disulfide bonds are formed between the protein sulfhydryl groups and the cysteine present in the digestion mixture.

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Summary

1. Human gamma globulin is split by papain or bromelin into particles of one-quarter size.

2. The splitting is accompanied by only a small increase in non-protein nitrogen.

3. In the ultracentrifuge the split products give rise to a single boundary of sedimentation rate $s_{20} = 4.1S$ in dilute solution.

4. Electrophoretic analysis of the digests reveals the presence of a number of separate components derived from the globulin.

5. These components differ in their solubility in ammonium sulfate and in ethyl alcohol.

6. The diffusion constant of the split products is 7.5×10^{-7} sq. cm./sec. The molecular weight is about 47,000.

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

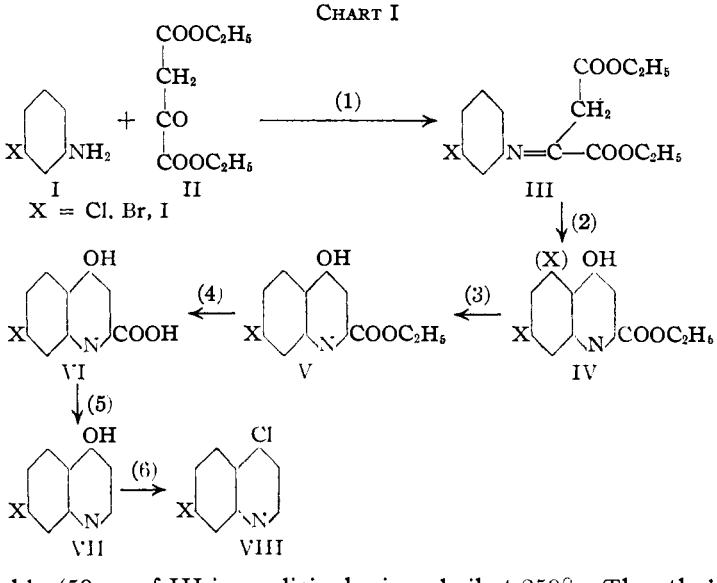
Some 7-Substituted 4-Aminoquinoline Derivatives

BY ALEXANDER R. SURREY AND HENRY F. HAMMER

In continuation of the search in these laboratories for effective antiparasitic agents, several 4-dialkylaminoalkylamino-7-halogen quinoline derivatives have been prepared. Although there have been several papers published recently[1,2,3] on 4-dialkylaminoalkylamino-6-methoxyquinolines, only the patent literature[4] on the synthesis of the corresponding 7-substituted compounds is available. In view of the high therapeutic activity reported for the 6-substituted quinolines on the asexual form of various protozoal organisms, it seemed desirable to study further the preparation of the 7-derivatives for a comparison of activity. Although some of these compounds have been reported in the patent, the preparation of the necessary intermediates has not been described in detail.

The 4-chloro-7-halogen quinolines have been prepared by a series of reactions (Chart I) starting with that of substituted anilines and ethyl ethoxalylacetate in glacial acetic acid.[5,6,7] In some experiments it was found to be advantageous to use an excess of the aniline (I) in order to obtain better yields (50–80%). Practically all of unreacted I can and should be removed in the isolation of the anils (III) inasmuch as small amounts of I interfere with the expected reaction in step 2. The formation of the crystalline quinoline derivative (IV) in yields of 50–80% resulted from the ring closure

CHART I



of III in medicinal mineral oil at 250°. The ethyl alcohol which formed during this reaction was collected by condensation. The quantity obtained served as an indication of the completeness of the reaction. This procedure eliminated any prolonged heating which would cause considerable decomposition. Practically no ethyl alcohol was collected until the reaction mixture reached 235°.

Where ring closure can give a mixture of isomers (as with the *m*-substituted anilines) the

(1) Magidson and Rubtsov, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1896 (1937).

(2) VanArendonk and Shonle, THIS JOURNAL, **66**, 1284 (1944).

(3) Bachman and Cooper, *J. Org. Chem.*, **9**, 302 (1944).

(4) U. S. Patent 2,233,970; March 4, 1941.

(5) Conrad and Limpach, *Ber.*, **20**, 944 (1887).

(6) Limpach, *ibid.*, **64**, 969 (1931).

