ether, and the ether was washed with five 100-ml. portions of 10% aqueous sodium hydroxide and with five 100 ml. portions of water, and dried over magnesium sulfate. The ether solution was then filtered and saturated with dry hydrogen chloride gas. The mixture of the hydrochloride of the desired base with the hydrochloride of N-(4-diethylamino-1-methylbutyl)-4-chloro-8-quinolinesulfonamide settled as an orange gum. The ether was removed by decanting and the gum was washed with anhydrous ether. It was then dissolved in absolute ethanol, the ethanolic solution was heated with Nuchar C and filtered, and absolute ether was added to the warm ethanolic solution until the first appearance of cloudiness. The ethanol–ether solution was then maintained at −5° for two weeks. There resulted from this, 7.3 g. (8%) of light, hygroscopic crystals, m. p. 155–156°.

Anal. Calcd. for $C_{27}H_{47}N_5O_2S\cdot 3HCl$: Cl, 17.3; N, 11.35. Found: Cl, 17.0; N, 11.59.

Summary

1. The repetition of some Russian work on 4-aminoquinolines, SN 3294 and 5063, confirmed their antimalarial activity.

2. The following modifications of SN 3294 and 7618 were made: 4-(4-Diethylamino-1-methylbutylamino)-6-dimethylaminoquinoline, 3-bromo-4-(4-diethylamino-1-methylbutylamino)-quinoline, 7-chloro-4-(3-dihexylaminopropylamino)-quinoline, 7-chloro-4-(3-dioctylaminopropylamino)-quinoline, 6-benzylthio-7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline, 4-(4-diethylamino-1-methylbutylamino)-8-quinolinethiol, N-(4-diethylamino-1-methylbutyl)-4-(4-diethylamino-1-methylbutyl-amino)-8-quinolinesulfonamide.

3. The preparation of some 4-haloquinolines required as intermediates for the above compounds is described.

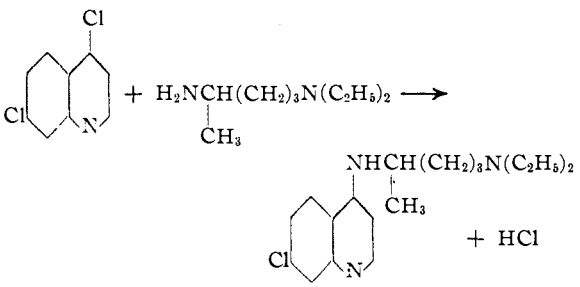
EVANSTON, ILLINOIS RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Synthesis of Antimalarials. V.[1] The Synthesis of Certain 4-Aminoquinoline Derivatives[2]

BY DAVID S. BRESLOW,[3] MELVIN S. BLOOM, JOSEPH C. SHIVERS, JOE T. ADAMS,[4] MARTIN J. WEISS, ROBERT S. YOST AND CHARLES R. HAUSER

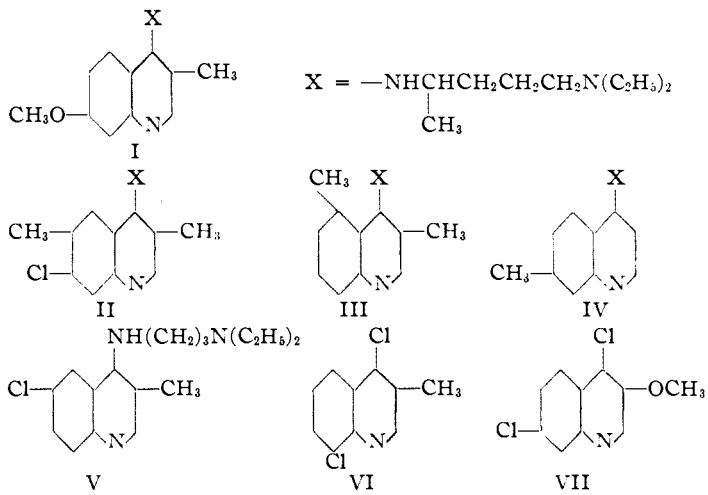
Certain 4-aminoquinolines having appropriate side chains are known to be active antimalarials. These compounds are obtained by coupling a 4-chloroquinoline with a primary amine. This may be illustrated with 4,7-dichloroquinoline and 1-diethylamino-4-aminopentane, the product of which may be considered the standard in this series.



In the present investigation several new 4-chloroquinolines have been synthesized and, in most cases, coupled with 1-diethylamino-4-aminopentane. Also, certain di- and triamines have been prepared and coupled with 4,7-dichloroquinoline. The couplings were effected by heating one mole of the 4-chloroquinoline with two moles of the di- or triamine; in certain cases, the reaction was effected in the presence of a small amount of phenol. The products were usually converted to their phosphate salts. The data on the couplings are summarized in Table II.

Variations in the Nucleus.—Compounds I through V have been synthesized and submitted for testing. Also, nuclei VI and VII have been prepared.

The nuclei for compounds I, II, III, V and VI,



(1) Paper IV of this series, THIS JOURNAL, **68**, 100 (1946).

(2) 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 Duke University.

(3) Present address: Hercules Experiment Station, Wilmington, Delaware.

(4) Present address: Carbide and Carbon Chemicals Corp., Charleston, West Virginia.

