[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Quinolines. V. Some Polysubstituted 4-(4′-Diethylamino-1′-methylbutylamino)-quinolines[1]

BY EDGAR A. STECK, LOUIS L. HALLOCK, ARNOLD J. HOLLAND AND LYNN T. FLETCHER

Chloroquine (SN 7618, 7-chloro-4-(4′-diethylamino - 1′ - methylbutylamino) - quinoline)[2,3] has been found to be the most effective of the quinoline antimalarials bearing the basic chain in position 4. In our program, which has involved the preparation of numerous analogous compounds bearing an alkyl group in the pyridine moiety,[4] we have attempted to evaluate the influence of the position and nature of several groups upon antiplasmodial activity. The 4-(4′-diethylamino-1′-methylbutylamino)-quinolines here discussed will include all possible bz-fluoro-3-methyl types, 3,6,5/7-trimethyl, 7-chloro-2-methyl, and also the 5/7-chloro-3-propyl.

As in our previous work,[4] the fundamental plan of synthesis was based upon the Conrad–Limpach synthesis, employing several recent modifications in the technique of cyclization. The bz-fluoro-3-methylquinoline series were obtained from the requisite fluoroanilines by reaction with ethyl α-ethoxalylpropionate. To separate the ethyl 5/7-fluoro-4-hydroxy-3-methylquinoline-2-carboxylates, which were prepared from *m*-fluoroaniline, fractional crystallization was required (*cf.* 4 c,d). Oxidation of the acids derived from the esters (which had been crystallized to constant m. p.) by use of alkaline permanganate solution was unexpectedly difficult. No pure specimens of the oxidation products from either series could be identified with certainty as 4-fluoroanthranilic acid,[5] and the attempt was abandoned. The series giving rise to the higher melting 4-chloro compound, was designated as the 7-fluoro type; the parent ester was not only the higher-melting of the two, but, more characteristically, less soluble in alcohol. The earlier experiences with the other isomeric 5/7-halo-3-methylquinolines[4c,d] have formed the basis for this decision. Separation of the ethyl 3,6,5/7-trimethyl-4-hydroxyquinoline-2-carboxylates by crystallization from alcohol was not attended by noteworthy difficulties. The attempts to prove conclusively the location of the 5/7-methyl group by oxidative means were not successful. Intractable mixtures of high-melting materials (polycarboxylic acids?) resulted. It was necessary to resort to an arbitrary designation of structure upon the above-noted basis.

The investigations of Strukov (1932), which were referred to by Gal'perin,[6] indicated a lack of antimalarial activity among several quinaldine types, but disagreement[7,8] or lack of testing data[9,10] concerning similar compounds led to interest in 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinaldine. Although it was expected[4c,d] that application of the Conrad–Limpach procedure to *m*-chloroaniline and ethyl acetoacetate would lead to both 5- and 7-chloro-4-hydroxyquinaldine, such was not the case. Despite careful study, only one discrete compound could be isolated. Oxidation with alkaline permanganate[4c] led to 4-chloroanthranilic acid, hence the product was proven to be the 7-chloro isomer. Price, *et al.*,[11] prepared 7-chloro-4-hydroxyquinaldine by this method, but a proof of structure was lacking. Conversion of the 4-hydroxy compound to the desired base was accomplished in the usual manner.

The application of the Conrad–Limpach procedure to *m*-chloroaniline and ethyl α-ethoxalylvalerate[12] was designed to yield a series of 5- and 7-chloro-3-propylquinolines. This investigation was hampered by poor yields, as in the preparation of the β-keto ester and its cyclization to the quinoline derivatives, and the tedious fractional crystallization required for the isomer separation. The fraction having the lower solubility in alcohol was demonstrated to be ethyl 7-chloro-4-hydroxy-3-propylquinoline-2-carboxylate through oxidation of its derived acid.