(7) Rubtsov and Lizgunova, *J. Gen. Chem.* (*U. S. S. R.*), **13**, 697 (1943).

TABLE I

R-4-(R'-AMINO)-QUINOLINES

Cpd.	R	R'	M. p., °C. (uncor.)	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	7-Chloro	4-Diethylamino-1-methylbutyl[a]	86–87	67.59	67.89	8.13	8.02	13.13	13.38
2	7-Chloro	4-Diethylaminobutyl[a]	75–80	66.77	66.83	7.86	7.72	13.75	13.82
3	7-Chloro	2-Diethylaminoethyl[b]	94–97	64.89	65.20	7.21	7.31	15.13	15.03
4	7-Chloro	3-Diethylamino-2-hydroxypropyl[c]	114–115	62.43	62.57	7.20	7.35	13.65	13.37
5	7-Chloro	3-Diethylaminopropyl[b,f]	55–57	65.87	66.02	7.59	7.56	14.40	14.22
6	7-Chloro	3-α-Pipecolinopropyl[b,f]	86–87	68.00	67.60	7.56	7.23	13.20	12.82
7	7-Chloro	4-Dimethylaminobutyl[d,g]	115–116	64.85	64.90	7.26	7.14	15.13	14.92
8	7-Bromo	4-Diethylamino-1-methylbutyl[d]	101–102	59.34	59.55	7.15	7.47	11.52	11.68
9	7-Bromo	4-Diethylaminobutyl[e]	72–76	58.29	58.22	6.91	7.52	11.99	11.88
10	7-Iodo	4-Diethylamino-1-methylbutyl[d]	113–116	52.55	52.95	6.37	6.56	10.21	10.34
11	6-Methoxy	4-Diethylamino-1-methylbutyl[d,h]	124–126	72.11	72.20	9.18	8.96	13.28	13.37
12	6-Methoxy-7-chloro	4-Diethylamino-1-methylbutyl[d]	144–145	65.21	65.32	8.06	7.44	12.00	11.97
13	5-Chloro	4-Diethylamino-1-methylbutyl[l]		67.59	67.17	8.13	8.36	13.13	13.12

TABLE II

SALTS OF R-4-(R'-AMINO)-QUINOLINES

Cpd.	Formula	M. p., °C. (uncor.)	Moisture found	Analyses, % Acid (dry) Calcd.	Acid (dry) Found	Base (dry) Calcd.	Base (dry) Found
1	$C_{18}H_{26}N_3Cl \cdot 2H_3PO_4$	215–216	0.33	38.0	38.5	62.0	62.2
2	$C_{17}H_{24}N_3Cl \cdot 2H_3PO_4$	233–234	.10	39.1	38.8		
3	$C_{15}H_{20}N_3Cl \cdot (H_3PO_4)^i$	193–195	1.4		48.5		51.0
4	$C_{15}H_{22}N_3OCl \cdot 2H_3PO_4$	209–210	0.31	38.9	39.0	61.1	61.8
5	$C_{16}H_{23}N_3Cl \cdot 2H_3PO_4$	220–222	.70	40.2	40.2	59.8	60.9
6	$C_{16}H_{24}N_3Cl \cdot C_{22}H_{16}O_6$[k]	192–194	.88	54.2	53.7	45.8	46.4
7	$C_{15}H_{20}N_3Cl \cdot 2H_3PO_4$	225–226	.36	41.4	42.7	58.6	59.0
8	$C_{18}H_{26}N_3Br \cdot 2H_3PO_4$	221–223	.80	34.9	35.0	65.1	66.4
9	$C_{17}H_{24}N_3Br \cdot 2H_3PO_4$	243–244	.18	35.8	35.4		
10	$C_{18}H_{26}N_3I \cdot 2H_3PO_4$	227–229	.70	32.3	32.2		
11	$C_{19}H_{29}N_3O \cdot 2H_3PO_4$	225–226	.30	38.2	38.0		
12	$C_{19}H_{28}N_3OCl \cdot 2H_3PO_4$	230–232		35.9	37.1	64.1	64.0

