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

The Preparation of Bz-Dichloro-4-aminoquinoline Derivatives

BY ALEXANDER R. SURREY AND HENRY F. HAMMER

In a previous paper[1] several 7-substituted-4-aminoquinoline derivatives were described. Inasmuch as these compounds showed considerable antimalarial activity, in some instances superior to quinacrine,[2] it seemed desirable to investigate the effect of dihalogen substitution in the benzenoid ring. For this purpose some trichloroquinolines as well as 4-chloro-5,7-dibromoquinoline were prepared and condensed with a primary-tertiary diamine. The reports thus far indicate that the compounds with a halogen atom in the 7-position show the greatest activity whereas the 5,6-, 6,8- and 5,8-dichloro derivatives show little if any antimalarial action.

All of the trichloroquinolines with the exception of 4,7,8-compound were prepared from the corresponding dichloroanilines and ethyl ethoxalylacetate by the usual Conrad–Limpach method. The reaction with 3,4-dichloroaniline gave a mixture of isomers which could be separated by fractional recrystallization at the trichloro stage to yield the 4,6,7- and 4,5,6-trichloroquinolines. The latter, however, was obtained in only small yields.

Nitration of 4,7-dichloroquinoline gave the 8-nitro compound in good yield. Reduction to the amino compound followed by a Gattermann reaction yielded the desired 4,7,8-trichloroquinoline. In order to prove the position of the nitro group the 4,7-dichloronitroquinoline was reduced catalytically to 8-amino-7-chloroquinoline and then compared with a sample prepared by the reduction of 7-chloro-8-nitroquinoline.[1] A mixed melting point determination of the two samples showed no depression. The structure of 4,6,7-trichloroquinoline was determined by oxidation with potassium permanganate to yield the known 4,5-dichloroanthranilic acid.[3]

Experimental Part[4]

Ethyl Bz-Dichloro-4-hydroxyquinaldate (Table I, R = $COOC_2H_5$).—The general procedures for preparing the ethyl arylaminomaleates from the substituted anilines and ethyl ethoxalylacetate, as well as their subsequent ring closure to yield quinoline derivatives, have been described previously.[1]

All of the esters in Table I were purified by recrystallization from either alcohol, pyridine or acetic acid except the 6,8-dichloro compound, which was recrystallized from acetone.

The mixture of isomers obtained on ring closure of ethyl 3,4-dichloroanilinomaleate could not be separated easily. The mixture was carried through to the trichloro step at which point separation into 4,5,6- and 4,6,7-trichloroquinoline was effected.

Bz-Dichloro-4-hydroxyquinaldic Acid (Table I, R = COOH).—The esters were hydrolyzed to the corresponding acids with dilute sodium hydroxide solution in quantitative yields. Analytical samples were prepared by reprecipitation from warm dilute aqueous alkali with hydrochloric acid followed by digestion with warm alcohol.

Bz-Dichloro-4-hydroxyquinoline (Table I, R = H).—The acids were decarboxylated in mineral oil at temperatures ranging from 240–270° to give practically theoretical yields of crude product. Purification was effected by reprecipitation from a dilute sodium hydroxide solution with a saturated sodium bicarbonate solution.

Decarboxylation of 5,7-dibromo-4-hydroxyquinaldic acid was carried out in diphenyl ether at 260° for two hours.

Trichloroquinoline.—Procedures similar to those already described were used to convert the hydroxy to the chloro compounds.[1]

A mixture of 51 g. of 4,5,6- and 4,6,7-trichloroquinolines was recrystallized from 250 cc. of benzene to yield 16 g. of material, m. p. 146–149°. An additional 2 g., m. p. 115–138°, was obtained from the filtrate on standing. The two fractions were combined and recrystallized from benzene and then Skellysolve B to give 14.5 g. of colorless needles, m. p. 154–155°. The other isomer, 4,5,6-trichloroquinoline, was obtained from the original benzene filtrate after evaporation to dryness and then repeated recrystallizations from alcohol and from Skellysolve B (ligroin, b. p 50–60°), m. p. 121.5–122.5° (see Table II).

4,7-Dichloro-8-nitroquinoline.—Ten grams of 4,7-dichloroquinoline was added slowly with stirring to 50 g. of a mixture of one part by weight of fuming nitric acid (d. 1.5) and two parts by weight of concentrated sulfuric acid at −10 to −5°. After all the solid had dissolved, the mixture was allowed to stand at room temperature for two hours and then poured into 200 cc. of ice-water. The light yellow solid was filtered off and washed thoroughly with water. The crude material was recrystallized from alcohol to yield 9.5 g. of almost colorless product, m. p. 149–151°.

