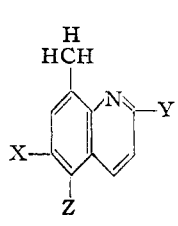
[CONTRIBUTION FROM THE ROSS CHEMICAL LABORATORY, ALABAMA POLYTECHNIC INSTITUTE]

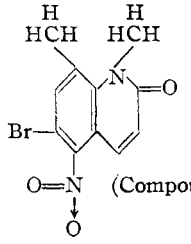
Some Derivatives of 6-Bromo-8-methylquinoline and 6-Chloro-8-methylquinoline[1]

BY THURMAN A. IRVING, JOSEPH L. GREENE, JR., JOE G. PETERSON AND JULIUS D. CAPPS

Results of previous work in this Laboratory concerning 8-bromo-6-methylquinoline[2] and some of its derivatives prompted this investigation of 6-bromo-8-methylquinoline and 6-chloro-8-methylquinoline. Adaptations of methods and procedures employed in the 8-bromo-6-methylquinoline study proved to be generally satisfactory for synthesizing compounds I through XXXVI.

TABLE I





(Compound XXXVI)

When X = Br compound	Y =	Z =	When X = Cl compound
I	H	NO_2	II
III	H	NH_2	IV
V	H	CH_3CONH–	VI
VII	H	C_6H_5CONH–	VIII
IX	H	AsO_3H_2	X
XI	Cl	NO_2	XII
XIII	Cl	NH_2	XIV
XV	Cl	CH_3CONH–	XVI
XVII	Cl	C_6H_5CONH–	XVIII
XIX	Cl	AsO_3H_2	XX
XXI	OH	NO_2	XXII
XXIII	OH	NH_2	XXIV
XXV	OH	CH_3CONH–	XXVI
XXVII	OH	C_6H_5CONH–	XXVIII
XXIX	OH	AsO_3H_2	XXX
XXXI	Cl	H	XXXII
XXXIII	OH	H	XXXIV

2-Acetamido-5-chloro-4-nitrotoluene = compound XXXV.

Experimental

6-Bromo-8-methylquinoline[3] and 6-Chloro-8-methylquinoline.[4]—2-Acetamido-5-halotoluenes or the corresponding free amines gave the necessary 6-halo-8-methylquinolines when subjected to Skraup ring-closures. 6-Chloro-8-methylquinoline picrate melted at 223–224°.

Anal. Calcd. for $C_{16}H_{11}ClN_4O_7$: N, 13.78. Found: N, 13.95.

6-Halo-8-methyl-5-nitroquinolines.—2-Amino-5-bromotoluene and 2-amino-5-chlorotoluene were nitrated with solutions of sodium nitrate in sulfuric acid according to procedure used by deArce, Greene and Capps[2] for nitration of 4-amino-3-bromotoluene. Ammonia water was employed to neutralize decomposed nitration mixtures prior to separating crude nitro compounds and recrystallizing them from hot 95% ethanol; 2-amino-5-bromo-4-nitrotoluene[5] m. p. 119–120°; 2-amino-5-chloro-4-nitrotoluene[6] m. p. 127–28°.

2-Amino-5-bromo-4-nitrotoluene and 2-amino-5-chloro-4-nitrotoluene were converted with acetic anhydride into 2-acetamido-5-bromo-4-nitrotoluene (m. p. 153–154°) and 2-acetamido-5-chloro-4-nitrotoluene[7] (yield 94%; m. p. 142–143°).

Anal. Calcd. for $C_9H_9ClN_2O_3$: Cl, 15.51; N, 12.26. Found: Cl, 15.51; N, 12.25.

The structure of 2-acetamido-5-bromo-4-nitrotoluene as produced was confirmed by removing the acetamido group, reducing the resulting 3-bromo-4-nitrotoluene to 4-amino-3-bromotoluene and acetylating. Reduction of our 2-amino-5-chloro-4-nitrotoluene gave 2,4-diamino-5-chlorotoluene that melted at 124–125° and formed 2,4-diacetamido-5-chlorotoluene melting at 266–267°; Reverdin and Crepieux[7] reported melting points of 123° and above 250°, respectively, for diamino and diacetamido compounds with these assigned structures.