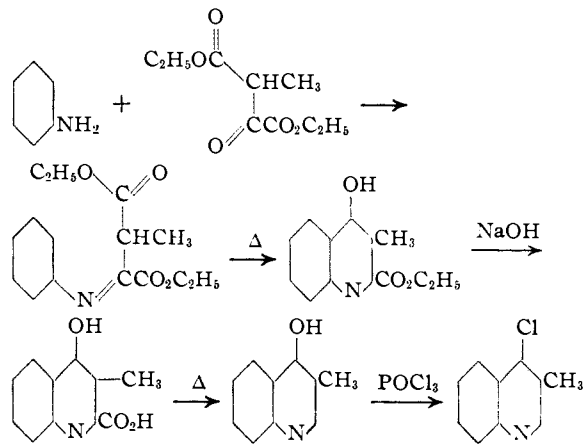
TABLE I

CYCLIZATIONS OF ANILINES WITH ETHYL α-ETHOXALYLPROPIONATE

Substituent	Yield, %	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Substituted Ethyl 3-Methyl-4-hydroxyquinoline-2-carboxylates									
7-Methoxy[a]	24[l,m]	189–191[n]	$C_{14}H_{15}O_4N$			5.36			5.38
6-Methyl-7-chloro[b]	60[f]								
5-Methyl-8-chloro[c]	62	120–121[p]	$C_{14}H_{14}O_3NCl$	60.1	5.04	5.01	60.8	5.04	4.95
6-Chloro[d,u]	73	242–243[q]	$C_{13}H_{12}O_3NCl$	58.8	4.55	5.27	59.5	4.87	5.02
8-Chloro[e,u]	68	146[q]							
Substituted 3-Methyl-4-hydroxyquinoline-2-carboxylic Acids									
7-Methoxy	98	250–251[r]	$C_{12}H_{11}O_4N$	61.8	4.76	6.01	61.6	4.86	6.02
6-Methyl-7-chloro[f]									
5-Methyl-8-chloro	72[s]	239–240[p]	$C_{12}H_{10}O_3NCl$	57.3	4.01	5.57	57.2	3.86	5.53
6-Chloro[g]	66	258[q]	$C_{11}H_8O_3NCl$			5.89			5.48
8-Chloro[g]	70[r]	230[p]	$C_{11}H_8O_3NCl$	55.6	3.39	5.89	55.9	3.77	5.68
Substituted 3-Methyl-4-hydroxyquinolines									
7-Methoxy		275–276[q]	$C_{11}H_{11}O_2N$	69.8	5.86	7.40	70.3	5.82	7.69
6-Methyl-7-chloro[f]									
5-Methyl-8-chloro	60	268–270[p]							
5-Methyl[g]	84[h]	260–261[p]	$C_{11}H_{11}ON$	76.3	6.40	8.09	76.0	6.50	8.39
6-Chloro[g]	99	325–327[o,q]	$C_{10}H_8ONCl$[i]	62.0	4.16	7.23	62.0	4.40	7.00
8-Chloro[g]	75[s]	219[p]	$C_{10}H_8ONCl$[j]	62.0	4.16	7.23	62.3	4.21	7.24
Substituted 3-Methyl-4-chloroquinolines									
7-Methoxy	78[t]	77– 78[w]	$C_{11}H_{10}ONCl$	63.6	4.85	6.75	63.2	4.85	6.82
6-Methyl-7-chloro	19[t,u]	129–130[q]	$C_{11}H_9NCl_2$	58.7	4.03	6.22	58.4	4.08	6.31
5-Methyl	67[t]	59– 60.5[k,x]	$C_{11}H_{10}NCl$			7.31			6.97
6-Chloro[g]	63[t]	118–119[w]	$C_{10}H_7NCl_2$	56.6	3.33	6.61	57.0	3.31	6.31
8-Chloro[g]	91[t]	98	$C_{10}H_7NCl_2$	56.6	3.33	6.61	56.9	3.67	6.34

[a] From 3-methoxyaniline. [b] From 3-chloro-4-methylaniline. [c] From 2-chloro-5-methylaniline. [d] From 4-chloroaniline. [e] From 2-chloroaniline. [f] Mixed with the 5-chloro-6-methyl isomer. [g] Obtained by the dechlorination of 5-methyl-8-chloro compound. [h] Yield on catalytic dechlorination. [i] *Anal.* Calcd. for Cl: 18.3. Found: 18.6. [j] *Anal.* Calcd. for Cl: 18.3. Found: 18.3. [k] B. p., 145–152°, 5 mm. [l] Yield after six recrystallizations from acetone. [m] The mixture of the 7- and the 5-methoxy isomers was obtained in 62% yield. [n] Sample recrystallized from acetone. [o] Sample recrystallized from glacial acetic acid. [p] Sample recrystallized from ethanol. [q] Sample recrystallized from methanol. [r] Hydrolyzed by refluxing twelve hours with 25% sulfuric acid. [s] Yield of recrystallized product. [t] Yield of pure compound. [u] Yield for hydrolysis of the ester, decarboxylation of the acid and formation of the chloro compound. The chloro compound was recrystallized four times from methanol to remove the 5-chloro-6-methyl isomer. [v] Sample recrystallized from 75% acetic acid. [w] Sample recrystallized from methanol-water. [x] Sample recrystallized from ethanol-water. [y] Reported recently by Steck, *et al.*[5]

which are substituted 3-methylquinolines, were prepared from appropriately substituted anilines and ethyl α-ethoxalylpropionate.[5] The anil, prepared from the amine and the α-keto ester, was cyclized in hot mineral oil to a quinoline ester which was hydrolyzed and decarboxylated. The resulting 4-hydroxyquinoline was converted to the corresponding 4-chloro derivative by means of phosphorus oxychloride. The results with substituted anilines are summarized in Table I. The method may be illustrated with aniline itself, thus



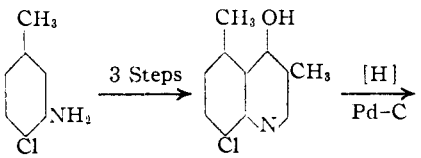
The corresponding reactions with *o*- and *p*-chloroanilines were effected without difficulty to

