2. The syntheses of aminoalkyl derivatives of 3-nitro-4-aminoquinoline, 3-amino-4-hydroxyquinoline and 3-amino-4-quinolinethiol are described.

3. The preparations of various 2-substituted derivatives of the previously undescribed thiazolo[4,5-c]quinoline are reported.

4. Several derivatives of (4-hydroxy-3-quinolyl)-urea have been prepared.

LAFAYETTE, INDIANA RECEIVED AUGUST 12, 1946

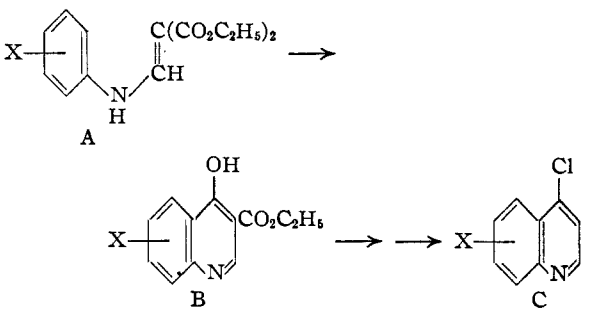
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthesis of 4-Hydroxyquinolines. VIII. Some Halogen Containing 4-Aminoquinoline Derivatives[1]

BY H. R. SNYDER, HERBERT E. FREIER,[2] PETER KOVACIC[3] AND EARLE M. VAN HEYNINGEN[4]

In connection with the development of antimalarial drugs it was desirable to have available for testing certain substances similar to SN-7618[5] but with a methoxyl group in the 5- or 6-position and other substances having a fluorine atom or a trifluoromethyl group in or near the position occupied by the chlorine atom of SN-7618.[5] This paper reports the synthesis of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-5-methoxyquinoline (SN-11,630)[5] (I), 7-chloro-4-(1-ethyl-4-piperidylamino)-6-methoxyquinoline (II), 4-(3-diethylaminopropylamino)-6-fluoroquinoline (SN-14,884)[5] (III), 4-(4-diethylamino-1-methylbutylamino)-7-fluoroquinoline (SN-13,986)[5] (IV), and 4-(4-diethylamino-1-methylbutylamino)-7-trifluoromethylquinoline (SN-11,524)[5] (V). The last of these compounds has been mentioned in the patent literature[6] and substances of the type represented by IV evidently have been studied[7] in Germany. A compound having the nucleus of II but with a different side chain was announced[8] while the present work was in progress.

The compounds reported herein were prepared by the condensation of a primary aromatic amine with ethoxymethylenemalonic ester, yielding an ethyl α-carbethoxy-β-arylaminoacrylate (A) which was converted to a 4-chloroquinoline (C) by cyclization, saponification, decarboxylation, and reaction with a mixture of phosphorus pentachloride and oxychloride.[9,10] The principal steps in the process are shown in the accompanying scheme.



The basic side chain was introduced by treatment of the 4-chloroquinoline with the appropriate diamine.

It was expected that the cyclization of each arylaminoacrylic ester (A) derived from a *meta*-substituted aniline would yield ultimately the 7-substituted 4-chloroquinoline as the major product, in analogy to the cyclization of the intermediate obtained from *m*-chloroaniline.[10] Of the *meta*-substituted esters studied in the present work, only the one derived from *m*-fluoroaniline gave a detectable amount of the 5-substituted quinoline; the pure 7-fluoro-4-hydroxyquinoline could be obtained by recrystallization from water. This structure, rather than that of 5-fluoro-4-hydroxyquinoline, is assumed for the isomer formed in larger quantity; the relationships of relative abundance in the cyclization mixture, of solubility of the 4-hydroxyhaloquinolines, and of activity of the final drugs in the 5- and 7-fluoro series then are the same as in the 5- and 7-chloro series. In an experiment in which the isomers were not separated, the mixture of 5- and 7-fluoro-4-chloroquinolines was treated with 1-diethylamino-4-aminopentane. Along with the expected mixture of the two fluorine-containing bases there was isolated a substance which contained no halogen and which, from its analysis, appeared to have been formed by replacement of

(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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(5) The Survey Number, designated SN-, refers to the number assigned a drug by the Survey of Antimalarial Drugs. The activities of these compounds will be tabulated in a forthcoming monograph.

(6) Andersag, Breitner and Jung, German Patent 683,692 (1939); *C. A.*, **36**, 4973 (1942).

(7) Curtis, Davis, Smadel, Southworth and Volwiler, "Pharmaceuticals and Insecticides at I. G. Farben Plants, Elberfeld and Leverkusen," Report No. 237, Office of the Publication Board, Department of Commerce, Washington, D. C.

