)_5NH_2 \longrightarrow$$
IV V
$$RCOCHBr(CH_2)_4NH_2\cdot 2HBr \longrightarrow$$
VI



VII VIII and β-VIII[5]

The previously reported[4] studies dealing with N-alkylated derivatives of VIII have been extended in the course of this research.

Experimental[7]

ε-Bromo-ε-quininyl-*n*-amylamine Dihydrobromide (VI).—Sodamide was prepared by adding 38 g. (1.65 moles) of clean sodium in small pieces to 2 liters of liquid ammonia in a 3-liter, three-necked flask. A pinch of ferric chloride was added as a catalyst and after the blue color had disappeared (usually several hours) the excess of ammonia was allowed to evaporate. The residual gray cake of sodamide was broken up with a flattened stirring rod and used directly in the following condensation.

A solution of 310 g. (1.34 moles) of ethyl quininate (I)[8] and 353 g. (1.34 moles) of ethyl ε-benzamidocaproate (II)[8] in 700 ml. of dry thiophene-free benzene was added to the sodamide and the flask was equipped with a sealed Hershberg-type stirrer driven by a powerful motor; a reflux condenser carrying a drying tube containing potassium hydroxide pellets was fitted to one side-neck and the

(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 California Institute of Technology.

(2) This paper and the following papers in this issue dealing with applications of the Ainley and King method[4] to the synthesis of potential antimalarials were presented in part before the Division of Medicinal Chemistry of the American Chemical Society at the Atlantic City meeting, April, 1946.

(3) Present address: United States Rubber Company, Passaic, New Jersey.

(4) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938).

(5) Catalytic reduction of VII yields a mixture of the racemic forms of the carbinol; the predominant form is here designated VIII, the other isomer β-VIII. β-VIII is probably identical with the VIII-isomer obtained by Work, *J. Chem. Soc.*, 194 (1946); it is not identical with the "iso base" described by Ainley and King.[4] The latter substance, a specimen of which was kindly provided by Dr. King, was not encountered in this work.

(6) R = CH_3O— 

(7) All melting points are corrected; microanalyses were carried out by Dr. G. Oppenheimer and staff of this Institute and by Huffman Microanalytical Laboratories, Denver 2, Colorado.

(8) Supplied by Dr. R. C. Elderfield (Columbia University).