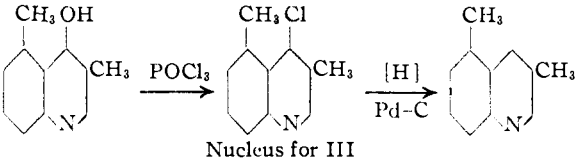
(5) After the present work was completed, Steck, Hallock and Holland, THIS JOURNAL, **68**, 129, 132 (1946), published results on the use of ethyl α-ethoxalylpropionate for the preparation of certain 3-methylquinolines having substituents in the 6- or 8-positions. However, only two of our nuclei, those obtained from *o*- and *p*-chloroaniline, were described by these workers and our data differ in certain respects from theirs; moreover, we have attached the nucleus from *p*-chloroaniline to a different side chain.

form 3-methyl-4,8-dichloroquinoline (VI) and 3-methyl-4,6-dichloroquinoline (nucleus of V), respectively; the latter nucleus was attached to γ-diethylaminopropylamine instead of the standard 1-diethylamino-4-aminopentane. However, cyclization of the anil from *m*-anisidine, used in the preparation of compound I, produced a mixture of isomeric quinoline esters the separation of which was tedious. After six recrystallizations from acetone, the desired 7-methoxy isomer was isolated in fair yield. It was converted without difficulty to the corresponding 4-chloroquinoline. The structure of the nucleus was proved by oxidation[6] of the 4-quinolinol and hydrolysis of the resulting amide to 4-methoxyanthranilic acid, which melted at 165–166° in agreement with the literature.[7] The isomeric 6-methoxyanthranilic acid melts at 85°.[8]

Cyclization of the anil from 2-chloro-4-aminotoluene, used in the preparation of compound II, likewise produced a mixture of isomeric quinoline esters. These were separated on a small scale and the desired 6-methyl-7-chloro isomer converted to the corresponding 4-quinolinol, which was used in the proof of structure of the nucleus. However, for the preparation of the drug it was found more convenient to convert the mixture of quinoline esters to a mixture of the corresponding 4-chloroquinolines from which the desired 6-methyl-7-chloro isomer was isolated in fair yield by four recrystallizations from methanol. The structure of the nucleus was established by oxidizing the 4-quinolinol, hydrolyzing the amide and deaminating the resulting anthranilic acid. The product was 3-methyl-4-chlorobenzoic acid which was identical with a synthetic sample prepared by oxidizing 4-chloro-*m*-xylene.[9]

To avoid the formation of isomers, the nucleus for compound III was prepared from 3-amino-4-chlorotoluene[10] instead of from 3-aminotoluene, and the chlorine was subsequently removed catalytically from the quinolinol using palladium charcoal.[11] Since one position ortho to the amino group is blocked, cyclization can take place in one direction only and this leads to the formation of the desired 5-methyl derivative. As final proof, the 4-chloroquinoline was dechlorinated to the known 3,5-dimethylquinoline.[12] These reactions may be indicated, thus





Nucleus for III

The nucleus for compound IV was prepared by the cyclization of 2-chloro-3-aminotoluene with ethoxymethylenemalonic ester,[13] followed by hydrolysis, decarboxylation and catalytic removal of the chlorine. The resulting quinolinol was converted to the desired 4-chloroquinoline in the usual manner. The presence of chlorine ortho to the amino group insured that the cyclization proceeded in the desired direction. As final proof of the structure, a sample of the 4-chloro-7-methylquinoline was dechlorinated to the known 7-methylquinoline.[12]

3-Methoxy-4,7-dichloroquinoline VII has been obtained by the cyclization of *m*-chloroaniline with ethyl methoxyethoxalylacetate, followed by hydrolysis, decarboxylation and treatment with phosphorus oxychloride. The reactions are analogous to those represented above with ethyl α-ethoxalylpropionate. However, in contrast to the latter reagent, ethyl methoxyethoxalylacetate has produced only a low yield of the quinoline ester, although the yields are good for the remainder of the steps. Moreover, even the low yield on cyclization could be duplicated only on small scale runs. Compound VII has also been prepared by iodinating methyl 4-hydroxy-7-chloroquinoline-2-carboxylate, replacing the iodine by methoxy, and hydrolyzing, decarboxylating and replacing the 4-hydroxy groups by chlorine in the usual manner. The yields appear to be good but thus far these reactions have been carried out only on a small scale. Although the melting point of the product obtained by this method has been slightly lower than that obtained by the cyclization method, there is little doubt that the products are identical, since the mixed melting point is in between. This is considered to establish the structure of the cyclization product as the desired 3-methoxy-7-chloro, rather than the 3-methoxy-5-chloro, isomer. The synthesis of compound VII was also attempted in other ways. Since it has been reported[14] that 3-nitro-4-hydroxyquinoline may be obtained from anthranilic acid and methazonic acid, it appeared possible that the reaction might be effected with 4-chloroanthranilic acid to form a product which might be reduced to the amino derivative and the amino replaced by methoxy. However, a preliminary experiment with anthranilic acid itself gave only a low yield. Nitration of 4-hydroxy-7-chloroquinoline in refluxing acetic acid, followed by reduction, gave an amine (assumed to be the

(6) The procedure used was that of Kretchy (*Monatsh.*, **4**, 156 (1883)) as modified by Drs. R. C. Elderfield and J. B. Wright of Columbia University (private communication).

(7) Ullman and Dootson, *Ber.*, **51**, 20 (1918).

(8) Buehler, Deebel and Evans, *J. Org. Chem.*, **6**, 216 (1941).

