mixed melting point with fluorenone-hydrazone prepared by the interaction of fluorenone and hydrazine was unchanged; hydrochloride, deep yellow crystals melting at 268° (dec.).

Reaction of 9-Chlorofluorene with Piperidine.—Colorless needles were deposited from a solution of 0.5 g. of 9-chlorofluorene in 5 cc. of piperidine kept at room temperature for a few hours. The product, 9-(N-piperidino)-fluorene, was recrystallized from ethyl alcohol and melted at 99°.

Anal. Calcd. for $C_{18}H_{19}N$: C, 86.69; H, 7.69. Found: C, 87.25; H, 8.04.

Summary

The reaction of 9-chlorofluorene in liquid ammonia at room temperature has been shown to produce dibiphenylene-ethylene, fluorene, fluorylidene-imine and a trace of 9-aminofluorene. In the presence of toluene there was also formed 1-aminodibiphenylene-ethane, the yield of which was increased significantly by supplementing the ammonia–toluene mixture with 9-aminofluorene. The complexity of the reaction can be accounted for by the presence of two labile substituents, namely hydrogen and chlorine, in the 9 position of the fluorene ring.

9-Bromofluorene in ammonia behaved essentially like the chloro analog. Of chief interest in a comparison of the dyiels of the products from the two halogen derivatives was the appreciably higher yield of 9-aminofluorene from 9-bromofluorene.

In confirmation of the view that intermolecular condensation plays an important part in these reactions, it was found that 9-chlorofluorene in liquid ammonia with 9-dimethylaminofluorene and 9-carbethoxyfluorene yielded 1-dimethylaminodibiphenylene-ethane and 1-carbethoxydibiphenylene-ethane, respectively. Reaction of 9-chloro-9-phenylfluorene with 9-aminofluorene in ammonia gave 9-phenylfluorene and fluorylideneimine.

9-Chlorofluorene with hydrazine formed fluorenone-hydrazone, and with piperidine, 9-(N-piperidino)-fluorene.

BELTSVILLE, MARYLAND RECEIVED[13] DECEMBER 12, 1945

(13) Original manuscript received June 30, 1939.

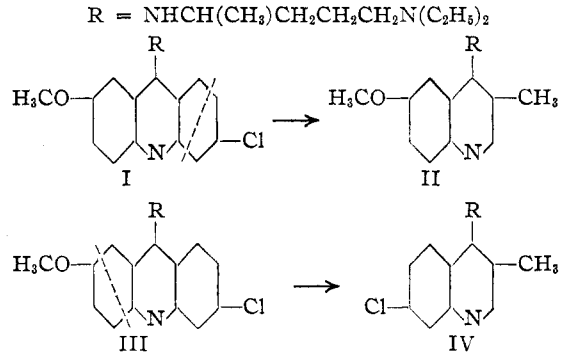
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

Quinolines. III. The Synthesis of 5- and 7-Chloro- and Bromo-3-methyl-4-dialkylaminoalkylaminoquinolines

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

The investigations on compounds derived from 4-aminoquinoline as antimalarials have been reported in few detailed papers,[1,2,3,4] the greater number being mentioned in the patent literature.[5,6] Compounds containing a methyl group in position 3 have been the subject of detailed investigation in these laboratories[7,8] to determine their merits as schizontocides. The present paper deals with the details of preparation of certain 5- and 7-halo-3-methyl-4-dialkylaminoalkylaminoquinolines. Data relative to the screening and clinical testing of these compounds will be published elsewhere.