Skraup ring-closures on 2-acetamido-5-bromo-4-nitrotoluene (8.0 g.) and 2-acetamido-5-chloro-4-nitrotoluene (11 g.) gave I (1.9 g. after recrystallization from 95% ethanol; m. p. 117–118°) and II (9.3% after recrystallization from 95% ethanol; m. p. 99–100°).

Anal. Calcd. for $C_{10}H_7BrN_2O_2$: N, 10.49. Found: N, 10.42. Calcd. for $C_{10}H_7ClN_2O_2$: N, 12.59. Found: N, 12.60.

2,6-Dihalo-8-methylquinolines.—6-Bromo-8-methylquinoline (18.7 g.) and 6-chloro-8-methylquinoline (25.0 g.) were converted into crude 6-bromo-1,8-dimethyl-2-quinolone (16.0 g.; 76% yield, m. p. 76–81°) and 6-chloro-1,8-dimethyl-2-quinolone (22.0 g., 75% yield, m. p. 64–65° on vacuum sublimed sample) by procedure employed by de Arce, Greene and Capps[2] for synthesis of 8-bromo-1,6-dimethyl-2-quinolone. Subjection of the crude quinolones to action of phosphorus oxychloride–phosphorus pentachloride mixture according to directions of de Arce, Greene and Capps[2] for making 8-bromo-2-chloro-6-methyl-5-nitroquinoline gave XXXI (76% yield recrystallized from hot 95% ethanol; m. p. 120–121°) and XXXII (78% yield recrystallized from hot 95% ethanol, m. p. 121–122°).

Anal. Calcd. for $C_{10}H_7ClBrN$: N, 5.46. Found: N, 5.28. Calcd. for $C_{10}H_7Cl_2N$: N, 6.61. Found: N, 6.60.

6-Halo-2-hydroxy-8-methylquinolines.—XXXI (2.0 g.) and XXXII (10.0 g.) were suspended in 25% by volume sulfuric acid (sp. gr. 1.84)–water solution prior to maintaining at 175–180° in a sealed autoclave for two hours. When the system had cooled to 25° in each case, the resulting solids were removed by filtration and washed with water. Re-solution of crude XXXIII in boiling glacial acetic acid followed by decolorizing carbon and Hyflo Super-Cel treatments gave colorless needles (1.5 g. or 84%); m. p. 280–281°. XXXIV was obtained from hot 95% ethanol in 9.1 g. yield, m. p. 265–166°.

(1) Condensed from portions of theses presented by Thurman A. Irving, Joseph L. Green, Jr., and Joe G. Peterson to the Graduate School of the Alabama Polytechnic Institute in partial fulfillment of the requirements for the degree of Master of Science. Presented in part before Southeastern Regional meeting of the American Chemical Society, Oak Ridge, Tennessee, June 10, 1949.

(2) H. D. de Arce, J. L. Greene, Jr., and J. D. Capps, THIS JOURNAL, **72**, 2971 (1950).

(3) H. Alt, *Ann.*, **252**, 322 (1889).

(4) T. Mazonski, T. Mielecki and E. Sucharda, *Roczniki Chemii*, **16**, 519 (1936).

(5) See also G. T. Morgan and A. Clayton, *J. Chem. Soc.*, **87**, 949 (1905).

(6) See also A. Claus and Stapelberg, *Ann.*, **274**, 285 (1893).

(7) F. Reverdin and P. Crepieux report m. p. 262° for 2-acetamido-5-chloro-4-nitrotoluene, *Ber.*, **33**, 2505 (1900).

Anal. Calcd. for $C_{10}H_8BrNO$: N, 5.88. Found: N, 6.06 Calcd. for $C_{10}H_8ClNO$: N, 7.24. Found: N, 7.28.