(9) Vollrath, *Ann.*, **444**, 266 (1867); see also Maillie, *Bull. soc. chim.*, [4] **29**, 290 (1921).

(10) Ullman and Gluck, *Ber.*, **49**, 2494 (1916).

(11) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 84 (1938).

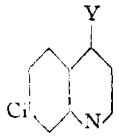
(12) Manske, *Canadian J. Res.*, **20B**, 133 (1942).

(13) The method of cyclization of this ester with aniline derivatives, first described by Jacobs and Gould [THIS JOURNAL, **61**, 2890 (1939)], has been greatly extended by Price and co-workers; see Price and Roberts, *ibid.*, **68**, in press (1946).

(14) Musajo and Chiancone, *Gazz. chim. ital.*, **67**, 218 (1937).

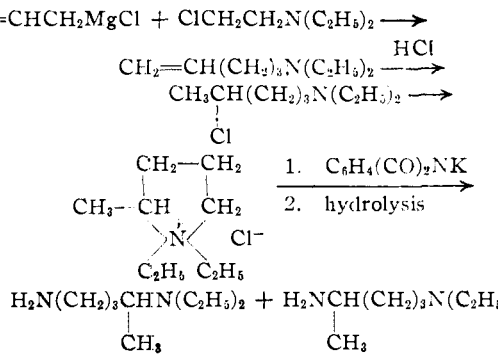
3-amino derivative) but, on diazotization followed by treatment with methanol, the amino group was replaced by hydrogen rather than by methoxy even when the diazonium fluoborate salt was used.[15] Although the Pfitzinger reaction with isatin and ethoxyacetone has been reported[16] we were unable to effect the corresponding reaction with isatin and methoxyacetaldoxime.

Variations in the Side Chain.—Compounds VIII and IX were prepared and submitted for testing. Compound X was presumably obtained, but it could not be isolated in the pure condition.



VIII, Y = $-NH(CH_2)_3CH(CH_3)N(C_2H_5)_2$
IX, Y = $-NH(CH_2)_3NH(CH_2)_3N(C_2H_5)_2$
X, Y = $-N(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$

The diamine for compound VIII, 4-diethylamino-1-aminopentane, was prepared by the method of Kharasch and Fuchs.[17] The method produces this diamine contaminated with 10% of the isomeric 1-diethylamino-4-aminopentane, the separation of which is troublesome. The mixture of isomers arises because the cyclic quaternary ammonium chloride, which reacts with potassium phthalimide, may cleave in two ways.



We had first tried certain other methods. The most promising of these involved the reduction of the carbonyl group of levulinonitrile, obtained from methyl vinyl ketone and hydrogen cyanide,[18] and the conversion of the resulting γ-hydroxyvaleronitrile to γ-diethylaminovaleronitrile, which could be reduced to the desired diamine. Unfortunately, the aluminum isopropoxide reduction of levulinonitrile gave poor yields of the corresponding alcohol.

The triamine for compound IX, γ-(γ'-diethylaminopropylamino)-propylamine, was prepared by the procedure of Whitmore and co-workers[19] involving the addition of γ-diethylaminopropylamine to acrylonitrile followed by catalytic reduction.

The diamine for compound X, 1-diethylamino-3-methylaminopropane, was prepared by the procedure of Cottle and co-workers.[20] Methylaniline was alkylated with γ-diethylaminopropyl chloride and the product was converted to the *p*-nitroso derivative which was hydrolyzed with alkali.

Experimental[21]

3-Amino-4-chlorotoluene.—3-Nitro-4-aminotoluene (Eastman Kodak Co.) was converted in 85% yield via the Sandmeyer reaction[22] to 3-nitro-4-chlorotoluene, b. p. 128–131° at 10 mm. (reported b. p. 135° at 15 mm.).[23] This was reduced in 82% yield with stannous chloride[24] to 3-amino-4-chlorotoluene, b. p. 115–117° at 18 mm., m. p. 30° (reported m. p. 29°).[10]

Synthesis of 3-Methyl-4-chloroquinolines: General Procedure.—A mixture of one mole of the substituted aniline, 1.03 moles of ethyl α-ethoxalylpropionate and 2 ml. of concentrated hydrochloric acid was kept *in vacuo* over sulfuric acid overnight or longer.[25] The resulting anil was added with stirring during fifteen minutes to 1500 ml. of mineral oil at 250–260°, the temperature generally maintained for an additional five to ten minutes and the reaction mixture then cooled, in certain cases, rapidly. The ester was filtered, washed thoroughly with petroleum ether (30–60°) and dried. It was sufficiently pure for the next step.

The crude ester (0.50 mole) was hydrolyzed by refluxing it for eight hours with one liter of 4% sodium hydroxide. The solution obtained was diluted to 1500 ml., charcoaled and filtered hot. The cooled solution was acidified to congo red, the acid filtered off, washed with water and dried.

The crude acid (0.33 mole) was added with stirring to one liter of mineral oil at about 275°. When the evolution of carbon dioxide had ceased (five to ten minutes) the mixture was cooled, petroleum ether was added and the 4-quinolinol filtered off. It was washed thoroughly with petroleum ether. If difficulty was encountered in obtaining a pure sample, the crude 4-quinolinol was treated with hot, dilute ammonium hydroxide before recrystallization to remove any unreacted acid.

The crude hydroxy compound (0.30 mole) was heated with 180 ml. of phosphorus oxychloride at 130–140° for one hour. The excess phosphorus oxychloride was distilled under reduced pressure and the residue was poured onto ice. The cold, acidic solution was filtered and the filtrate was made alkaline with cold 20% sodium hydroxide. The 4-chloro compound was filtered off and recrystallized from dilute methanol or dilute ethanol. In certain cases it was distilled before recrystallization.