[a] Recrystallized from ether. [b] From Skellysolve B. [c] From benzene. [d] From Skellysolve D. [e] From benzene and Skellysolve A. [f] 3-Diethylaminopropylamine and 3-α-pipecolinopropylamine were furnished by the National Research Council. [g] We are grateful to Miss Mary Jackman for the preparation of 4-dimethylaminobutylamine. [h] Magidson and Rubtsov, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1896 (1937). [i] Ratio of acid to base is not stoichiometric; % chlorine found, 6.27. [k] 2-Hydroxy-3-naphthoic acid salt. [l] Boiling point, 149° at 0.001 mm., $n^{25}D$ 1.5816.

above-described method gives a mixture of high-melting hydroxy esters (IV) which can be separated rather easily by recrystallization. This is especially true where the 7-substituted compound is desired since it appears to be the higher-melting and more insoluble isomer. The yields of V in step 3 were 45–50%. The ethyl 7- and 5-halo-4-hydroxy-2-quinolinecarboxylates (IV) were separated by recrystallization from glacial acetic acid or pyridine. The quantities of solvents needed in this separation depended to some extent on the amounts and kinds of solvents employed in the washing of the crude mixtures of isomers. Where an attempt was made to wash the mixture free of all dark material with ether or acetone, the product required larger amounts of solvent for solution. This is undoubtedly due to the removal of some of the more soluble isomer. The 7-isomer was obtained in sufficiently pure condition, after one recrystallization, to use in the next step.

The esters (V) were hydrolyzed with sodium hydroxide and the crude acids (VI) thus obtained were decarboxylated in mineral oil at 270°. The crude yields in steps 4 and 5 were almost quantitative. The 4-hydroxy-7-substituted quinolines (VII) were treated with phosphorus oxychloride to give the desired 4-chloro-7-substituted quinolines (VIII). The yields varied from 40 to 90%. The presence of undecarboxylated VI as an impurity in compound VII usually resulted in poor yields.

In order to determine whether the structure of 4,7-dichloroquinoline was correct, it was catalytically reduced to 7-chloroquinoline and then nitrated to give 7-chloro-8-nitroquinoline. A mixed melting point determination with a sample of 7-chloro-8-nitroquinoline prepared by the Skraup reaction on *m*-chloroaniline followed by nitration according to the procedure of Fourneau, Tréfouel, Tréfouel and Wancolle[8] gave no depression. Inasmuch as all the mixtures of ethyl 7- and 5-halo-4-hydroxy-2-quinolinecarboxylates (IV) behaved similarly to the corresponding mixtures of chloro esters, it was assumed that the

(8) Fourneau, Tréfouel, Tréfouel and Wancolle, *Bull. soc. chim.*, **47**, 758 (1930).

higher melting and more insoluble compound was the 7-isomer (V).

The 4-chloro-7-substituted quinolines (VIII) were condensed with several primary–tertiary diamines alone or in the presence of phenol. The crude bases (Table I) were distilled under low pressure. The distillates which solidified slowly on standing could be recrystallized from various solvents. Most of the solid bases were converted to the diphosphates (Table II). These are white microcrystalline powders which are very soluble in water. The 4-(3-α-pipecolinopropylamino)-7-chloroquinoline was converted to a light tan salt with 2-hydroxy-3-naphthoic acid. This salt is only slightly soluble in water.

Experimental

Ethyl 7- and 5-Chloro-4-hydroxy-2-quinoline Carboxylates.—A solution of 94 g. (0.5 mole) of ethyl ethoxalylacetate and 102 g. (0.8 mole) of *m*-chloroaniline, in 360 cc. of glacial acetic acid, was stirred for four hours at 40–50° and then allowed to stand at room temperature for fifteen to eighteen hours. The solution was poured into ice water, neutralized with 35% sodium hydroxide solution, and extracted with ether. The ether was washed with 1.4 liter of 0.5 *N* hydrochloric acid and 1.4 liter of 0.5 *N* sodium hydroxide (each in four portions) and dried over anhydrous potassium carbonate. About 39 g. of *m*-chloroaniline could be recovered from the acid washings. After removal of the ether, the residual oil (116 g.) was added to 780 cc. of mineral oil at 250° over a period of about ten to twelve minutes and stirring was continued at 250° for about five minutes longer. Practically the theoretical amount of alcohol was collected by condensation. The reaction mixture was allowed to cool to 70° with stirring, and the solid was filtered off, washed with Skellysolve C and dried; yield 85 g.