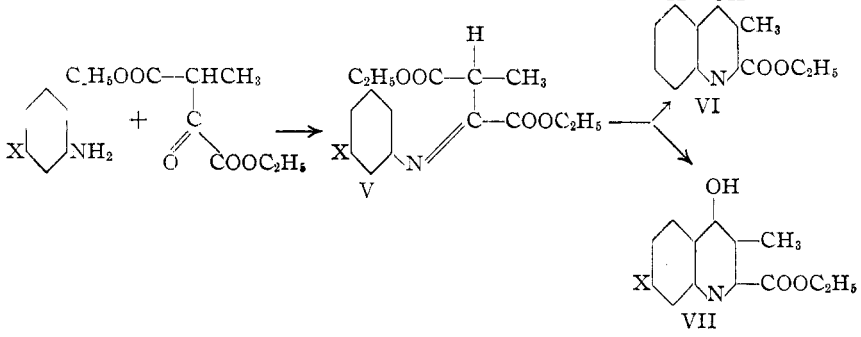
A relationship may be considered to exist between quinacrine and certain quinolines, as indicated by Gilman and Spatz[3] in their studies of "open models" of the acridine derivative. In these types, one of the benzenoid nuclei has been sheared from its attachment to the quinoline moiety of the acridine. The 6a and 7-substituted compounds of the 3-methyl type might also be visualized as products resulting from a scission of one or the other of the benzenoid cycles of the acridine as indicated (I to II and III to IV).



The preparation of the 7-substituted quinolines of the desired type was accomplished by application of the Conrad–Limpach[9,10] synthesis to *m*-chloro- and *m*-bromoaniline. As shown in the equations below, the cyclization of ethyl α-(*m*-substituted-phenylimino)-β-methylsuccinates (V) can theoretically give rise to both 5- and 7-substituted quinolines (VI and VII). That such behavior was encountered was indicated by the unsharp melting point of the cyclization product and by the ultimate isolation and proof of structure of two compounds from each *m*-haloaniline. Each

(1) Magidson and Rubtsov, *J. Gen. Chem., U.S.S.R.*, **7**, 1896 (1937).
(2) Holcomb and Hamilton, THIS JOURNAL, **64**, 1310 (1942).
(3) Gilman and Spatz, *ibid.*, **66**, 621 (1944).
(4) Van Arendonk and Shonle, *ibid.*, **66**, 1284 (1944).
(5) Andersag, Breitner and Jung, U. S. Patent 2,233,970; *C. A.*, **35**, 3771[7] (1941).
(6) Andersag, Breitner and Jung, German Patent 683,692; *C. A.*, **36**, 4973[8] (1942).
(7) Steck, Hallock and Holland, THIS JOURNAL, **68**, 129 (1946).
(8) Steck, Hallock and Holland, *ibid.*, **68**, 132 (1946).
(9) Conrad and Limpach, *Ber.*, **20**, 944 (1887).
(10) Limpach, *ibid.*, **64**, 969 (1931).

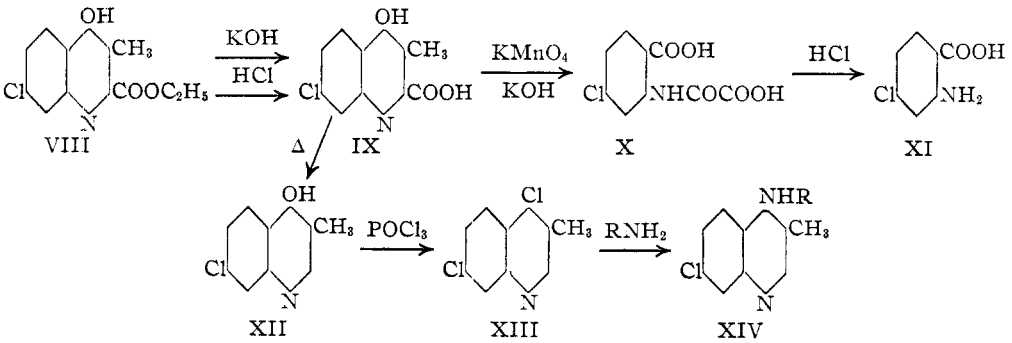
of the two series was carried through the usual reactions to obtain the 4-chloroquinoline type for later conversion to a dialkylaminoalkylamino derivative.



The separation of the isomeric quinoline esters (VI and VII) was first accomplished by fractional crystallization from alcohol or acetone, but the process was tedious. A better procedure was found to be the formation of the hydrochlorides in glacial acetic acid and the use of the widely differing solubilities at 35–40° for the separation. The bases were then re-formed by treatment with sodium acetate. It was rather surprising to find that approximately equal amounts of the isomers were obtained from both *m*-chloro and *m*-bromoaniline (*cf.* refs. 11–16).