Of the bz-fluoro-4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinolines which were tested, none showed activity comparable to the related chloro compound. Neither 4-(4′-diethylamino-1′-methylbutylamino)-3,5,6-trimethylquinoline nor its 3,6,7-trimethyl isomer exhibited marked antiplasmodial action. Although 7-chloro-4-(4′-diethylamino - 1′ - methylbutylamino) - quinaldine did show promise at first, its toxicity was unfavorable. This behavior was of interest because several other quinaldine types had not been of particular value.[6,8] Insufficient amounts of the bases of the 5/7-chloro-3-propylquinoline compounds were available for testing. Most of the antimalarial tests were carried out under the direction

(1) A portion of this paper was presented before the 109th meeting of the A. C. S. in Atlantic City, N. J., April 9, 1946.

(2) (a) Andersag, Breitner and Jung, U. S. Patent 2,233,970; (b) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(3) Loeb, *et al.*, *J. Am. Med. Assoc.*, **130**, 1069 (1946).

(4) Steck, Hallock and Holland, THIS JOURNAL, **68**, (a) p. 129 (1946); (b) p. 132; (c) p. 380; (d) p. 1241.

(5) Steck and Fletcher, *ibid.*, **70**, 439 (1948).

(6) Gal'perin, *Med. Parasitol. Parasitic Diseases (U. S. S. R.)*, **7**, 1896 (1937); *Am. Rev. Soviet Med.*, **1**, 220 (1943–1944).

(7) Krichevskii, Shternberg and Gal'perin, *J. Microbiol., Epidemol. and Immunobiol. (U. S. S. R.)*, **14**, 642 (1935).

(8) Holcomb and Hamilton, THIS JOURNAL, **64**, 1309 (1942).

(9) Van Arendonk and Shonle, *ibid.*, **66**, 1284 (1944).

(10) Kermack and Smith, *J. Chem. Soc.*, 356 (1930).

(11) Price, Leonard and Reitsema, THIS JOURNAL, **68**, 1259 (1946).

(12) Steck and Holland, *ibid.*, **70**, 440 (1948).

TABLE I

BZ-FLUORO-3-METHYLQUINOLINE DERIVATIVES

Compound	Yield, %[a]	Appearance	Solvent[b]	M. p.[c]	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ethyl Bz-Fluoro-3-methyl-4-hydroxyquinoline-2-carboxylates										
5-F	45[d,e]	Yellowish needles	E	198–199	62.64	4.84	5.62	62.87	4.84	5.44
6-F	89[d]	White platelets	aAc	233.5–234				62.36	4.61	5.68
7-F	53[d,e]	White needles	E	224.5–225				62.60	4.78	5.73
8-F	80[d]	Creamy needles	aE	133–135				62.33	5.19	5.81
Bz-Fluoro-3-methyl-4-hydroxyquinoline-2-carboxylic Acids										
5-F	92	White needles	E	240D	59.73	3.65	6.33	59.86	3.69	6.44
6-F	97	Yell.-white microcryst.	P	255–255.5D				59.91	3.75	6.06
7-F	94	White needles	E	246D				59.77	3.72	6.45
8-F	93	Creamy needles	E	222–223D				59.93	3.56	6.40
Bz-Fluoro-3-methyl-4-hydroxyquinolines										
5-F	96	White needles	I	>275	67.79	4.55	7.90	68.11	4.52	7.96
6-F	96	White prism.-needles	E	281–282				67.75	4.39	7.77
7-F	95	White prisms	E	288				67.89	4.47	7.83
8-F	92	White tablets	a	216–217				68.02	4.73	8.08
Bz-Fluoro-3-methyl-4-chloroquinolines										
5-F	95	White leaflets	aM	70–71	61.39	3.61	7.16	61.16	3.99	7.65
6-F	92	White needles	Sk	57.5–58				61.45	3.52	7.39
7-F	94	White needles	aM	88.5–89				61.48	3.81	7.20
8-F	88	White needles	Sk	101–102				61.26	3.55	7.06
Bz-Fluoro-3-methylquinoline derivatives										
Bz-Fluoro-3-methyl-4-(1′-methyl-4′-diethylaminobutylamino)-quinolines										
5-F	88	Bright yellow oil[g]		185–188/0.6[f]	71.88	8.89	13.24	72.14	9.02	12.93
6-F	80	Golden oil		160–162/0.1[f]				72.11	8.83	13.53
7-F	80	Bright yellow oil[h]		205–210/1[f]				72.07	9.31	12.98
8-F	83	Lemon oil		162–164/0.2[f]				72.13	8.89	13.30