6-Halo-1,8-dimethyl-5-nitro-2-quinolones.—I (25 g.) was converted into the corresponding dimethyl sulfate-addition product and oxidized with 30% hydrogen peroxide according to modifications of conditions previously employed by Capps[8] for changing 6-methyl-8-nitroquinoline into 1,6-dimethyl-8-nitro-2-quinolone. The quantity of dimethyl sulfate was reduced to 20 ml. and the oil-bath was maintained at 150–170° for first hour followed by a reduction to 145° for an additional 1.5 hours. The temperature range during addition of peroxide was 55–65°. A small amount of XXXVI was crystallized from warm (not over 60°) glacial acetic acid for analysis; yield of crude quinolone 17.8 g. (65%); m. p. purified quinolone 158–159° dried 25° and 35 mm.

Anal. Calcd. for $C_{11}H_9BrN_2O_3$: N, 9.43. Found: N, 9.60.

II (23 g.) was converted into crude 6-chloro-1,8-dimethyl-5-nitro-2-quinolone (15 g., 57%) under essentially same conditions as referred to above for changing 6-halo-8-methylquinolines into crude 6-halo-1,8-dimethyl-2-quinolones; m. p. 121–122° dec. for crude.

2,6-Dihalo-8-methyl-5-nitroquinolines.—XXXVI (17.8 g.) and crude 6-chloro-1,8-dimethyl-5-nitro-2-quinolone (10.0 g.) were changed respectively into XI (12.5 g., 69%, m. p. 160–161°) and XII (7.4 g., 73%, m. p. 137–138°) in a similar manner to that used for changing 6-halo-1,8-dimethyl-2-quinolones into 2,6-dihalo-8-methylquinolines. While forming XI the oil-bath was kept at 140–150° for 1.75 hours, and glacial acetic acid was used as recrystallizing solvent; the oil-bath was kept at 130–135° for 3.5 hours in case of XII formation and recrystallization was from hot 95% ethanol.

Anal. Calcd. for $C_{10}H_6ClBr_2N_3O_2$: N, 9.29. Found: N, 9.21. Calcd. for $C_{10}H_6Cl_2N_2O_2$: Cl, 27.59. Found: Cl, 27.25.

6-Halo-2-hydroxy-8-methyl-5-nitroquinolines.—XI (8.0 g.) and XII (10.0 g.) gave XXI (6.5 g., 87%, m. p. 311–312°) and XXII (9.2 g., m. p. 271–272°) under conditions similar to those used by de Arce, Greene and Capps[2] for hydrolyzing 8-bromo-2-chloro-6-methyl-5-nitroquinoline except that 200 ml. of 50% by volume sulfuric acid–water solution was employed and recrystallization was from boiling glacial acetic acid.

Anal. Calcd. for $C_{10}H_7BrN_2O_3$: N, 9.90. Found: N, 10.08. Calcd. for $C_{10}H_7ClN_2O_3$: N, 11.74. Found: N, 11.88.

Nitration of 6-Halo-8-methylquinolines, XXXI, XXXII, XXXIII, and XXXIV.—Each of these substances was nitrated under conditions similar to those employed by de Arce, Greene and Capps[2] for the nitration of 8-bromo-6-methylquinoline. 6-Bromo-8-methylquinoline (100 g.) and 6-chloro-8-methylquinoline (30 g.) gave I (98 g., 82% yield) and II (31.8 g., 85%), respectively. XXXI (6.4 g.) and XXXII (25 g.) gave XI (6.3 g., 84% and XII (29 g., 95% yield). XXII (12 g., 97% yield) resulted from XXXIV (10 g.), while a compound melting at 271–272° was obtained from XXXIII as compared with 311–312° for melting point of XXI.