The formation of isomeric quinolines (VI and VII) from the cyclization of the azomethine, V, necessitated proof of the structures of the two series for both the chloro and bromo types. A number of degradation procedures have been devised for the elucidation of the structures of alkaloids.[17] Of these, several seemed applicable to this investigation, but the use of oxidative means seemed to be the most direct method. There have been a number of studies on the oxidation of quinolines[18] and these indicate that the cleavage of the pyridine moiety occurs with some ease in alkaline permanganate solutions; several of these[19–24] have been carried out on compounds more or less similar to those prepared in this work. The oxidation[22] of 4-hydroxyquinoline and of 4-hydroxyquinoline-2-carboxylic acid both led to the formation of 2-carboxyphenyloxamic acid. It seemed desirable to oxidize our compounds at either of these stages in the synthesis despite the fact that 3-methylquinoline did not oxidize appreciably on treatment with potassium permanganate.[23]

It was fortunate that the 3-methyl group in the present series of quinolines had no great influence upon the course of the oxidations by aqueous alkaline permanganate solution. The oxidation of the acid (IX) obtained from the high-melting ester from the chloro series (VIII, m. p. 229.5–230°) led to a mixture of products, from which 4-chloroanthranilic acid (XI) was isolated after hydrolysis (presumably of X) with hydrochloric acid. This demonstrated that the high-melting ester (VIII) was ethyl 3-methyl-4-hydroxy-7-chloroquinoline-2-carboxylate. Both isomeric 5- and 7-chloro compounds were converted to the 4-dialkylaminoalkylamino derivatives as shown for the 7-chloro isomer.



The oxidation of the bromo-3-methyl-4-hydroxyquinoline derived from the high-melting ester (m. p. 227–228°) was carried out essentially as described for IX and the product isolated was 4-bromoanthranilic acid. As in the chloro series, the higher melting ester was the one substituted in position 7, as demonstrated by the product of the oxidation. Each of the isomeric bromo compounds was subjected to the usual series of re-

(11) La Coste and Bodewig, *Ber.*, **18**, 2940 (1885).
(12) Fourneau, *et al.*, *Bull. soc. chim.*, (4) **47**, 748 (1930).
(13) Untermohlen, *J. Org. Chem.*, **8**, 546 (1943).
(14) Claus and Tournier, *Ber.*, **20**, 2879 (1887).
(15) Bartow and McCollum, THIS JOURNAL, **26**, 703 (1904).
(16) Moudgill, *ibid.*, **43**, 2257 (1921).
(17) *Cf.* Small, "Alkaloids," in Gilman, "Organic Chemistry," John Wiley and Sons, New York, N. Y., 1943.
(18) von Miller, *Ber.*, **23**, 2252 (1890); **24**, 1900 (1891).
(19) La Coste and Bodewig, *ibid.*, **18**, 429 (1885).
(20) Einhorn and Lauch, *Ann.*, **243**, 356 (1887).
(21) Friedländer and Ostermaier, *Ber.*, **14**, 1920 (1881); **15**, 332 (1882).
(22) Kretschy, *Monatsh.*, **4**, 157 (1883); **5**, 16 (1884).
(23) Doebner and von Miller, *Ber.*, **18**, 1645 (1885); von Miller and Brunner, *ibid.*, **24**, 192 (1891).
(24) Conrad and Limpach, *ibid.*, **20**, 951 (1887).

actions, which resulted in the formation of the 3-methyl-4-(1′-methyl-4′-diethylamino-butylamino)-5 or 7-bromoquinolines (*cf.* VIII to XIV).

3-Methyl-4,7-dichloroquinoline (XIII) was caused to react with 1-methyl-4-diethylaminobutylamine (XV), with 4-diethylaminobutylamine (XVI) and with 2-hydroxy-3-diethylaminopropylamine (XVII). The isomeric 3-methyl-4,5-dichloroquinoline was interacted with (XV) and with (XVI), but the 5- and 7-bromo-3-methyl-4-chloroquinolines were merely converted into the 4-(1′-methyl-4′-diethylaminobutylamino) derivatives by reaction with XV. 3-Methyl-4-(1′-methyl-4′-diethylaminobutylamino)-7-chloroquinoline has been claimed specifically in patents[5,6] relating to the synthesis of a number of quinoline derivatives.