[a] Not purified, as used for next step. [b] Legend: Ac = acetone, E = ethanol, I = propanol-2, M = methanol, P = propylene glycol, Sk = Skellysolve A, a = aqueous. [c] Uncorrected, °C. D = decomposes. [d] Yields obtained upon cyclization of crude azomethines (75–88% yields). [e] The yields of isomeric esters are those produced by the separation of crude mixtures, which were formed in 85–90% yields. [f] B. p., °C. (mm.). [g] Converted into the methane-*bis*-1,1′-(2-hydroxy-3-naphthoate) by precipitation from hydrochloric acid solution with the sodium salt of the organic acid; yellow powder, m. p. >300°. *Anal.* Calcd. for $C_{19}H_{28}FN_3 \cdot C_{23}H_{16}O_6 \cdot 2H_2O$: base, 42.79; H_2O, 4.86. Found: base, 43.34; H_2O, 5.23; SN 8798-S1. [h] As [g], yellowish powder, m. p. >300°. Found: base, 43.06; H_2O, 4.85; SN 8797-S1.

of the National Research Council, and the data have been tabulated.[13]

Experimental

Fluoroanilines.—The fluoronitrobenzenes were prepared from the corresponding nitroanilines by the method of Schiemann.[14,15] Conversion of the diazonium borofluorides, which were obtained in 92–99% yields, into the fluoronitrobenzenes was best accomplished by mixing the salts with sand before decomposition. The yield of pure *o*-fluoronitrobenzene was 11–16%; *m*-, 48–51%; *p*-, 40–49%. Neutral iron reduction[16,4c] of the nitro compounds led to yields of 72–83% of the corresponding fluoroanilines.

Ethyl α-ethoxalylpropionate and ethyl α-ethoxalylvalerate were prepared as described in previous contributions.[4a,12]

Bz-Fluoro-3-methylquinoline Series.—The general pattern of synthesis for the isomeric bz-fluoro-3-methylquinolines was that earlier described by us.[4] Separation of the 5/7-fluoro compounds, obtained from *m*-fluoroaniline, was accomplished by fractional crystallization from alcohol. The isomer which was the less soluble (designated as the 7-fluoro, see discussion) of higher m. p., was considerably more facile of purification. In Table I are the data relative to the several series. Distillation of all the 4-(4′-diethylamino-1′-methylbutylamino)-bz-fluoro-3-methylquinolines was tedious.

3,6,5/7-Trimethylquinoline Series.—3,4-Dimethylaniline[17] was employed in the preparation of the trimethylquinoline derivatives. The isomeric esters were fractionally crystallized from alcohol and each obtained pure with fair ease; the lower-melting isomer was the more soluble of the two. Unequivocal designation as to structures could not be made, as noted in the discussion. The data presented in Table II relate to the compounds of this series.

7-Chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinaldine.—Only one compound was obtained from the reaction of *m*-chloraniline with ethyl acetoacetate after the method of Conrad and Limpach. An oxidation of the 4-hydroxy compound by permanganate (*cf.* ref. 4c) demonstrated that the chlorine was in position 7, as shown in Table III, wherein the several quinaldines are described.