The results of the four steps described above are summarized in Table I. The yields given are for crude products unless otherwise indicated.

(15) We are indebted to Dr. Mary Sherrill, Mount Holyoke College, for the procedure.

(16) Cross and Henze, THIS JOURNAL, **61**, 2730 (1939).

(17) Kharasch and Fuchs, *J. Org. Chem.*, **9**, 359 (1944).

(18) U. S. Patent 2,188,340; *C. A.*, **34**, 3764 (1940).

(19) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Yanko, THIS JOURNAL, **66**, 725 (1944).

(20) We are indebted to Dr. D. L. Cottle and co-workers, of Rutgers University, for the procedure which will appear in a forthcoming paper in THIS JOURNAL.

(21) Analyses by F. Marx and Lois E. May, Department of Chemistry, Columbia University, New York, N. Y.; Arlington Laboratories, Fairfax, Virginia; Dr. T. S. Ma, Department of Chemistry, University of Chicago, Chicago, Illinois; and Passie Saperstein, M. Lovelace, Peggie Otto and B. A. Taylor of this Laboratory.

(22) Wynne, *J. Chem. Soc.*, **61**, 1072 (1892).

(23) Shaw and Turner, *ibid.*, 1884 (1932). These workers prepared this compound by nitrating *p*-chlorotoluene.

(24) Cohen and Dakin, *ibid.*, **79**, 1128 (1901).

(25) Anils from ethyl ethoxalylacetate have previously been prepared in this manner (Kermack and Weatherhead, *J. Chem. Soc.*, 1164 (1940)), and also by warming the components in glacial acetic acid (Cavallito and Haskell, THIS JOURNAL, **66**, 1166 (1944)). We have employed the latter method with ethyl α-ethoxalylpropionate and *o*-chloroaniline.

Dechlorination of 3,5-Dimethyl-4-hydroxy-8-chloroquinoline.—To 25.9 g. (0.125 mole) of this compound, dissolved in a solution of 10.2 g. (0.125 mole) of anhydrous sodium acetate in 200 ml. of glacial acetic acid was added 1.9 g. of palladium-charcoal catalyst. The solution was shaken at 70–75° under a hydrogen pressure of fifteen pounds. The calculated amount of hydrogen was absorbed in ninety minutes. The catalyst was filtered off, the solvent distilled *in vacuo* and the residue poured into ice water. The mixture was made neutral with sodium hydroxide and the solid filtered off. The crude 3,5-dimethyl-4-hydroxyquinoline gave a negative test for chlorine on sodium fusion. This dechlorinated 4-hydroxyquinoline was then converted to the 4-chloro derivative as described above. The data are given in Table I.

Proofs of Structure of 3-Methylquinolines (A). Nucleus of Compound I.—A sample (6 g.) of the 4-quinolinol from *m*-methoxyaniline was refluxed five hours with a solution of 25 g. of potassium permanganate and 2.5 g. of potassium hydroxide in 1500 ml. of water.[6] The manganese dioxide was filtered off. The filtrate was acidified with dilute sulfuric acid, the excess permanganate destroyed by the addition of sodium bisulfite and the solution chilled. The precipitate was filtered off and hydrolyzed by heating in a pressure bottle with 60 ml. of concentrated hydrochloric acid for three hours at 130°. The reaction mixture was diluted with water, extracted with ether and the aqueous phase evaporated to dryness. The residue was taken up with water, filtered and the acid precipitated by the addition of sodium acetate. The acid was identified as 4-methoxyanthranilic acid, m. p. 165–166°,[7] after one recrystallization from ethanol.

(B) **Nucleus of Compound II.**—A sample of the cyclization product from 3-chloro-4-methylaniline was recrystallized repeatedly from a mixture of pyridine and alcohol until the product melted at 233–240°. The ester was hydrolyzed, the acid decarboxylated and the 4-quinolinol (m. p. 305–309°) was oxidized and hydrolyzed as described above. The resulting acid (0.5 g.), melting at 166–168°, was dissolved in 5 ml. of hot 6 *M* hydrochloric acid. The solution was cooled to −10°, and 0.2 g. of sodium nitrite in 2 ml. of water added, followed by 10 ml. of 30% hypophosphorous acid. The cold solution was stirred for one hour, placed in the refrigerator overnight and the acid filtered off. This acid melted at 203° after recrystallization from dilute ethanol. It was presumably 3-methyl-4-chlorobenzoic acid, an authentic sample of which melted at 207–207.5°; a mixed melting point was 204–206°. The low melting point of the acid is presumably due to a trace of the isomer being carried through all the steps.

(C) **Nucleus of Compound III.**—A sample of 3,5-dimethyl-4-chloroquinoline was catalytically dechlorinated as described above to 3,5-dimethylquinoline which was converted to its picrate, m. p. 218–219° (reported m. p. 220°).[12]

Synthesis of 4-Chloro-7-methylquinoline.—In a two-liter three-necked flask equipped with a mercury-sealed stirrer, thermometer, nitrogen inlet tube and air condenser were placed 800 ml. of Dowtherm A, 142 g. (1.0 mole) of 2-chloro-3-aminotoluene and 216 g. (1.0 mole) of ethoxymethylenemalonic ester. The mixture was stirred and heated to 150–160° with a rapid stream of nitrogen bubbling through the liquid; ethanol was evolved as the anil formed. After fifteen minutes the temperature was raised to 245°; ethanol was again evolved as cyclization took place. After twenty minutes at this temperature, the reaction mixture was cooled rapidly. The solid was filtered off and washed with petroleum ether (30–60°). There was obtained 193 g. (73%) of ethyl 4-hydroxy-7-methyl-8-chloroquinoline-3-carboxylate (yellow solid) m. p. 264–266°. A sample, recrystallized from pyridine-alcohol, melted at 265–266°.