Experimental

m-**Chloroaniline.**—The commercial sample of the amine was redistilled, b. p. 98–100° (9 mm.), $n^{20}D$ 1.5942.

m-**Bromoaniline.**[25]—*m*-Bromonitrobenzene was prepared from nitrobenzene[26] in yields of 84–86%, then reduced with iron powder in the presence of a small quantity of hydrochloric acid[27–29] rather than with tin and hydrochloric acid.[30] The yield of *m*-bromoaniline (b. p. 77–80° (0.5 mm.), m. p. 18°) was 67%.

Ethyl Ethoxalylpropionate.—This ester was prepared as described previously.[7]

1-Methyl-4-diethylaminobutylamine (XV).—A commercial sample of the amine was redistilled b. p. 71–72° (6 mm.), $n^{25}D$ 1.4415.

4-Diethylaminobutylamine (XVI).—The amine was prepared from ethyl cyanoacetate in the manner described by Huber, *et al.*,[31] b. p. 74–76° (9 mm.), $n^{25}D$ 1.4433.

2-Hydroxy-3-diethylaminopropylamine (XVII).—Redistillation of a commercial sample of the base gave a product boiling at 78–79° (3 mm.), $n^{25}D$ 1.4580.

Ethyl 5- and 7-Halo-3-methyl-4-hydroxyquinoline-2-carboxylates.—The condensation of *m*-chloro and *m*-bromoaniline with ethyl ethoxalylpropionate was carried out as described before.[7] There was no particular difference in the yields (78–88%) of azomethine obtained when no solvent, or methylene chloride or glacial acetic acid was employed.

The cyclization of the azomethines in medicinal grade mineral oil[7] was accomplished with little difficulty, and the resulting isomer-mixtures were easily freed of oil (*cf.* ref. 8). In both the chloro and bromo series, the yields were excellent, varying from 90–97%. The crude mixture of 5- and 7-chloro compounds melted *ca.* 186–195° and the mixture of bromo melted *ca.* 180–190°.

Separation of Isomeric Chloro and Bromo Compounds.—One hundred grams of crude isomer mixture was dissolved in 400 cc. warm glacial acetic acid, the solution cooled to 40° and then dry hydrogen chloride was added until there was no further rise in temperature. The solution was cooled to 35–40°, the crystals (A) were collected and washed with glacial acetic acid. The combined filtrates (B) were retained. Isolation of the 7-halo isomer (VII) from the hydrochloride (A) was accomplished by suspending it in 500 cc. of water and adding sodium acetate until the mixture was neutral to congo red. This isomer (A) when collected and dried comprised 47–53% of the total product.

The combined filtrates (B) were poured into ten times their volume of water and then sodium acetate added to congo red neutrality. The solid thus obtained was collected and dried; this was the 5-halo isomer (VI) which resulted in yields of *ca.* 45% (from the mixture).

After the separation as outlined, the isomer (A) from the chloro series melted at 222–225° and (B) at 218–220°. The bromo series isomer (A) melted at 221–224° while the isomer (B) melted at 211–215°. Each of the fractions was ordinarily recrystallized before further use, but there was no difficulty in obtaining one pure 4-chloro compound (*e. g.*, XIII) when the unpurified isomer was used.