Separation of Isomers.—(Procedure A) A mixture of ethyl 7- and 5-chloro-4-hydroxy-2-quinoline carboxylates was dissolved in five times its weight of hot glacial acetic acid. The solution was allowed to cool to 40° with stirring and was filtered. The 7-chloro isomer was washed with Skellysolve C and air dried; yield about 50%, m. p. 244–246°. The bulk of the crude 5-chloro isomer was recovered from the acetic acid filtrate by dilution with water. The pure 7-isomer was obtained by recrystallization from pyridine; m. p. 250–251°.

Anal. Calcd. for $C_{12}H_{10}NO_3Cl$: N, 5.57. Found: N, 5.83.

The pure ethyl 5-chloro-4-hydroxy-2-quinoline carboxylate was obtained with difficulty from the crude material after repeated recrystallizations from pyridine and alcohol and finally dioxane; m. p. 197–198°

Anal. Found: N, 6.00.

(Procedure B) A mixture of ethyl 7- and 5-chloro-4-hydroxy-6-methoxy-2-quinoline carboxylates (46 g.) was stirred in fifteen times its weight of hot pyridine for twenty minutes. The suspension was allowed to cool to 20° and the solid was filtered off, washed with Skellysolve C, and dried. The yield of 7-isomer was 72.7%. After two recrystallizations from glacial acetic acid the product melted at 281–282°.

Anal. Calcd. for $C_{13}H_{12}NO_4Cl$: N, 4.97. Found: N, 5.02.

Ethyl 7-bromo-4-hydroxy-2-quinoline carboxylate was prepared in a similar manner. Procedure A was used in the isomer isolation. The product was recrystallized from glacial acetic acid; m. p. 251–252°.

Anal. Calcd. for $C_{12}H_{10}NO_3Br$: N, 4.73. Found: N, 4.95.

Ethyl 7-iodo-4-hydroxy-2-quinoline carboxylate (A), m. p. 249–250°

Anal. Calcd. for $C_{12}H_{10}NO_3I$: N, 4.39. Found: N, 4.42.

The same method is used for the preparation of ethyl 6-methoxy-4-hydroxy-2-quinoline carboxylate, m. p. 214–215°, from alcohol.

Anal. Calcd. for $C_{13}H_{13}NO_4$: N, 5.66. Found: N, 5.56.

7-Chloro-4-hydroxy-2-quinoline Carboxylic Acid.—Forty-five grams of the 7-isomer (V) was refluxed for two hours with 53 cc. of 35% sodium hydroxide solution and 400 cc. of water. It was diluted with 300 cc. of hot water and acidified, while being stirred, with dilute hydrochloric acid. The solid was filtered off, washed with water and dried at 100°. The crude yield was 40 g. (The crude yields of all the acids were practically quantitative.) A sample recrystallized from pyridine for analysis melts at 277–278° dec.

Anal. Calcd. for $C_{10}H_6NO_3Cl$: N, 6.26. Found: N, 6.14.

The following compounds were prepared in a similar manner: 7-Bromo-4-hydroxy-2-quinoline carboxylic acid, m. p. 278–279° dec. *Anal.* Calcd. for $C_{10}H_6NO_3Br$: N, 5.22. Found: N, 5.34. 7-Iodo-4-hydroxy-2-quinoline carboxylic acid, m. p. 279–280° dec. *Anal.* Calcd. for $C_{10}H_6NO_3I$: N, 4.45. Found: N, 4.63. 6-Methoxy-4-hydroxy-2-quinoline carboxylic acid, m. p. 286–287° dec. *Anal.* Calcd. for $C_{11}H_9NO_4$: N, 6.39. Found: N, 6.41. 7-Chloro-6-methoxy-4-hydroxy-2-quinoline carboxylic acid, m. p. 281–282° dec. *Anal.* Calcd. for $C_{11}H_8NO_4Cl$: neut. equiv., 254; methoxyl, 12.2. Found: neut. equiv., 252; methoxyl, 12.0. 5-Chloro-4-hydroxy-2-quinoline carboxylic acid, m. p. 270° dec. *Anal.* Calcd. for $C_{10}H_6NO_3Cl$: N, 6.26. Found: N, 6.60.