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

(9) Gould and Jacobs, THIS JOURNAL, **61**, 2890 (1939).

(10) Price and Roberts, *ibid.*, **68**, 1204 (1946).

TABLE I

Substituents	Recrystallization solvent	M. p.,[a] °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Ethyl α-Carbethoxy-β-phenylaminoacrylates						
4-F	....	(Not isolated)				
3-F	....	(Not isolated)				
3-F_3C	C_2H_5OH	45–46	54.38	4.86	54.41	4.94
3-Cl, 5-CH_3O	Pet. ether (60–68°)	62–64	54.96	5.52	55.04	5.75
3-Cl, 4-CH_3O	C_2H_5OH	101–101.5	54.96	5.52	55.08	5.82
3-Carbethoxy-4-hydroxyquinolines						
6-Fluoro	C_5H_5N	288–289	61.27	4.28	61.19	4.40
7-Fluoro	....	.....	...	..	...	..
7-Trifluoromethyl	$CH_3O(CH_2)_2OH$	294–297	54.74	3.53	54.90	3.63
5-Methoxy-7-chloro	....[b]	310–312[c] (dec.)	55.43	4.30	55.65	4.27
6-Methoxy-7-chloro	CH_3CO_2H[b]	299 (dec.)	55.43	4.30	55.27	4.34
3-Carboxy-4-hydroxyquinolines						
6-Fluoro	C_5H_5N	248–249 (dec.)	57.97	2.91	58.18	3.02
7-Fluoro	....	.....	...	..	...	..
7-Trifluoromethyl	95% C_2H_5OH	250 (dec.)	51.37	2.35	51.64	2.42
5-Methoxy-7-chloro	....[d]	.....	...	..	...	..
6-Methoxy-7-chloro	CH_3CO_2H[e]	276 (dec.)	52.08	3.18	52.08	3.31
4-Hydroxyquinolines						
6-Fluoro	H_2O	221–223	66.25	3.70	66.52	3.43
7-Fluoro	H_2O	.....	...	..	...	..
7-Trifluoromethyl	50% C_2H_5OH	268–270	56.34	2.84	56.28	2.99
5-Methoxy-7-chloro	50% C_2H_5OH	246–250 (dec.)	57.29	3.85	57.06	3.98
6-Methoxy-7-chloro	....[f]					
4-Chloroquinolines						
6-Fluoro	Pet. ether	76.5–77	59.52	2.77	59.80	2.86
7-Fluoro	Pet. ether	73.5–74	59.52	2.77	59.72	2.87
7-Trifluoromethyl	CH_3OH[b]	71–72	51.85	2.18	51.92	2.12
5-Methoxy-7-chloro	CH_3OH	134–135	52.66	3.09	52.58	3.12
6-Methoxy-7-chloro	C_2H_5OH[f]	161.5–162.5	52.66	3.09	52.78	3.10

[a] All melting points are uncorrected unless otherwise indicated. [b] Sublimed. [c] In an aluminum block. [d] Difficult to purify. [e] Also from cellosolve. [f] Surrey and Hammer, THIS JOURNAL, **68,** 113 (1946).

both the chlorine and fluorine atoms by dialkylaminoalkylamino groups.

Experimental[11]

1. **Ethyl α-Carbethoxy-β-phenylaminoacrylates.**—A mixture of equimolar quantities of *m*-trifluoromethylaniline[12] and ethoxymethylenemalonic ester was allowed to stand at room temperature for one-half hour and then heated to 50°. The temperature was raised from 50 to 70° over a period of one and one-half hours while the alcohol formed was removed under diminished pressure. The residual yellow oil crystallized on standing and corresponded in weight to the theoretical yield. It was recrystallized from 95% ethanol.

Additional details concerning ethyl α-carbethoxy-β-(*m*-trifluoromethylphenylamino)-acrylate appear in Table I. In the preparation of analogous compounds the reaction mixtures were heated directly to temperatures of about 110° for one hour; other details are shown in Table I.

2. **3-Carbethoxy-4-hydroxyquinolines.**—To 100 ml. of refluxing diphenyl ether was added 16.5 g. of the acrylate over a period of twenty minutes; refluxing was continued for an additional twenty minutes. The alcohol formed was allowed to escape through an air condenser. After the mixture had cooled to room temperature, 25 ml. of petroleum ether (b. p. 85–110°) was added. The light brown product was collected by filtration and washed with petroleum ether; wt. 12 g. (84% yield). Details of the preparations appear in Table I.