Proof of Structure of Chloro Series.—Twenty-two and eight-tenths grams (0.086 mole) of pure ethyl 3-methyl-4-hydroxy-7-chloroquinoline-2-carboxylate ((VIII) isomer A from chloro series) was hydrolyzed by refluxing for two hours with a mixture of 30 cc. of 35% potassium hydroxide and 185 cc. of water. At the end of the hydrolysis (to IX), the solution was diluted with 1100 cc. of water and warmed to 75°. A solution of potassium permanganate (65 g. in 1200 cc. of water, warmed to 75°) was then added, with stirring, during half an hour. The mixture was treated with Filter-cel and Darco S-51, filtered hot and the solid washed well with hot water. The combined filtrates were concentrated to *ca.* 200 cc. and cooled; the solid was collected, refluxed with 100 cc. of 6 *N* hydrochloric acid for two and half hours and then filtered while hot. The filtrates were neutralized with sodium hydroxide, chilled, and the resulting solid crystallized twice from 50% alcohol after Darco treatment to give a yield of 3.2 g. of pale brown needles, m. p. 236–237°. 4-Chloroanthranilic acid (XI) has been reported[32] to crystallize in the form of brown needles, m. p. 235–236°, while the isomeric 6-chloro compound (which would have been produced from a 5-chloroquinoline) has the m. p. 146–147°.[32a]

Anal. Calcd. for $C_7H_6O_2NCl$: C, 48.99; H, 3.52. Found: C, 48.07; H, 3.32.

The **acetyl derivative** was prepared in the usual manner and crystallized from dilute alcohol, light tan needles, m. p. 214° (literature[32] gives m. p. 214° and 210°).

Anal. Calcd. for $C_9H_8O_3NCl$: N, 6.56. Found: N, 6.78.

Proof of Structure of Bromo Series.—Sixteen grams (0.067 mole) of pure 3-methyl-4-hydroxy-7-bromoquinoline (from isomer A of the bromo series) was dissolved, with some difficulty, in a solution of 14 g. of potassium hydroxide in 1200 cc. of water and warmed to 80°. To the stirred solution was added (during *ca.* thirty minutes) a solution of 50 g. of potassium permanganate in one liter of water at 80°, and the reaction-mixture treated as described for the chloro series (v.s.). The tan needles (2.6 g.) obtained after two crystallizations from dilute alcohol melted at 219–219.5°; the melting point of 4-bromo-anthranilic acid has been given[33] as 222°, while the 6-bromo isomer had the melting point 136°.[34]

Anal. Calcd. for $C_7H_6O_2NBr$: N, 6.48. Found: N, 6.40.

The **acetyl derivative,** prepared in the usual fashion, crystallized from dilute alcohol in the form of creamy white needles, m. p. 220–221° (literature[34] gives m. p. 217°).

Anal. Calcd. for $C_9H_8O_3NBr$: N, 5.43. Found: N, 5.22.

3-Methyl-4-dialkylaminoalkylamino-5 or 7-haloquinolines.—The 5- or 7-halo-3-methyl-4-dialkylaminoquinolines were prepared from the above described isomers by the procedure previously outlined.[7] The yields and other data are listed in Table I.

Acknowledgment.—The authors with to express their sincere appreciation for the valuable advice given by Drs. C. M. Suter and J. S. Buck

(25) This preparation was carried out by Drs. N. F. Albertson and R. O. Clinton of this Laboratory.

(26) Johnson and Gauerke, "Organic Syntheses," Coll. Vol. I, 2nd. ed., John Wiley and Sons, New York, N. Y., 1941, p. 123.

(27) Mahood and Schaffner, *ibid.*, Coll. Vol. II, p. 160.

(28) Steele and Adams, THIS JOURNAL, **52**, 4531 (1930).

(29) Fierz-David, *Helv. Chim. Acta*, **20**, 1028 (1937).

(30) Natelson and Gottfried, THIS JOURNAL, **61**, 1001 (1939).

(31) Huber, Clinton, Boehme and Jackman, *ibid.*, **67**, 1618 (1945).

(32) (a) Cohn, *Monatsh.*, **22**, 485 (1901); (b) Spring and Woods, *J. Chem. Soc.*, 627 (1945).

(33) Claus and Scheulen, *J. prakt. Chem.*, (2) **43**, 206 (1891).

(34) Friedländer, *et al.*, *Ann.*, **388**, 31 (1912).