Anal. Calcd. for $C_9H_4Cl_2N_2O_2$: N, 11.52; Cl, 29.2. Found: N, 11.18; Cl, 28.7.

8-Amino-4,7-dichloroquinoline.—The nitro compound (33 g.) in 1700 cc. of alcohol was reduced catalytically with Raney nickel at room temperature and 1000 lb. pressure of hydrogen. The product (26 g.) after recrystallization from alcohol melted at 110–111.5°.

Anal. Calcd. for $C_9H_6Cl_2N_2$: N, 13.15. Found: N, 12.91.

4,7,8-Trichloroquinoline.—A solution of 6.2 g. of sodium nitrite in 20 cc. of water was added with stirring to a suspension of 17 g. of 8-amino-4,7-dichloroquinoline in 170 cc. of concentrated hydrochloric acid and 120 cc. of water at −5 to 0°. A suspension of 19 g. of copper powder in 20 cc. of water was added slowly to the solution of the diazotized amine. When no more gas was evolved, the mixture was allowed to stand for one-half hour at room temperature and then made strongly alkaline with concentrated ammonium hydroxide. The solid was filtered off, washed with water, dried, and extracted with five 40-cc. portions of warm chloroform. The material obtained after evaporation of the combined chloroform was recrystallized from alcohol and then Skellysolve C to yield 12 g. of 4,7,8-trichloroquinoline, m. p. 125–126°.

Anal. Calcd. for $C_9H_4Cl_3N$: N, 6.03; Cl, 45.76. Found: N, 6.28; Cl, 45.44.

8-Amino-7-chloroquinoline.—The 4,7-dichloro-8-aminoquinoline, 3 g. in 100 cc. of absolute alcohol, was reduced catalytically with palladium on charcoal in the presence

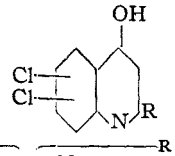
(1) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(2) The Board for the Coördination of Antimalarial Studies, *Science*, **103**, 8 (1946).

(3) Villiger, *Ber.*, **42**, 3529 (1909).

(4) All melting points are uncorrected. Microanalyses were done by Miss P. Curran and Mrs. G. Barnett. Titrations and halogen analyses were carried out under the direction of Mr. M. E. Auerbach.

TABLE I



	Yield, %	R = $COOC_2H_5$ M. p., °C.	Nitrogen, % Calcd.	Found	R = COOH M. p., °C.	Nitrogen, % Calcd.	Found	R = H M. p., °C.	Nitrogen, % Calcd.	Found
5,7-Dichloro	55	253–254	4.89	5.19	267–268	5.42	5.41	345–346	6.54	6.69
5,8-Dichloro	50	153–154	4.89	4.98	260–261	258.1[a]	256.8–256.3	256–257	6.54	6.55
6,8-Dichloro	42	147.5–148.5	4.89	4.80	254–255	5.42	5.38	309–311	6.54	6.74
5,7-Dibromo	70	256–257	3.73	3.63	330–332	4.03	3.90	321–322	4.62	4.59

[a] Neutral equivalent.

TABLE II

TRICHLOROQUINOLINES

Cl	M. p., °C.	Yield, %	Nitrogen, % Calcd.	Found	Picrate M. p., °C.	Nitrogen, % Calcd.	Found
4,5,6	121.5–122.5	..	Cl, 45.76	Cl, 45.79	168.5–169.5	12.14	11.97
4,5,7[a]	105–106	50	6.03	5.94	169.5–171	12.14	12.15
4,5,8	140–141	95	6.03	5.83	[b]	...	...
4,6,7[a]	154–155	..	6.03	5.80	191.5–192.5	12.14	12.40
4,6,8	168–169	85	6.03	5.72	[b]	...	...
4,7,8	125–126	[c]	6.03	6.28	151–152	12.14	12.10
			Cl, 45.76	Cl, 45.44			
4,5,7[d]	131–132	60	4.35	4.14	178–179	10.18	10.31

[a] Mentioned in German Patent 683,692. [b] Formed no picrate. [c] Prepared from 8-amino compound. [d] 4-Chloro-5,7-dibromoquinoline.