5-Amino-6-halo-8-methylquinolines.—I (10.0 g.), II (25.0 g.), XI (10.0 g.), XII (10.0 g.), XXI (17.0 g.), and XXII (10.0 g.) were reduced with hydrogen in presence of Raney nickel catalyst; reagent grade acetone was employed as the solvent for all of the nitro compounds except XXI, absolute ethanol being used for it. Pressures of 40 pounds per square inch at 50° served for the reduction of I, II and XII; while 500 p. s. i. at 80°, 300 p. s. i. at 80°, and 100 p. s. i. at 80° was resorted to for the reduction of XI, XXI, and XXII, respectively. III (6.5 g., 73%, m. p. 116–117°) and XIII (6.0 g., m. p. 127–128°) were isolated *via* the hydrochlorides according to procedure reported by de Arce, Greene and Capps[2] for 5-amino-8-bromo-6-methylquinoline before recrystallizing from 50:50 by volume ethanol–water. XXIII (13.5 g., 89%, m. p. 238–239°) precipitated from the absolute ethanol upon addition of water and was recrystallized from 95% ethanol. The method employed by Capps[8] for recovery of 8-amino-7-methylquinoline was used for recovery of IV (20 g., 92%, m. p. 113–114°) and XIV (8.5 g., 96%, m. p. 132–133°), while the method employed by Capps[8] for recovery of 5-amino-2-hydroxy-6-methylquinoline was used for the isolation of XXII (8.5 g., 97%, m. p. 276–277°).

Anal. Calcd. for $C_{10}H_9BrN_2$: N, 11.82. Found: N, 11.72. Calcd. for $C_{10}H_9ClN_2$: N, 14.55. Found: N, 14.57. Calcd. for $C_{10}H_8ClBrN_2$: N, 10.32. Found: N, 10.10. Calcd. for $C_{10}H_8Cl_2N_2$: N, 12.34. Found: N, 12.32. Calcd. for $C_{10}H_9BrN_2O$: N, 11.07. Found: N, 10.80. Calcd. for $C_{10}H_9ClN_2O$: N, 13.43. Found: N, 13.27.

5-Acetamido-6-halo-8-methylquinolines.—III (2.0 g.), IV (1.0 g.), XIII (1.0 g.), XIV (1.5 g.), XXIII (2.0 g.), and XXIV (2.0 g.) were acetylated under conditions similar to those employed by de Arce, Greene and Capps[2] for acetylation of 5-amino-8-bromo-6-methylquinoline giving V (1.9 g., 81%, m. p. 235–236° from 95% ethanol), VI (1.0 g., 82%, m. p. 225–226° from 95% ethanol), XV (0.99 g., 84%, m. p. 272–273° from 95% ethanol), XVI (1.5 g., 84%, m. p. 265–266° from 95% ethanol), XXV (1.5 g., 64%, m. p. 318–319° dec. from 2-pentanol), and XXVI (1.3 g., 54%, m. p. greater than 340° from glacial acetic acid).

Anal. Calcd. for $C_{12}H_{11}BrN_2O$: N, 10.04. Found: N, 10.16. Calcd. for $C_{12}H_{11}ClN_2O$: N, 11.94. Found: N, 12.10. Calcd. for $C_{12}H_{10}ClBrN_2O$: N, 8.93. Found: N, 9.18. Calcd. for $C_{12}H_{10}Cl_2N_2O$: N, 10.41. Found: N, 10.22. Calcd. for $C_{12}H_{11}BrN_2O_2$: N, 9.49. Found: N, 9.51. Calcd. for $C_{12}H_{11}ClN_2O_2$: N, 11.18. Found: N, 11.13.

5-Benzamido-6-halo-8-methylquinolines.—III (2.0 g.), IV (1.0 g.), XIII (0.60 g.), XIV (1.5 g.), XXIII (2.0 g.), and XXIV (3.0 g.) were benzoylated according to instructions recorded by de Arce, Greene and Capps[2] for benzoylation of 5-amino-8-bromo-6-methylquinoline yielding VII (2.0 g., 69%, m. p. 210–211° from 80:20 by volume ethanol–water), VIII (1.0 g., 79%, m. p. 193–194° from 95% ethanol), XVII (0.50 g., 60%, m. p. 252–253° from 95% ethanol), XVIII (1.2 g., 65%, m. p. 253–254° from 95% ethanol), XXVII (2.1 g., 75%, m. p. 297–298° from 95% ethanol), and XXVIII (3.5 g., 93%, m. p. 331–332° from glacial acetic acid). Since crude XXVII resulting from first crystallization from 95% ethanol melted over an 80° range, dibenzoylation was suspected and the selective treatment used previously by de Arce, Greene and Capps[2] for removal of a 2-benzoxy group was applied with apparent success.