3. **3-Carboxy-4-hydroxyquinolines.**—A mixture of 56.5 g. (0.2 mole) of the crude ester and 395 ml. of 10% sodium hydroxide solution was refluxed for two and one-half hours. The solution was allowed to cool to room temperature and any diphenyl ether present was extracted with petroleum ether (b. p. 85–110°). The aqueous solution was made faintly acidic with 10% hydrochloric acid and the precipitate was filtered from the cooled solution. The acid was washed with water and dried at 80°; wt. 48 g. (95%).

Other saponifications were effected in the same way except that because of its low solubility 3-carbethoxy-7-chloro-4-hydroxy-5-methoxyquinoline was saponified in a 50% alcohol solution. The yields were practically quantitative. Other details appear in Table I.

4. **4-Hydroxyquinolines.**—3-Carboxy-4-hydroxy-7-trifluoromethylquinoline was heated in an Erlenmeyer flask for two or three minutes at 260°; the product solidified during the heating. From 49.5 g. (0.19 mole) of the carboxyquinoline, decomposed in 16.5-g. portions, there was obtained 39 g. (94% yield) of crude material.

Decarboxylation of the other carboxyquinolines was effected by heating in 8 parts of refluxing Dowtherm (a mixture of phenyl ether and biphenyl) for thirty to forty minutes. The cooled solution was then diluted with

(11) The microanalyses were carried out by Miss Theta Spoor, Miss Lillian Hruda and Mr. Howard Clark.

(12) Kindly supplied by Dr. G. C. Finger.

TABLE II

4-(R'-AMINO)-QUINOLINES

R =	R' =	Solvent	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
6-Fluoro	3-Diethylaminopropyl	$C_6H_4(CH_3)_2$	65–65.5	69.78	8.05	70.05	7.99
7-Fluoro	4-Diethylamino-1-methylbutyl	Pet. ether	85–86	71.25	8.64	71.38	8.40
7-Trifluoromethyl	4-Diethylamino-1-methylbutyl	.....	83–85	64.56	7.42	64.47	7.23
5-Methoxy-7-chloro	4-Diethylamino-1-methylbutyl	.....	An oil	65.22	8.07	65.14	8.16
6-Methoxy-7-chloro	1-Ethyl-4-piperidyl	$CHCl_3$-C_6H_6	218.5–220 (dec.)	63.83	6.93	63.95	6.75

petroleum ether (b. p. 85–110°) and the product removed by filtration. The yields by this method were generally above 85%.

5. **4-Chloroquinolines.**—A mixture of 4 g. of phosphorus pentachloride and 4.61 g. of phosphorus oxychloride was heated to 90° and 3.9 g. of 4-hydroxy-7-trifluoromethylquinoline was added. The reaction mixture was then heated at 130° for forty minutes. After the phosphorus oxychloride was removed by distillation, the residue was stirred with 30 ml. of ice water, collected on a filter and washed with cold water. Neutralization of the combined filtrate and washings with 10% sodium hydroxide solution gave a small additional amount of the chloro compound. The total yield of crude material was 3.8 g. (90%).

The yields of the crude chloroquinolines were as follows: 4-chloro-6-fluoroquinoline, 77%; 4-chloro-7-fluoroquinoline, 70%; 4,7-dichloro-6-methoxyquinoline, 77%; 4,7-dichloro-5-methoxyquinoline, 21%.

6. **4-Alkylaminoquinolines.** (a) **4-(4-Diethylamino-1-methylbutylamino)-7-trifluoromethylquinoline.**—(Procedure A.) A mixture of 20 g. of the chloroquinoline and 62 g. of 1-diethylamino-4-aminopentane was heated at 190° for four hours. The subsequent removal of excess 1-diethylamino-4-aminopentane left a brown viscous oil (wt. 39 g.) which was dissolved in 800 ml. of 95% alcohol. A solution of 60.8 g. of picric acid in 850 ml. of 95% alcohol was added, and the mixture was heated to boiling and then allowed to cool. The crude picrate was purified by repeated triturations with 500-ml. portions of hot alcohol. The pure picrate weighed 51 g. (72% yield) and melted at 205–209°.

Anal. Calcd. for $C_{31}H_{32}N_9O_{14}N_3$: C, 45.87; H, 3.97. Found: C, 45.99; H, 4.23.

The picrate was decomposed by shaking with a mixture of benzene and concentrated hydrochloric acid. The acid solution was made basic with 10% sodium hydroxide solution and the amine extracted with 600 ml. of toluene. After being washed well with water, the toluene solution was dried over sodium sulfate and then decolorized with Norit. The toluene was removed by distillation under a pressure of 20 mm. while nitrogen was passed through the ebullition tube. The residual viscous oil solidified on standing for a few hours. The somewhat sticky solid was washed three times with petroleum ether (b. p. 30–60°) and then dried in a vacuum desiccator. The hygroscopic, crystalline product weighed 15 g. (67% yield based on the picrate). The physical constants and analyses of the various drugs appear in Table II.