5/7-Chloro-3-propylquinoline Series.—The use of ethyl α-ethoxalylvalerate[12] as the β-keto ester in the usual

(13) Wiselogle, editor, "Antimalarial Drugs, 1941–1945," Edwards Bros., Ann Arbor, Mich., 1946. All drugs identified by Survey Numbers (SN) in the files of the Antimalarial Survey office have been systematically tabulated in this work, together with the antimalarial activities.

(14) Schiemann and Pilarsky, *Ber.*, **62**, 3035 (1929).

(15) Ruddy, Starkey and Hartung, THIS JOURNAL, **64**, 828 (1942).

(16) West, *J. Chem. Soc.*, 494 (1925).

(17) Purchased from Chas. Pfizer and Co., Inc.

TABLE II

3,5,6- AND 3,6,7-TRIMETHYLQUINOLINE DERIVATIVES

Compound	Yield, %[a]	Appearance	Solvent[b]	M. p.[c]	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ethyl Trimethyl-4-hydroxyquinoline-2-carboxylates										
3,5,6-Trimethyl	45[d]	Yellowish prisms	aE	183–184	69.48	6.61	5.40	69.74	6.59	5.39
3,6,7-Trimethyl	48[d]	White needles	aE	224–225				69.48	6.67	5.69
Trimethyl-4-hydroxyquinoline-2-carboxylic Acids										
3,5,6-Trimethyl	91	Yellow microcryst.	P	250–251D	67.52	5.66	6.06	67.24	5.81	6.37
3,6,7-Trimethyl	95	White needles	P	263–264D				67.32	5.83	6.01
Trimethyl-4-hydroxyquinolines										
3,5,6-Trimethyl	89	Whitish prisms	E	267–268	76.97	7.00	7.48	76.86	6.94	7.58
3,6,7-Trimethyl	91	Pale yellow needles	aE	>280				76.80	7.25	7.21
Trimethyl-4-chloroquinolines										
3,5,6-Trimethyl	90	White needles	Sk	67–68	70.07	5.88	6.81	70.14	5.64	6.94
3,6,7-Trimethyl	85	Creamy platelets	aE	106–107				70.08	5.73	6.85
Trimethyl-4-(4′-diethylamino-1′-methylbutylamino)-quinolines										
3,5,6-Trimethyl	70	Yellow oil		186–190/0.6[e]	77.06	10.15	12.80	76.88	10.29	13.20
3,6,7-Trimethyl	76	White needles	Sk	79.5–80				77.23	10.45	13.07
Trimethyl-4-(4′-diethylamino-1′-methylbutylamino)-quinoline salts										
3,5,6-Trimethyl B[f]	95	Pale yellow needles	E-I	162–162.5	46.52[g]			46.40[g]	0.05[h]	
3,6,7-Trimethyl M[i]	99	Yellow microcryst.		>300	45.63[g]			42.0[g]	1.80[h]	

[a], [b] and [c] as in Table I. [d] Yields of esters from crude cyclizate, which resulted in 86–92% yield from the azomethine (formed in 80–90% yields). [e] B. p., °C. (mm.). [f] Di-(2-hydroxy-3-naphthoate), formed in alcohol-propanol-2; SN 10988. [g] Per cent. base. [h] Per cent. water. [i] Methane *bis*-1,1′-(2-hydroxy-3-naphthoate), precipitated; SN 10437.