Anal. Calcd. for $C_{17}H_{13}BrN_2O$: N, 8.21. Found: N, 8.03. Calcd. for $C_{17}H_{13}ClN_2O$: N, 9.44. Found: N, 9.22. Calcd. for $C_{17}H_{12}ClBrN_2O$: N, 7.46. Found: N, 7.18. Calcd. for $C_{17}H_{12}Cl_2N_2O$: N, 8.46. Found: N, 8.25. Calcd. for $C_{17}H_{13}BrN_2O_2$: N, 7.84. Found: N, 7.67. Calcd. for $C_{17}H_{13}ClN_2O_2$: N, 8.96. Found: N, 8.82.

6-Halo-8-methyl-5-quinolinearsonic Acids.—III, IV, XIII, XIV, XXIII and XXIV were diazotized and converted into arsonic acids according to procedure reported by Capps and Hamilton[9] for changing certain 2-chloroaminoquinolines into 2-chloroquinolinearsonic acids. IX, X, XIX, XX, XXIX and XXX resulted in yields of 10.5, 17, 7.7, 6.7, 8.8 and 6.5%, respectively, with melting points of 244–245° dec., 255–256°, greater than 330°, 302–303°, greater than 330°, and 325–326°.

Anal. Calcd. for $C_{10}H_9BrNAsO_3$: N, 4.04; As, 21.65. Found: N, 3.95; As, 21.70. Calcd. for $C_{10}H_9ClNAsO_3$: As, 24.84. Found: As, 24.70. Calcd. for $C_{10}H_8ClBrNAsO_3$: N, 3.68; As, 19.69. Found: N, 3.62; As, 19.41. Calcd. for $C_{10}H_8Cl_2NAsO_3$: As, 22.29. Found:

(8) J. D. Capps, THIS JOURNAL, **69**, 176 (1947).

(9) J. D. Capps and C. S. Hamilton, THIS JOURNAL, **60**, 2105 (1938).

As, 22.50. Calcd. for $C_{10}H_9BrNAsO_4$: N, 3.78; As, 20.69. Found: N, 3.62; As, 20.48. Calcd. for $C_{10}H_9ClNAsO_4$: As, 23.59. Found: As, 23.60.

Summary

1. 2-Acetamido-5-bromotoluene and 2-acetamido-5-chlorotoluene were converted by means of the Skraup reaction into 6-bromo-8-methylquinoline (77% yield) and 6-chloro-8-methylquinoline (67% yield), respectively. Each of these 6-halo-8-methylquinolines nitrated chiefly in the 5-position as was indicated by the fact that 2-acetamido-5-halo-4-nitrotoluenes yielded the same nitroquinolines when subjected to Skraup ring-closure conditions. The samples of 2-acetamido-5-halo-4-nitrotoluenes used were shown to be authentic ones by employing well characterized reactions to change them into substances possessing established structures. A picrate of 6-chloro-8-methylquinoline was prepared and analyzed.

2. 6-Bromo-2-chloro-8-methylquinoline and 2,6-dichloro-8-methylquinoline were synthesized from the corresponding 1-methyl-2-quinolones that were in turn obtained from 6-bromo-8-methylquinoline and 6-chloro-8-methylquinoline, respectively. Hydrolysis of these 2-chloroquinolines in an autoclave gave 2-hydroxyquinolines. Nitration of the 2-chloroquinolines gave 2-chloro-5-nitroquinolines; these same 2-chloro-5-nitroquinolines were also produced from the 6-halo-8-methyl-5-nitroquinolines *via* the 1-methyl-2-quinolones. Although 6-chloro-2-hydroxy-8-methylquinoline gave upon nitration some of the same substance as resulted from the hydrolysis of 2,6-dichloro-8-methyl-5-nitroquinoline, no 6-bromo-2-hydroxy-8-methyl-5-nitroquinoline was isolated after nitrating 6-bromo-2-hydroxy-8-methylquinoline; hydrolysis of 6-bromo-2-chloro-8-methyl-5-nitroquinoline did yield 6-bromo-2-hydroxy-8-methyl-5-nitroquinoline.