(b) **7-Chloro-4-(4-diethylamino-1-methylbutylamino)-5-methoxyquinoline** was prepared in a similar manner with the modification that the reaction mixture was heated at 160–165° for seven hours. The base was obtained in 60% yield (based on 4,7-dichloro-5-methoxyquinoline). The picrate melted with decomposition at 176–178°.

Anal. Calcd. for $C_{31}H_{34}N_9O_{15}Cl$: C, 46.07; H, 4.25. Found: C, 45.98; H, 4.37.

(c) **7-Chloro-4-(1-ethyl-4-piperidylamino)-6-methoxyquinoline.**—(Procedure B) The method employed is based on that of Fuson, Parham and Reed[13] for the preparation of 7-chloro-4-(1-ethyl-4-piperidylamino)-quinoline. A mixture of 4,7-dichloro-6-methoxyquinoline (4.56 g.), 1-ethyl-4-aminopiperidine (2.57 g.) and phenol (5 g.) was heated for six and one-half hours at 160–164° and then for seventy minutes at 170°. The crude product was obtained from the reaction mixture as described[13] and weighed 4.75 g. (74.5% yield).

The picrate melted at 248° (dec.) after darkening at 240°.

Anal. Calcd. for $C_{29}H_{28}N_9O_{15}Cl$: C, 44.76; H, 3.62. Found: C, 44.98; H, 3.72.

(d) **4-(3-Diethylaminopropylamino)-6-fluoroquinoline.**—(Procedure C) This method is similar to that described by Surrey and Hammer[8] for the preparation of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline. The reaction mixture was heated at 160° for three and one-half hours and then at 165° for two hours. The base was obtained by distillation in 68% yield.

The picrate melted at 200–201°, from alcohol.

Anal. Calcd. for $C_{28}H_{28}N_9O_{14}F$: C, 45.84; H, 3.85. Found: C, 45.84; H, 3.73.

(e) **4-(4-Diethylamino-1-methylbutylamino)-7-fluoroquinoline** was prepared in a similar manner in 38% yield.

7. **Separation of 7-Fluoro-4-hydroxyquinoline from 5-Fluoro-4-hydroxyquinoline.**—A 9-g. quantity of the mixture of hydroxyquinolines, m. p. 219–234°, was recrystallized from 700 cc. of water and decolorized with Darco. Fine white crystals, wt. 4.8 g., m. p. 241–246°, were obtained. Another recrystallization gave 2.6 g. of material, m. p. 245–247°. Material melting at this point could be used to prepare pure 4-chloro-7-fluoroquinoline.

In another run, a similar procedure gave material melting at 247–249°.

8. **Amination of the Mixture of 5- and 7-Fluoro-4-chloroquinolines.**—A procedure similar to that of Surrey and Hammer[8] was used.

The mixture of chloroquinolines (7.4 g.), m. p. 60–69°, was heated with 1-diethylamino-4-aminopentane (14.2 g.) for three hours at 165–170°. Following the removal of excess 1-diethylamino-4-aminopentane, the reaction mixture was subjected to distillation under a pressure of 0.001 to 0.0001 mm. The expected product distilled at a temperature of 145–150° with the bath temperature at 195–220°.

After the first fraction was collected, a dark red, viscous oil distilled at 220–225° with the bath temperature at 330–335°. There was obtained about 1 g. of material which did not crystallize on standing.

Anal. Calcd. for $C_{27}H_{47}N_5$: C, 73.42; H, 10.72; N, 15.85. Found: C, 73.24; H, 10.09; N, 15.51.

Addition of this material to alcoholic picric acid resulted in the formation of a dark, viscous oil which, on crystallization from water, gave a yellow *picrate*, m. p. 58–78°. The picrate decomposes on standing.

Anal. Calcd. for $C_{45}H_{56}N_{14}O_{21}$: C, 47.87; H, 4.99. Found: C, 47.78; H, 5.13.

9. **Rate of Reaction of 4-Chloroquinolines with Amines.**—The analytical method followed was that of Volhard. Standard 0.0100 *N* silver nitrate and standard 0.0101 *N* potassium thiocyanate were used. In a titration, exactly 0.05 ml. of the reaction mixture was withdrawn by a graduated pipet. To this were added about 10 ml. of standard silver nitrate (accurately measured), 0.6 ml. of 6 *N* nitric acid and 10 drops of saturated ferrous ammonium sulfate solution; the solution was covered with

(13) Fuson, Parham and Reed, THIS JOURNAL, **68**, 1239 (1946).