TABLE III

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

*The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

SN*	Cl	R'	M. p., °C.	Yield, %	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found	Nitrogen Calcd.	Found
	5,6	3-Diethylamino-2-hydroxypropyl[a]	114.5–115.5	85	56.15	55.84	6.18	5.77	12.27	11.80
							Cl, 20.72	20.79	8.19[b]	8.16
	5,7	3-Diethylamino-2-hydroxypropyl[c]	124.5–126	70	56.15	56.05	6.18	6.28	12.27	12.21
12705	5,8	3-Diethylamino-2-hydroxypropyl[c]	102.5–103.5	73	56.15	56.51	6.18	6.37	12.27	12.26
13475	6,7	3-Diethylamino-2-hydroxypropyl[d]	135–136	80	56.15	56.56	6.18	6.09	12.27	12.10
	6,8	3-Diethylamino-2-hydroxypropyl[c]	139.5–141	80	56.15	55.91	6.18	6.30	12.27	12.12
	7,8	3-Diethylamino-2-hydroxypropyl[e]	136–137.5	75	56.15	55.97	6.18	5.91	12.27	12.17
							Cl, 20.72	20.61	8.19[b]	8.22
12015	5,7	4-Diethylamino-1-methylbutyl[f,g]		70	61.02	60.78	7.11	6.98	11.85	12.01
12513	5,8	4-Diethylamino-1-methylbutyl[h]		80	61.02	61.28	7.11	6.93	11.85	12.15
12599	6,8	4-Diethylamino-1-methylbutyl[c]	131–132.5	85	61.02	60.79	7.11	7.12	11.85	11.94
	6,8	2-*p*-Chlorophenyl-4-diethylaminobutyl[c,i]	134–136	55	61.25	61.58	5.77	5.92	9.32	8.94
							Cl, 23.64	23.30	6.22[b]	6.21
13591	5,7[k]	3-Diethylamino-2-hydroxypropyl[l]	108–109.5	75	44.56	44.59	4.91	5.54	9.75	9.98

[a] Recrystallized from Skellysolve B. [b] Titration of basic nitrogen by the Toennies and Callan method [*J. Biol. Chem.*, **125**, 259 (1938)]. [c] From Skellysolve C (b. p. 70–90°). [d] From benzene and Skellysolve A (b. p. 30–50°). [e] From benzene. [f] Mentioned in German Patent 683,692. [g] Distilled at 135–140° (0.001 mm.) [h] Distilled at 150–155° (0.001 mm.). [i] The preparation of 2-*p*-chlorophenyl-4-diethylaminobutylamine will be published by Dr. C. E. Kwartler and Mr. P. A. Lucas of these laboratories. [k] 5,7-Dibromo. [l] From ether.

of sodium acetate. After removing the alcohol, the product was steam distilled to yield colorless needles, m. p. 69–71°, which became discolored on standing. A mixed melting point determination with a sample, m. p. 68–70°, obtained on reduction of 7-chloro-8-nitroquinoline, showed no depression.

Proof of Structure of 4,6,7-Trichloroquinoline: (a) **Hydrolysis.**—Fifteen grams of 4,6,7-trichloroquinoline was refluxed for six hours with 150 cc. of concentrated hydrochloric acid and poured into water. The 6,7-dichloro-4-hydroxyquinoline thus obtained was purified by reprecipitation from dilute sodium hydroxide; yield, 10.5 g.

(b) **Oxidation.**—The hydroxy compound was oxidized with potassium permanganate, according to reported procedures, to yield 4,5-dichloroanthranilic acid, m. p. 207.5–209°.[3,5]

Anal. Calcd. for $C_7H_5Cl_2NO$: N, 6.79; neut. equiv., 206. Found: N, 6.87; neut. equiv., 207.4.

Bz-Dichloro-4-(R'-amino)-quinoline (Table III).—One mole of the 4-chloro compound was heated with two moles of the primary-tertiary diamine, according to previously described procedures.[1] The crude yields ranged from 85–98%.

Summary

The preparation of several trichloroquinolines

(5) Villiger reported a m. p. of 213–214° for the 4,5-dichloro- and 176–177° for the 5,6-dichloroanthranilic acid.

and 4-chloro-5,7-dibromoquinoline and their condensation with a primary–tertiary diamine are described.

Nitration of 4,7-dichloroquinoline yields the 8-nitro derivative which was converted to 4,7,8-trichloroquinoline.