TABLE III

PY-ALKYL-5/7-CHLOROQUINOLINE DERIVATIVES

Compound	Yield, %[a]	Appearance	Solvent[b]	M. p.[c]	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ethyl 5/7-Chloro-4-hydroxy-3-propylquinoline-2-carboxylates										
5-Chloro	45[d,e]	Whitish needles	aE	170.5–171	61.34	5.49	4.77	61.18	5.33	4.80
7-Chloro	50[d,e]	White prisms	aE	218–218.5				61.27	5.46	4.93
5/7-Chloro-4-hydroxy-3-propylquinoline-2-carboxylic Acids										
5-Chloro	96	Yellow needles	Ac	185–185.5D	58.54	4.54	5.25	58.68	4.30	5.59
7-Chloro	94	Creamy white needles	aE	205D				58.60	4.56	5.43
5/7-Chloro-4-hydroxy-py-alkylquinolines										
2-Me-7-Cl	81[d]	Creamy needles	aE	315–316[n]	62.03	4.17	7.24	62.13	4.32	7.44
3-Pr-5-Cl	89	White platelets	aE		65.01	5.46	6.32	65.02	5.40	6.41
3-Pr-7-Cl	93	White prismatic needles	E	276–276.5				65.31	5.91	6.58
4-5/7-Dichloro-py-alkylquinolines										
2-Me-7-Cl	87	White prisms	Sk	103.5–104	56.87	3.34	6.63	56.69	3.60	6.47
3-Pr-5-Cl	88	Colorless liq., $n^{25}D$ 1.6122		116–117(0.4)[f,g]	60.02	4.62	5.83	60.26	4.79	5.72
3-Pr-7-Cl	90	White needles	Sk	52–52.5[h]				60.00	4.53	5.94
5/7-Chloro-4-(4′-diethylamino-1′-methylbutylamino)-py-alkylquinolines										
2-Me-7-Cl	75	Bright yellow oil		206–210(0.8)[f]	68.40	8.46	12.62	68.22	8.94	12.94
3-Pr-5-Cl	63	Golden oil		173–175(0.2)[f]	69.68	8.91	11.61	69.98	8.91	11.79
3-Pr-7-Cl	60	Orange-yellow oil		200–202(0.4)[f]				69.88	8.84	12.09
5/7-Chloro-4-(4′-diethylamino-1′-methylbutylamino)-py-alkylquinoline Salts										
2-Me-7-ClS[i]	71	White needles	aE-I	147.5–149	35.59[k]	3.29[l]		36.02[k]	3.23[l]	
3-Pr-S-Cl P[j]	*ca.* 90	Bright yell. needles	aE	219–220			3.42[m]			3.36[m]
3-Pr-7-Cl P[j]	*ca.* 90	Lemon yell. needles	E	218–219						3.34[m]

[a] to [f] as in Table I. [g] The picrate crystallized (alc.) as yellow needles, m. p. 213.5–214°. *Anal.* Calcd. for $C_{18}H_{14}Cl_2N_4O_7$: N, 11.94. Found: N, 11.80. [h] As [g] m. p. 218.5–219°. Found: N, 12.10. [i] Disulfate monohydrate, SN 7135. [j] Picrate. [k] Sulfuric acid. [l] Water. [m] Basic N (determined by $HClO_4$ titration). [n] Price, *et al.*,[11] give m. p. 313.5–315°.

synthesis left much to be desired, for the first steps were accompanied by many difficulties. Considerable gum formation during the pyrolytic cyclization was responsible for much of the tediousness involved in the separation of isomers by fractional crystallization. Since there was but slight success in use of the method employed with the related 3-methyl type (*cf.* ref. 4c), fractionation was accomplished from alcohol, or, alternating, alcohol and aqueous acetone. The less soluble of the fractions was the 7-chloro isomer, for the bz-chloro-4-hydroxy-3-propylquinoline-2-carboxylic acid produced by its hydrolysis was oxidized to 4-chloroanthranilic acid by alkaline permanganate.[4c] An inadequate amount of the desired 5- and 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-3-propylquinolines was obtained for screening as antimalarials, but all pertinent information relative to them and intermediates required is given in Table III.

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Summary

A group of 4-(4′-diethylamino-1′-methylbutylamino)-quinolines has been prepared, including all possible bz-fluoro-3-methyl derivatives, and also 3,6,5/7-trimethyl, 7-chloro-2-methyl and the 5/7-chloro-3-propyl types.