Anal. Calcd. for $C_{13}H_{12}O_3NCl$: C, 58.8; H, 4.55; N, 5.27; Cl, 13.3. Found: C, 59.0; H, 4.69; N, 5.37; Cl, 13.2.

The ester was saponified in 97% yield to the corresponding acid m. p. 269°. Recrystallization from dioxane-water did not change the melting point.

Anal. Calcd. for $C_{12}H_8O_3NCl$: C, 55.6; H, 3.39; N, 5.90; Cl, 14.9. Found: C, 55.5; H, 3.61; N, 5.99; Cl, 15.1.

The acid was decarboxylated by heating in Dowtherm A at 250° for seventy-five minutes to form 4-hydroxy-7-methyl-8-chloroquinoline; yield 99%. A sample, recrystallized from pyridine–alcohol, melted at 304–305°.

Anal. Calcd. for $C_{10}H_8ONCl$: C, 62.0; H, 4.16; N, 7.24. Found: C, 61.7; H, 4.63; N, 7.42.

The compound was dechlorinated catalytically in 87% yield as described above to form 4-hydroxy-7-methylquinoline. A sample, recrystallized from water, melted at 222–223.5°. Sodium fusion showed the absence of chlorine.

Anal. Calcd. for $C_{10}H_9ON$: N, 8.80. Found: N, 8.63.

The hydroxy compound was converted by phosphorus oxychloride to 4-chloro-7-methylquinoline, b. p. 140–142° at 9.5 mm. (m. p. 28°); yield 65%.

Anal. Calcd. for $C_{10}H_8NCl$: C, 67.6; H, 4.54; N, 7.89; Cl, 20.0. Found: C, 67.4; H, 4.47; N, 8.10; Cl, 19.6.

The structure of the nucleus was proved by catalytic dechlorination of 4-chloro-7-methylquinoline to 7-methylquinoline, which was converted into a picrate, m. p. 239–241° (reported m. p. 242°).[12]

Synthesis of 3-Methoxy-4,7-dichloroquinoline (VII) (Cyclization Method).—Ethyl methoxyethoxalylacetate was prepared in excellent yield by a modification of the method used for the preparation of ethyl α-ethoxalylpropionate.[26] Powdered sodium (23 g., 1 g. atom) was placed in a one-liter three-necked flask equipped with a mercury-sealed stirrer, reflux condenser and dropping funnel and was covered with 330 ml. of anhydrous ether. Absolute ethanol (46 g., 1 mole) was added dropwise with stirring. After all the sodium had reacted, 171 g. (1 mole) of ethyl oxalate was added slowly and then 118 g. (1 mole) of ethyl methoxyacetate was added dropwise. The stirring was discontinued and the mixture was allowed to stand at room temperature for three days, during which time it changed from yellow to red. The ether and most of the alcohol were distilled off using a steam-bath. The residue was cooled in an ice-bath, covered with 300 ml. of ether and stirred with 28 ml. (1 mole) of concentrated sulfuric acid in 200 ml. of ice-water. When all of the gummy mass had dissolved, the two layers were separated, the aqueous phase was extracted once with ether and the combined ether solutions were dried over anhydrous sodium sulfate. The solvent was removed and the residue distilled through a 20-cm. Vigreux column. A considerable amount of low-boiling material was collected in a Dry Ice-trap, after which the pressure dropped to 2 mm.; b. p. 102–112° at 2 mm., yield 185 g. (85%) of pale yellow liquid.

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.86, 49.57; H, 6.77, 6.77.

Ice-cold ethyl methoxyethoxalylacetate (3.2 g., 0.025 mole) was mixed with 5.8 g. (0.026 mole) of ice-cold *m*-chloroaniline and 0.04 ml. of concentrated hydrochloric acid was added to the mixture. The oil after standing *in vacuo* over concentrated sulfuric acid overnight, was added rapidly to 20 ml. of mineral oil at 260–270°. The reaction mixture was cooled and petroleum ether added. The red oil was digested with two portions of ligroin (70–90°) on a steam-bath and the resulting gummy solid recrystallized from dilute ethanol. There was obtained 1.5 g. (17%) of yellow crystals melting at 197–200° and, after further recrystallization, at 200–202°, analyzing correctly for ethyl 3-methoxy-4-hydroxy-7-chloroquinoline; the yield could not be duplicated on larger runs.

Anal. Calcd. for $C_{13}H_{12}O_4NCl$: C, 55.4; H, 4.30; N, 4.97; Cl, 12.6. Found: C, 55.7; H, 4.53; N, 5.27; Cl, 12.3.

The ester was saponified in 78% yield to the correspond-

(26) Cox and McElvain, "Organic Syntheses," Coll. Vol. 11, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 272.

ing acid, m. p. 280° after recrystallization from ethanol-ligroin.

Anal. Calcd. for $C_{11}H_8O_4NCl$: C, 52.1; H, 3.18; N, 5.52. Found: C, 52.2; H, 3.85; N, 5.74.

The acid was decarboxylated in 98% yield to 3-methoxy-4-hydroxy-7-chloroquinoline, m. p. 285° after recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_8O_2NCl$: C, 57.3; H, 3.85; Cl, 16.9. Found: C, 57.7; H, 4.15; Cl, 16.9.

The 4-hydroxy compound was converted in 88% yield to 3-methoxy-4,7-dichloroquinoline, m. p. 115.5–116.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_7ONCl_2$: N, 6.14. Found: N, 6.14.