3. 6-Bromo-8-methyl-5-nitroquinoline, 6-chloro-8-methyl-5-nitroquinoline, 2-chloro derivatives, and 2-hydroxy derivatives of these nitroquinolines were reduced in presence of Raney nickel to amines. Pressures as high as 500 pounds per square inch at 80° were resorted to during some of these reductions. Acetamido and benzamido derivatives of the amines were prepared. The amines were also converted by means of the Bart reaction into arsonic acids.

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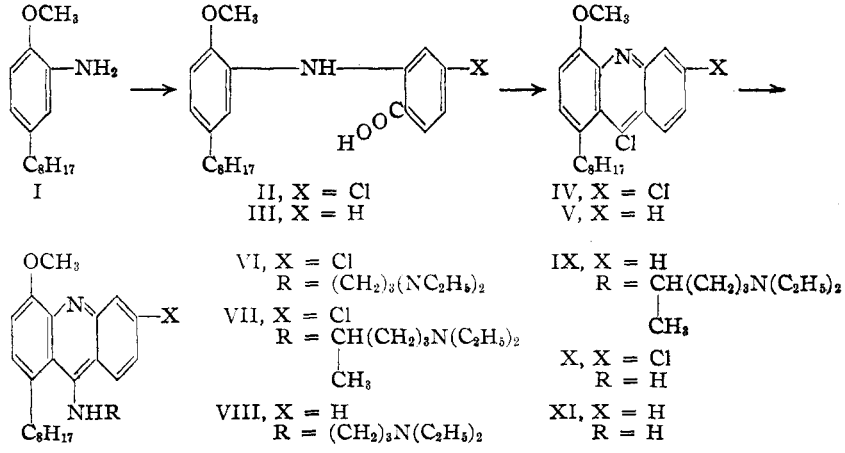
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

Acridines Derived from *p*-(1,1,3,3-Tetramethyl)-butylphenol[1]

BY JOSEPH B. NIEDERL AND MURRAY B. HUNDERT[2]

Ehrlich's accidental discovery of the therapeutic properties of acridine initiated a vigorous search for other active derivatives which culminated in the production of many synthetic antimalarials, the most widely known of which is 3-chloro-7-methoxy-9-(5-diethylamino-2-pentylamino)-acridine dihydrochloride, more commonly known as "Atabrine." In an effort to find substances of enhanced activity, the possibility that alkyl substituted acridines containing the bactericidal 1,1,3,3-tetramethylbutyl[3] group would result in more effective antimalarial and bactericidal compounds was investigated.



Accordingly, the dihydrochlorides of 1-(1,1,3,3-tetramethyl) - butyl - 4 - methoxy - 6 - chloro - 9-(3-diethylaminopropylamino)-acridine (VI), 1-(1,1,3,3 - tetramethyl) - butyl - 4 - methoxy - 6 - chloro - 9 - (5 - diethylamino - 2 - pentylamino)-acridine (VII), 1-(1,1,3,3,-tetramethyl)-butyl-4-methoxy-9-(3-diethylaminopropylamino)-acridine (VIII), and 1-(1,1,3,3-tetramethyl)-butyl-4-methoxy - 9 - (5 - diethylamino - 2 - pentylamino) - acridine (IX) were synthesized from *p*-(1,1,3,3-tetramethyl)-butylphenol through the anisidino[4]

(1) Presented before the Division of Organic Chemistry at the Atlantic City meeting of the American Chemical Society, September, 1949.

(2) Abstracted from the thesis presented by M. B. Hundert to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, November, 1949.

(3) J. B. Niederl, *Ind. Eng. Chem.*, **30**, 1269 (1938).

(4) J. B. Niederl and M. I. Dexter, THIS JOURNAL, **63**, 1475 (1941).