7-Chloro-4-hydroxyquinoline.—The crude acid (VI) was added with stirring to 200 cc. of mineral oil at 270°. The temperature was kept at 270° for an additional five minutes and then allowed to cool to 90°. The solid was filtered off, washed with Skellysolve C and dried at 100°; crude yield 34 g. (The crude yields of the 7-halo-4-hydroxyquinolines were practically quantitative.) A sample recrystallized from water melts at 277–279°.

Anal. Calcd. for C_9H_6NOCl: N, 7.81. Found: N, 7.80.

The following compounds were prepared by the same procedure: 7-Bromo-4-hydroxyquinoline, m. p. 279–281°, from alcohol and water. *Anal.* Calcd. for C_9H_6NOBr: N, 6.25. Found: N, 5.95. 7-Iodo-4-hydroxyquinoline, m. p. 346–348° dec., from alcohol and water. *Anal.* Calcd. for C_9H_6NOI: N, 5.17. Found: N, 5.14. 6-Methoxy-4-hydroxyquinoline;[9] a sample was vacuum sublimed and then recrystallized from alcohol, m. p. 237–238° (immersed at 232°). *Anal.* Calcd. for $C_{10}H_9NO_2$: methoxyl, 17.72. Found: methoxyl, 18.10, 17.99. 7-Chloro-6-methoxy-4-hydroxyquinoline, m. p. 239–240°, from alcohol and water. *Anal.* Calcd. for $C_{10}H_8NO_2Cl$: N, 6.69. Found: N, 6.75. 5-Chloro-4-hydroxyquinoline, m. p. 256–257°, from alcohol. *Anal.* Calcd. for C_9H_6NOCl: N, 7.81. Found: N, 7.95.

4,7-Dichloroquinoline.—The crude 7-chloro-4-hydroxyquinoline (34 g.) was refluxed for two hours with 110 cc. of phosphorus oxychloride (added in two portions). Most of the oxychloride was distilled off under reduced pressure and the residue was poured into ice-water. The mixture was made alkaline with ammonium hydroxide and the product taken up in methylene chloride. The dichloroquinoline distilled at 148° at 10 mm., m. p. 83.5–84.5°; yield 32 g. (This represents a 91% yield based on ethyl 7-chloro-4-hydroxy-2-quinoline carboxylate.)

Anal. Calcd. for $C_9H_5NCl_2$: N, 7.07. Found: N, 7.04.

The same procedure was used for the following compounds: 7-Bromo-4-chloroquinoline, yield 65%, m. p. 100.5–101.5°, from 95% alcohol. *Anal.* Calcd. for C_9H_5NClBr: N, 5.77. Found: N, 5.68. 4-Chloro-7-

(9) Bachman and Cooper, *J. Org. Chem.*, **9**, 302 (1944).

iodoquinoline, yield 60%, m. p. 95.5–97°, from Skellysolve C. *Anal.* Calcd. for C_9H_5NClI: N, 4.83. Found: N, 4.88. 4-Chloro-6-hydroxyquinoline, yield 60%, m. p. 75–77°: picrate, m. p. 220–221°. *Anal.* Calcd. for $C_{15}H_{11}N_4O_8Cl$: N, 13.28. Found: N, 13.05. 4,7-Dichloro-6-methoxyquinoline, yield 36%, m. p. 159–160°, from absolute alcohol. *Anal.* Calcd. for $C_{10}H_8NOCl_2$: N, 6.14. Found: N, 6.05. 4,5-Dichloroquinoline, yield 75%, m. p. 115.5–116.5°; from methanol and then vacuum sublimed. *Anal.* Calcd. for $C_9H_5NCl_2$: N, 7.07. Found: N, 6.88.

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline.—(Procedure A) A mixture of 49.5 g. (0.25 mole) of 4,7-dichloroquinoline and 79 g. (0.5 mole) of 4-diethylamino-1-methylbutylamine was heated with stirring and refluxing for seven hours at 160–180° (inside temperature). Since the reaction was exothermic, temperature of the reaction mixture was raised slowly at first to prevent a sudden rise in temperature. The reaction was complete when a sample of the reaction mixture dissolved in dilute nitric acid did not give a precipitate with a saturated solution of sodium acetate.