3-Methoxy-4,7-dichloroquinoline (X) (Iodination Method).—4-Hydroxy-7-chloroquinoline-2-carboxylic acid was esterified to methyl 4-hydroxy-7-chloroquinoline-2-carboxylate, m. p. 275–277°, according to the method of Ainley and King.[11] The ester (40.5 g., 0.17 mole) was added to 275 ml. of glacial acetic acid, the mixture was stirred and 29.6 g. (0.18 mole) of iodine monochloride[27] dissolved in 80 ml. of glacial acetic acid was added. Stirring was continued for four hours, 750 ml. of water was added and the reaction mixture was heated at 80° for twenty minutes. Excess iodine was destroyed with 40% sodium bisulfite solution, the solution was filtered, the product washed with acetic acid and dried, m. p. 250°, yield 56%. Recrystallization from dioxane–water gave a product melting at 252°.

The 3-iodoquinoline (5.2 g., 0.014 mole) was heated in a sealed tube at 120° for two hours with 0.043 mole of sodium methoxide in excess methanol. The reaction mixture was poured into water and acidified, 2.6 g. (68%) of presumably methyl 3-methoxy-4-hydroxy-7-chloroquinoline-2-carboxylate being obtained, m. p. 245–248°. After recrystallization from dilute methanol it melted at 262–263°. The ester was hydrolyzed in 78% yield and the resulting acid was decarboxylated in 70% yield. 3-Methoxy-4-hydroxy-7-chloroquinoline (0.4 g.) was treated with 2 ml. of phosphorus oxychloride, 0.4 g. (92%) of 3-methoxy-4,7-dichloroquinoline being obtained. Several recrystallizations from dilute ethanol gave a compound melting at 112–113°. A mixed melting point with the compound obtained from the cyclization procedure was 113–116°.

Anal. Calcd. for $C_{10}H_7ONCl_2$: C, 52.7; H, 3.10; N, 6.14; Cl, 31.1. Found: C, 52.5; H, 3.33; N, 6.62; Cl, 31.2.

Synthesis of Di- or Triamines for Side Chains.—4-Diethylamino-1-aminopentane was prepared and separated from the isomeric 1-diethylamino-4-aminopentane by the method of Kharasch and Fuchs.[17,28]

γ-(γ'-Diethylaminopropylamino)-propylamine was prepared by the procedure of Whitmore and co-workers.[19] The product boiled at 147–151° at 25 mm.; picrate, m. p. 199° (Whitmore, *et al.*,[19] reported b. p. 142–144° at 25 mm.; picrate, m. p. 197–198°).

1-Diethylamino-3-methylaminopropane, b. p. 76–77° at 23 mm., was prepared according to the procedure of Cottle and co-workers[20] except that 1-diethylamino-3-chloropropane hydrochloride was prepared by saturating an ethereal solution of 1-diethylamino-3-chloropropane[29] with hydrogen chloride.

(27) Woollett and Johnson, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 343.

(28) We are indebted to Dr. and Mrs. Kenneth N. Campbell, University of Notre Dame, for separating the isomers by fractional distillation. The mixture of diamines was distilled once from sodium and then fractionated. From 100 g., three fractions were obtained: 7.5 g., b. p. 102° at 37 mm., $n^{20}D$ 1.4436; 30 g., b. p. 104° at 37 mm., $n^{20}D$ 1.4462–1.4468; and 60 g., b. p. 104° at 37 mm., $n^{20}D$ 1.4471–1.4475. Kharasch and Fuchs reported two fractions: 1-diethylamino-4-aminopentane, b. p. 102° at 37 mm., $n^{20}D$ 1.4435; and 4-diethylamino-1-aminopentane, b. p. 104° at 37 mm., $n^{20}D$ 1.4475.

(29) Breslow, Walker, Yost and Hauser, THIS JOURNAL, **67**, 1472 (1945).

Coupling of 4-Chloroquinolines with Amines. General Procedure.—The 4-chloroquinoline (0.10 mole), 0.21 mole of the diamine and, in certain cases, 10 g. of phenol were heated in an oil-bath with stirring, the temperature and duration of heating depending on the structure of both the quinoline and the diamine. Generally, an exothermic reaction took place when the coupling temperature was reached, and the reaction mixture was kept at that temperature. The reaction mixture was cooled and was treated with 100 ml. of 20% sodium hydroxide.

If the oil which separated solidified, it was filtered off and was washed thoroughly with petroleum ether to remove excess diamine. The residual solid was dissolved in 300 ml. of 20% acetic acid and the solution was charcoaled and filtered to remove unreacted 4-chloroquinoline. The solution was then made alkaline with ammonia, the solid was filtered off, washed with water, dried and recrystallized. The free bases were white, crystalline solids.

If the oil would not crystallize, it was extracted with ether or with ethyl acetate, the solution was dried over anhydrous potassium carbonate, the solvent was removed and the residue was distilled, first at 20 mm. to remove excess diamine and then in high vacuum. The free bases were obtained as yellow or orange oils. The free base was converted into a diphosphate salt as follows:[30] the free base was dissolved in four–five volumes of water containing two moles of phosphoric acid and the hot solution was charcoaled. About ten volumes of methanol were added and then isopropyl alcohol was added to the hot solution until cloudy. The oil which separated solidified on long standing in the cold and the solid was recrystallized from water–methanol–isopropyl alcohol in the same proportions as above. The diphosphates were obtained as white, crystalline compounds.

The data are summarized in Table II.