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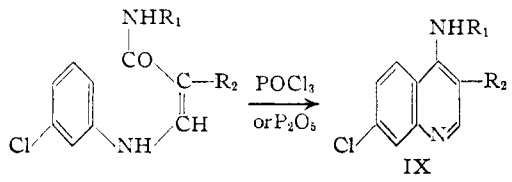
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

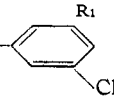
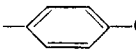
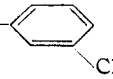
A Synthesis of Substituted 4-Aminoquinolines[1]

BY CHARLES C. PRICE[2] AND VIRGIL BOEKELHEIDE

A number of 4-aminoquinoline derivatives, especially those with a 7-chlorine atom, have been found to possess marked antimalarial activity.[3,4] The usual procedure for their preparation involves treatment of the requisite 4-chloroquinoline with the proper diamine side-chain. The synthesis of 4-hydroxyquinolines, necessary as intermediates in this type of preparation, has been discussed in a recent series of papers from this Laboratory.[5]

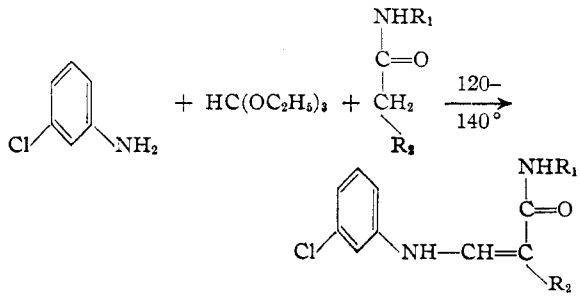
The present investigation was undertaken to find a general method of synthesis of the quinoline nucleus which would directly introduce an amino or a substituted amino group at the 4-position of the quinoline nucleus. This has been accomplished successfully by the cyclodehydration of a number of β-anilinoacrylamides according to the following scheme.



	R1	R2
I,		—$COOC_2H_5$
II,		—$COOC_2H_5$
III,		—CN
IV,		—CN
V,	$-(CH_2)_3CH_3$	—CN
VI,	$-(CH_2)_5CH_3$	—CN
VII,	$-(CH_2)_2CN$	—CN
VIII,	$-(CH_2)_5CN$	—CN

Although this method of ring closure has been widely used in the synthesis of isoquinolines,[6] and was also used by Drozdov[7] in the synthesis of atabrine, it has apparently never been applied to the synthesis of quinolines before. Since the quinolines desired were those with a halogen in the 7-position, the reaction was studied only with β-*m*-chloroanilinoacrylamides. Undoubtedly the reaction could be extended to other β-arylaminoacrylamides.

A desirable feature of this method of preparing quinolines is the ready availability of the β-arylaminoacrylamides. Claisen[8] discovered that aniline would react with ethoxymethylenemalonic ester to give β-anilino-α-carbethoxyacrylic ester. Band[9] had previously shown that β-anilino-α-carbethoxyacrylic ester would react with another molecule of aniline to give β-anilino-α-carbethoxyacrylanilide. Unfortunately, this reaction is suitable only when it is desired that the amide group be the same as the amino group on the β-carbon atom. Otherwise a mixture of products results. It was found, however, that the desired β-*m*-chloroanilinoacrylamides could be obtained by suitably modifying the above reaction. This was done by first preparing the proper amide of an acid having an adjacent active methylene group and by then allowing this amide to react directly with ethyl orthoformate and *m*-chloroaniline.[5c] This method proved to be very satisfactory and is illustrated below.



The use of β-*m*-chloroanilinoacrylamides made it necessary to establish the structure of the quinoline produced by this reaction. If cyclization occurred *para* to the chlorine already present in the benzene ring, the resulting quinoline would

(1) 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 the University of Illinois.

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(3) (a) Andersag, Breitner and Jung (to Winthrop Chemical Co.), U. S. Patent 2,233,970; *C. A.*, **35**, 3771 (1941); (b) (to I. G. Farbenindustrie, German Patent 683,692; *C. A.*, **36**, 4973 (1942).

(4) Iensch, *Z. angew. Chem.*, **50**, 891 (1937).

(5) (a) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946); (b) Price, Leonard and Herbrandson, *ibid.*, **68**, 1251 (1946); (c) Snyder and Jones, *ibid.*, **68**, 1253 (1946); (d) Price and Roberts, *ibid.*, **68**, 1255 (1946); (e) Price, Leonard and Reitsema, *ibid.*, **68**, 1256 (1946); (f) Leonard, Herbrandson and van Heyningen, *ibid.*, **68**, 1279 (1946).

(6) Kindler and Peschke, *Arch. Pharm.*, **272**, 236 (1934).

(7) Drozdov, *J. Gen. Chem.* (U. S. S. R.), **8**, 1192 (1938).

(8) Claisen, *Ann.*, **297**, 77 (1897).

(9) Band, *ibid.*, **285**, 145 (1895).