The hot reaction mixture was poured into about 300–350 cc. of 50% acetic acid solution (less acid can be used provided enough is present to dissolve completely the oily reaction mixture) and made alkaline with 35% sodium hydroxide solution. Toward the end of the neutralization, a layer of ether was added and the alkaline mixture was extracted with ether several times. The combined ether extracts were dried over anhydrous potassium carbonate and the ether removed by distillation. The residue was heated at 160-170° (bath temperature) at 0.5 mm. to recover the excess of 1-methyl-4-diethylaminobutylamine (about 25 g.). On standing, the crude residual oil crystallized.

In most instances the crude bases (yields 40–95%) were purified by distillation under low pressures (170–200° and 0.002–0.1 mm.). Inasmuch as the distillation temperatures varied directly with the bath temperatures, no true boiling points were recorded. The distillates were collected over a wide range. However, on standing they solidified and could be recrystallized from various solvents (Table II).

7-Bromo-(4-diethylaminobutylamino)-quinoline.—(Procedure B) Seventy grams (0.288 mole) of 7-bromo-4-chloroquinoline, 83 g. (0.576 mole) of 4-diethylaminobutylamine, 57.5 g. of phenol, and 0.02 g. of sodium iodide were heated with stirring and refluxing at an inner temperature of 160° for fifteen hours. At the end of this time, no test for unreacted chloro-bromoquinoline was obtained with dilute nitric acid and saturated sodium acetate solution as described above.

The hot phenol melt was poured into an excess (500–600 cc.) of 35% sodium hydroxide solution with stirring. The bases which separated were extracted exhaustively with ether and then extracted from the ether with 3 *N* hydrochloric acid solution. The combined aqueous solutions of the hydrochlorides were made neutral to congo red paper with solid sodium acetate and washed twice with ether. The aqueous acid solution was made alkaline by the addition of 35% sodium hydroxide solution and the oil that separated was extracted exhaustively with ether. After drying over anhydrous potassium carbonate, the combined ether extracts were evaporated and the residual oil was heated in vacuum at a bath temperature of 180° and a pressure of 0.5 mm. to remove any unreacted 4-diethylaminobutylamine. The base was purified as in Procedure A.

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline Diphosphate.—To a solution of 14.8 g. of crude 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline in 30 cc. of methanol was added, with cooling, 19.2 g. of a phosphoric acid solution made from 10 g. of 85% phosphoric acid and 12.5 cc. of methanol. Isopropyl alcohol was then added to throw out all the salt from solution as an oil. The alcohol layer was decanted, acetone added, and the oil was triturated and stirred until it solidified. The mixture was then filtered, the diphosphate washed with acetone and quickly placed in a vacuum desiccator. The yield was 24 g.

The salt was purified by dissolving in 96 cc. (four times its weight) of warm water, adding 48 cc. of methanol, heating the solution with charcoal on the steam-bath, and then filtering. Isopropyl alcohol was added to the filtrate to slight turbidity. The solution was allowed to stand a day at room temperature, and the salt was filtered off and washed with isopropyl alcohol and then acetone. The yield was 15 g., m. p. 215–216°.

7-Chloro-8-nitroquinoline.—Four grams of 4,7-dichloroquinoline (m. p. 83–84°) was dissolved in 90 cc. of absolute alcohol and to it was added an equivalent amount of sodium hydroxide in alcoholic solution. The mixture was catalytically reduced in the presence of Raney nickel. After the theoretical amount of hydrogen was absorbed (within one hour), the catalyst was filtered off and the filtrate evaporated to an oil.

The oil was nitrated according to the method of Fourneau, Tréfouel, Tréfouel and Wancolle[8] to give a product melting at 178–180°. A mixed melting point determination with a sample of 7-chloro-8-nitroquinoline (m. p. 181–182°), prepared by a Skraup reaction on *m*-chloroaniline followed by nitration,[8] gave a melting point of 180–181°.

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Summary

A series of reactions is described for the preparation of 7-substituted 4-chloroquinolines. The steps include condensation of substituted anilines with ethyl ethoxalylacetate, ring closure in mineral oil, separation of isomers where necessary, hydrolysis, decarboxylation, and treatment with phosphorus oxychloride.

The condensation of the benzenoid-substituted 4-chloroquinolines with various dialkylaminoalkylamines to give crystalline 4-dialkylaminoalkylaminoquinolines is described. The preparation of water-soluble diphosphates of these bases is also described.

RENSSELAER, N. Y. RECEIVED[10] NOVEMBER 16, 1944

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