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[CONTRIBUTION FROM THE GEORGE WILLIAMS HOOPER FOUNDATION, UNIVERSITY OF CALIFORNIA, AND THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Paralytic Shellfish Poison. I. Occurrence and Concentration by Ion Exchange[1,2,3]

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The paralytic form of shellfish poisoning in man has been recognized for over a century as a clinical entity.[4] Shellfish become poisonous when they feed on the marine plankton organism, *Gonyaulax catenella* Whedon and Kofoid. This was established by Sommer and co-workers,[5] who showed: (1) that in the three-year period studied, there was a close correlation between the toxicity of shellfish and the number of *Gonyaulax catenella* per liter present in sea water; (2) that non-toxic bivalves kept in the laboratory became toxic when supplied with fresh sea water rich in this dinoflagellate; and (3) that the poison could be obtained directly from this plankton organism.

The California mussel, *Mytilus californianus* Conrad, has proved to be a better source of the poison, on a scale sufficient for chemical study, than the dinoflagellate. It has been estimated that the average mussel filters 38 liters of sea water a day to obtain its food supply of plankton.[5] Extensive beds of these mussels are found along the rocky Pacific coast of North America. From April to November selected beds along the coast 150 miles north and south of San Francisco were sampled semimonthly and the poison titer of the mussels determined. A large-scale collection was made when the poison content reached or exceeded 4000 MU. per 100-g. mussel.[6]

Daily collections can be made only during the last four or five days of the minus tide period, which occurs every two weeks with the new or full moon. Usually there is only one such period in the entire season during which the mussels are sufficiently toxic to warrant collection. In summer the lower low tide is at daybreak or shortly afterward. In the two-hour period when the beds were accessible, the mussels were pried loose from the rocks and carried up on the beach above tidewater. There they were sorted, washed and opened.[7] The "livers" or digestive glands were dissected out and preserved in acidified ethanol.

In the three-year period, 1944–46, a total of 4360 kg. of mussels containing 160 × 10^6 MU of poison was collected. The extraction of one of the many collections is shown in Table I. This collection was made south of Pedro Point, San Mateo County, California, on July 18, 1946.

(1) The work described in this paper was initiated under a contract between the Federal Security Agency and the University of California and Northwestern University. It was continued under a contract with the Chemical Corps, Camp Detrick, Frederick, Maryland.

(2) Since the mass poisoning in the San Francisco area in 1927, Dr. Karl F. Meyer, Director of the George Williams Hooper Foundation for Medical Research, University of California, has sponsored research on shellfish poison. He was responsible for renewed interest in the problem in 1944, when the contracts for further research in this field were made. The members of the Northwestern group are greatly indebted to Dr. Meyer for making the facilities of the Foundation available to them each summer during the collection period.

(3) The authors wish to thank Dorothy Butler, Ardath Clark Van Tuyl, Patricia Garbutt, Esther Kline and Ruth Nell for their technical assistance.

(4) (a) K. F. Meyer, H. Sommer and P. Schoenholz, *J. Preventive Med.*, **2**, 365 (1928); (b) H. Sommer and K. F. Meyer, *Arch. Path.*, **24**, 560 (1937).

(5) H. Sommer, W. F. Whedon, C. A. Kofoid and R. Stohler, *Arch. Path.*, **24**, 537 (1937).

(6) The mouse unit (MU.), or average lethal dose, is defined as the amount of mussel poison contained in 1.0 ml. of aqueous solution that, injected intraperitoneally into a 20-g. white mouse, will cause death in fifteen minutes. Directions for carrying out this bioassay, together with the tables for calculating the number of MU in the test solution from the weight of the mouse and the dying time, were furnished by H. Sommer to the other workers in this field. These tables are based on graphs[4b] recorded in the literature.

(7) Many of the people in the collecting party were members of the Hooper Foundation who volunteered their services. The authors are especially indebted to Lucile Foster, Florence Hockin, Vera Kreekis, Adelien Larson, Alma McDole, Ethel Meyer, Edward Sherry, Susanne Sommer and Richard Sommer.