Acknowledgments for Chemicals.—γ-Diethylaminopropylamine (Dr. H. Adkins, University of Wisconsin), "Dowtherm A" (Dr. E. C. Britton, Dow Chemical Co.), 1-diethylamino-4-aminopentane and ethyl methoxyacetate (Dr. R. C. Elderfield, Columbia Univ.), γ-diethylaminopropyl chloride (Dr. R. C. Fuson, University of Illinois), *m*-anisidine and 2-chloro-3-aminotoluene (Dr. H. Gilman, Iowa State College), ethyl α-ethoxalylpropionate (Dr. C. S. Hamilton, University of Nebraska), potassium phthalimide (Dr. E. B. Hartshorn, Dartmouth College), 2-chloro-4-aminotoluene (Dr. R. E. Lutz, University of Virginia), ethoxymethylenemalonic ester (Dr. C. C. Price, University of Illinois), 4,7-dichloroquinoline (Dr. B. Riegel, Northwestern University), 4-hydroxy-7-chloroquinoline-2-carboxylic acid (Dr. C. M. Suter, Winthrop Chemical Co.).

Summary

1. The following new potential antimalarials in the 4-aminoquinoline series have been synthesized: 3-methyl-4-(4'-diethylamino-1'-methylbutylamino)-7-methoxyquinoline (I), 3,6-dimethyl-4-(4'-diethylamino-1'-methylbutylamino)-7-chloroquinoline (II), 3,5-dimethyl-4-(4'-diethylamino-1'-methylbutylamino)-quinoline (III), 4-(4'-diethylamino-1'-methylbutylamino)-7-methylquinoline (IV), 3-methyl-4-(γ-diethylaminopropylamino)-6-chloroquinoline (V), 4-(4'diethylaminopentylamino)-7-chloroquinoline

(30) The method used was one developed in the laboratories of the Winthrop Chemical Co., as modified by Dr. Nathan L. Drake of the University of Maryland.

TABLE II

COUPLING OF 4-CHLOROQUINOLINES WITH DI- OR TRIAMINES

	4-Chloroquinoline	Di- or triamine	Reaction temp., °C.	Time, hr.	No.[a]	SN[b]	Product (free base) Yield, %	B. p., °C.	Mm.
1	3-Methyl-7-methoxy	$H_2NCH(CH_2)_3N(C_2H_5)_2$ $\vert$ CH_3	200–210[c]	20	I	10,566	57	164–170	0.002
2	3,6-Dimethyl-7-chloro	$H_2NCH(CH_2)_3N(C_2H_5)_2$ $\vert$ CH_3	200–210[c]	20	II	10,565	87	185–195	.002
3	3,5-Dimethyl	$H_2NCH(CH_2)_3N(C_2H_5)_2$ $\vert$ CH_3	210–220[c]	18	III	10,448	87	170–178	.005
4	7-Methyl	$H_2NCH(CH_2)_3N(C_2H_5)_2$ $\vert$ CH_3	180–185	7	IV	13,139	82	99–100.5 (m. p.)[h]	
5	3-Methyl-6-chloro	$H_2N(CH_2)_3N(C_2H_5)_2$	180[c]	8	V	11,420	76	131–140	.005
6	7-Chloro	$H_2N(CH_2)_3CHN(C_2H_5)_2$ $\vert$ CH_3	140–145	5	VIII	10,451	78	129–129.5 (m. p.)[i]	
7	7-Chloro	$H_2NCH_2CH_2CH_2NH$ $\vert$ $(C_2H_5)_2NCH_2CH_2CH_2$	140–145	5	IX	12,706	81	66–68[d] (m. p.)[j]	
8	7-Chloro	$HN(CH_2)_3N(C_2H_5)_2$ $\vert$ CH_3	210–220[c]	17	X		46	170–200[e]	.05–0.1

	Phosphate M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. PO_4	Found C	Found H	Found PO_4
1	180–181	$C_{20}H_{31}ON_3 \cdot 2H_3PO_4$	45.7	7.10	36.2	45.2	7.05	36.3
2	127–128	$C_{20}H_{30}NCl \cdot 2H_3PO_4 \cdot H_2O$	42.7	6.82	33.8	42.9	7.01	33.8
3	143–144	$C_{20}H_{31}N_3 \cdot 2H_3PO_4 \cdot {}^1/_2H_2O$	46.3	7.39	36.7	46.5	7.54	36.9
4		$C_{19}H_{29}N_3$	76.2	9.76	[f]	76.0	9.65	
5	239–240	$C_{17}H_{24}N_3Cl \cdot 2H_3PO_4 \cdot {}^1/_2CH_3OH$	40.7	6.03	36.7	40.6	6.44	37.0
6		$C_{18}H_{26}N_3Cl$	67.6	8.19	[g]	68.2	8.41	
7		$C_{19}H_{29}N_4Cl \cdot 2H_2O$	59.3	8.64		59.4	8.69	

[a] Number assigned in this paper. [b] The Survey Number, designated SN, identifies a drug in the record of the Survey of Antimalarial Drugs. The antimalarial activities of these compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph. [c] In the presence of 10 g. of phenol. [d] Hydrate. Formed an oil on drying over calcium chloride or phosphorus pentoxide. [e] Decomposed on standing at room temperature and on warming with dilute acids. [f] Neutral equivalent: Calcd.: 149.7. Found: 150.2. [g] Neutral equivalent, Calcd.: 159.9. Found: 159.7. [h] Sample recrystallized from benzene–petroleum ether (30–60°). [i] Sample recrystallized from ethanol. [j] Sample recrystallized from methanol.

(VIII), and 4-[γ-(γ′-diethylaminopropylamino)-propylamino]-7-chloroquinoline (IX). Also 4-(N-methyl-N-γ-diethylaminopropylamino)-7-chloroquinoline (X) presumably was obtained.

2. The nuclei 3-methyl-4,8-dichloroquinoline (VI) and 3-methoxy-4,7-dichloroquinoline (VII) were prepared.

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