4 ml. of ether. The titration was conducted with potassium thiocyanate to a red-pink end-point that persisted on shaking. It was shown that the chloroquinoline did not hydrolyze under these conditions. As a general rule, a small amount of color in the reaction mixture did not interfere with observation of the end-point.

A. **Reaction of 4,7-Dichloroquinoline with 1-Diethylamino-4-aminopentane.**—A mixture of 1 g. (0.005 mole) of 4,7-dichloroquinoline and 2.30 g. (0.014 mole) of 1-diethylamino-4-aminopentane was heated at 170–175° under an atmosphere of dry nitrogen. When a sample was to be taken, the reaction flask was allowed to cool for several minutes. Then the sample was removed and the flask immediately lowered into the bath. Titrations were performed as above.

TABLE III

Time, min.	$AgNO_3$, ml.	Reaction, %
0	0	0
25	0.38	5
60	1.09	15
120	2.00	28
180	4.93	68
225	6.57	91
300	6.72	93

The reaction product was isolated by removal of excess 1-diethylamino-4-aminopentane by distillation under reduced pressure. The crude picrate melted at 197–200°. (The pure material melts at 205°.)[14]

B. **Reaction of 4,7-Dichloro-5-methoxyquinoline with 1-Diethylamino-4-aminopentane.**—In each of the following experiments, 1 g. (0.004 mole) of chloroquinoline and 3.0 g. (0.019 mole) of 1-diethylamino-4-aminopentane were treated as in A. The temperature of the mixture of the first experiment was 175–180°; of the second, 160–165°.

TABLE IV

Time, min.	$AgNO_3$, ml.	Reaction, %
	(1)	
30	3.99	78
80	5.07	100
140	5.08	100
	(2)	
0	0	0
40	2.80	50
60	3.68	66
95	4.81	87
115	5.49	99
145	5.54	100

The product from the second experiment was the more readily purified.

(14) C. C. Price, private communication.

Summary

A number of halogen-containing 4-aminoquinoline derivatives were prepared by a series of reactions involving the initial condensation of various anilines with ethoxymethylenemalonic ester. The intermediates are described.

An analytical procedure was devised for following the course of reaction of 4-chloroquinolines with amines.

URBANA, ILLINOIS RECEIVED SEPTEMBER 23, 1946

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

Synthesis of 4-Hydroxyquinolines. IX. 4-Chloro-7-cyanoquinoline and 4-Chloro-5-cyanoquinoline[1]

BY CHARLES C. PRICE,[2] H. R. SNYDER, ORVILLE H. BULLITT, JR.,[3] AND PETER KOVACIC[3a]

In continuation of the studies on antimalarial agents, 4-chloro-7-cyanoquinoline and 4-chloro-5-cyanoquinoline were synthesized as intermediates for the preparation of 4-dialkylaminoalkylaminoquinolines.

A modification of the method of Price and Roberts[4] was utilized for the preparation of 4-chloro-7-cyanoquinoline. 3-Carbethoxy-4-hydroxy-7-nitroquinoline was obtained in the usual manner from *m*-nitroaniline and ethoxymethylenemalonic ester. Subsequent reduction of the nitro group and hydrolysis of the carbethoxyl group gave 7-amino-3-carboxy-4-hydroxyquinoline in good yield. A satisfactory procedure was devised for decarboxylation of the acid. The structure of 7-amino-4-hydroxyquinoline was proved by conversion to 7-chloro-4-hydroxyquinoline which was identical with the authentic material. The preparation of the 7-cyano compound by the Sandmeyer reaction of 7-amino-4-hydroxyquinoline could be effected only in low yield; the occurrence of tautomerization[5] in the 4-hydroxyquinoline could account for the difficulties involved in diazotization.

In the early work involving the cyclization of ethyl α-carbethoxy-β-(*meta*-substituted)-anilinoacrylates, there was no indication of the presence of isomers when the syntheses were carried out on a laboratory scale. Only one isomer was isolated from a Price–Roberts synthesis with *m*-chloroaniline,[4] *m*-nitroaniline, *m*-trifluoromethylaniline,[6] 3-chloro-5-methoxyaniline[6] and 3-chloro-4-methoxyaniline.[6] After the discovery that the cyclization of ethyl α-carbethoxy-β-(*m*-fluoro-

(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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(4) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

(5) Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, New York, N. Y., 1942, p. 552.

(6) Snyder, Freier, Kovacic and Van Heyningen, THIS JOURNAL, **69**, 371 (1947).