TABLE I

5- AND 7-CHLORO- OR BROMO-3-METHYLQUINOLINE DERIVATIVES

Compound	Yield, %	Appearance	Solvent[a]	M. p.,[b] °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ethyl 3-Methyl-4-hydroxyquinoline-2-carboxylates										
5-Chloro	47[c]	Fine white needles	A	220–220.5	58.76	4.55	5.27	58.80	4.74	5.60
7-Chloro	50	White needles	A	229.5–230				59.00	4.65	5.67
5-Bromo	45	Creamy white needles	aE	219.5–220	50.34	3.90	4.52	50.67	4.12	4.68
7-Bromo	53	White needles	E	228–228.5				50.15	3.98	4.57
3-Methyl-4-hydroxyquinoline-2-carboxylic Acids										
5-Chloro	96	Creamy white needles	P	245 d.	55.59	3.47	5.89	55.97	3.63	5.98
7-Chloro	98	White needles	P	268 d.				55.72	3.73	6.01
5-Bromo	99	White needles	P	>285	46.83	2.86	4.97	46.93	3.19	5.22
7-Bromo	96	Yellowish-white needles	P	>300				47.15	3.03	5.27
3-Methyl-4-hydroxyquinolines										
5-Chloro	96	Creamy white needles	aE	>250	62.02	4.16	7.24	61.96	4.28	7.34
7-Chloro	98	White prismatic needles	aE	>300				62.29	4.20	7.42
5-Bromo	97	White needles	aE	>300	50.44	3.39	5.88	50.95	3.56	5.90
7-Bromo	98	White needles	224	>300				50.60	3.89	5.86
3-Methyl-4-chloroquinolines										
5-Chloro	89	White platelets	aE	71.5–72	56.87	3.34	6.63	57.12	3.52	6.85
7-Chloro	95	White prismatic needles	aAc	87.5–88[d]				57.02	3.48	6.96
5-Bromo	92	White prismatic needles	aE	100–100.5	46.81	2.75	5.46	47.04	3.04	5.59
7-Bromo	96	White prismatic needles	aE	105–105.5				47.10	2.93	5.62

3-Methyl-4-dialkylaminoalkylaminoquinolines

Nucleus	Side chain[e]	Yield, %	Appearance	B. p., °C. (mm.)[f]	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
5-Chloro	XV	78	Golden oil	190–193 (0.5)	68.40	8.46	12.62	68.22	8.29	12.80
	XVI	82	Lemon-yellow oil	185–190 (0.5)	67.41	8.18	13.13	67.88	8.13	13.34
7-Chloro	XV	88	Bright yellow oil	190–194 (0.5)[g]	68.40	8.46	12.62	68.18	8.06	12.96
	XVI	84	Golden oil	180–184 (0.4)	67.41	8.18	13.13	67.33	8.44	13.40
	XVII	81	Golden oil	185–188 (0.6)	63.44	7.52	13.06	63.53	7.87	13.28
5-Bromo	XV	86	Lemon-yellow oil	204–206 (0.6)	60.31	7.46	11.11	59.93	7.66	11.48
7-Bromo	XV	80	Golden oil	210–215 (1.0)[h]				60.89	7.69	11.30

[a] A = acetic acid, Ac = acetone, E = ethanol, P = propylene glycol, 224 = 2-methyl pentanediol-2,4, a = aqueous. [b] Corrected; d. = decomposes. [c] Yields of the isomeric esters are those as obtained on isomer separation. [d] Reported (ref. 5) m. p. 87°. [e] The numbers given to side chains refer to those listed in discussion. [f] Uncorrected. [g] Reported (ref. 5) b. p. 220–230° (0.5 mm.). [h] Reported (ref. 5) b. p. 230° (0.5 mm.).

during the course of this investigation. The capable technical assistance of Miss N. K. Peck and Mrs. E. J. Altier, as well as the microanalytical determinations by the Misses P. Curran and A. Rainey, was also of importance in these researches.

Summary

Several 3-methyl-4-dialkylaminoalkylaminoquinolines have been prepared in which position 5 or 7 was substituted by chlorine or bromine. These were obtained by application of the Conrad and Limpach synthesis to the *m*-haloanilines. The isomers formed were separated by employing glacial acetic acid in the crystallization of the hydrochlorides.

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