Chlorination of Quinoline

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Chlorination of Quinoline at 160-190° without solvent gave a mixture of compounds. The five major components were isolated and identified as 3,4-dichloro-, 3,4,6-, 3,4,8-trichloro-, 3,4,6,8-tetrachloro- and 3,4,6,7,8-pentachloroquinolines.

Halogenations of azoaromatics are surprisingly little understood as pointed out in recent reviews (1,2). In 1882, Smith and Davis (3) chlorinated quinoline exhaustively to hexachloroethane and hexachlorobenzene. Recently, Taplin (4) chlorinated quinoline in vapor phase to heptachloroquinoline. Edinger and Lubberger (5) chlorinated quinoline in the presence of sulfur to give 3-chloroquinoline. Din and Choudhury (6), obtained 5-, 8-chloro- and 5,8-dichloroquinolines from sulfuric acid-silver sulfate mixture. In the presence of aluminum chloride, Gordon and Pearson (7) also obtained 5,8-dichloroquinoline, and a tetrachloroquinoline on further chlorination. Kwart and Miller (8) in their study of chlorinolysis of 4-benzylthio-7-chloroquinoline with chlorine in acetic acid observed the expected 4,7-dichloroquinoline and a pentachloroquinoline.

We have taken an exploratory look at the direct chlorination of quinoline and obtained a mixture of more than ten components. However, when the major components were isolated and identified, order appeared out of the seemingly random reaction. The results are reported here.

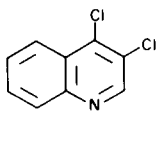
A typical chlorination run at 160-190° showed the following components on GLC:

TABLE I

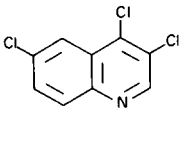
GLC Analysis of Chlorination Products

Peak Number	Area %	Retention Time
1	0.5	2.0 min.
2	14.9	2.8 min.
3	9.7	4.4 min.
4	4.3	5.7 min.
5	18.9	6.7 min.
6	17.1	9.6 min.
7	5.2	12.0 min.
8	2.0	13.8 min.
9	1.8	18.0 min.
10	14.8	21.6 min.
11	5.4	23.6 min.
12	2.7	38.0 min.

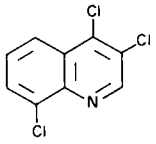
After repeated distillations under reduced pressure and crystallization, the five major components were isolated and assigned the following structures:



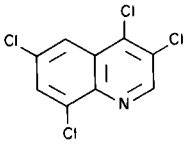
I
Peak 2



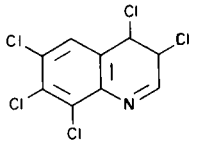
II
3



III
5

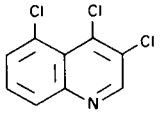


IV
6

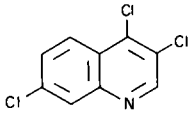


V
10

Structure determination was by a combination of mass-spectroscopy, IR, NMR and microanalysis. Structure determination of compound I was based on comparison with 3,4-dichloroquinoline reported by Surrey and Cutler (9), who also reported 3,4,5- and 3,4,7-trichloroquinolines, VI and VII.

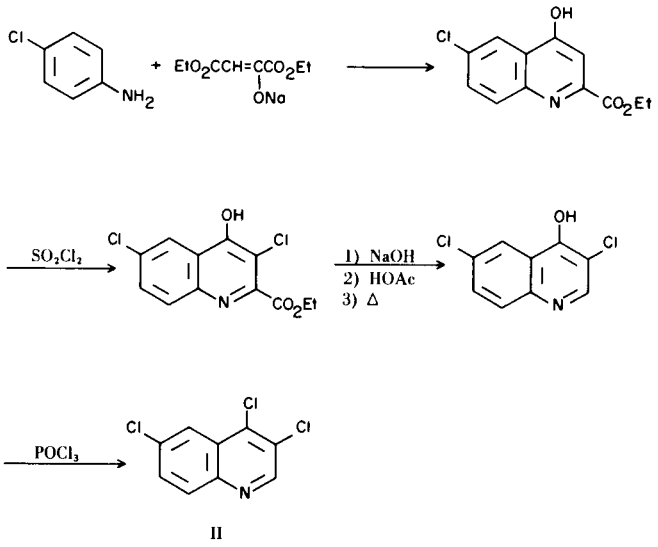


VI



VII

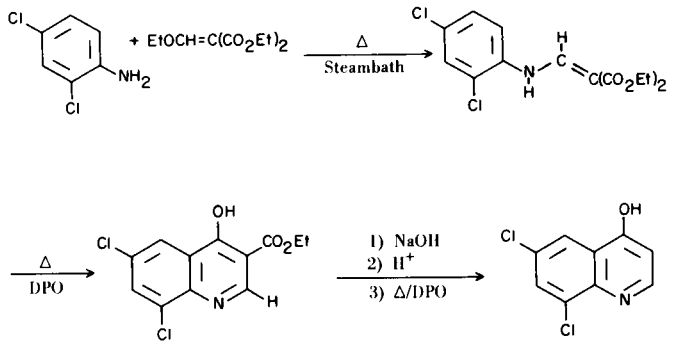
NMR-spectroscopy could not distinguish between II and VII, or III and VI. The melting points of III and its 4-anilino derivative (118-119°, 132-133°) differed sufficiently from that of VI and its 4-anilino derivative (85.0-85.5°, 115-116°) (9) to distinguish between them. Melting points of II and its 4-anilino derivative (113-114°, 149-150°) and VII and its 4-anilino derivative (114.0-114.5°, 149.0-149.5°) (9) were so close that the component corresponding to peak 3 was at first mistakenly assigned structure VII. However, direct synthesis of II by the following route (9) showed that the correct structure was II.

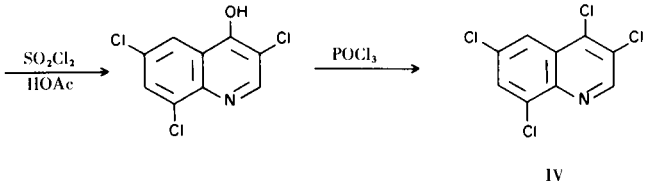


II

Starting with *o*-chloroaniline, and carrying out the same sequence of reactions, 3,4,8-trichloroquinoline was obtained and found to be identical with the component assigned to structure III. Compound VII was also synthesized by the method of Surrey and Cutler (9). Comparison of IR and NMR showed the non-identity of II and VII.

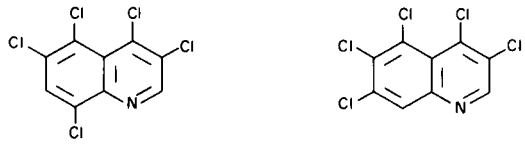
From 2,4-dichloroaniline, by the method of Riegel *et.al.* (10), 3,4,6,8-tetrachloroquinoline (IV) was prepared and was found to be identical to the component corresponding to peak 6.





IV

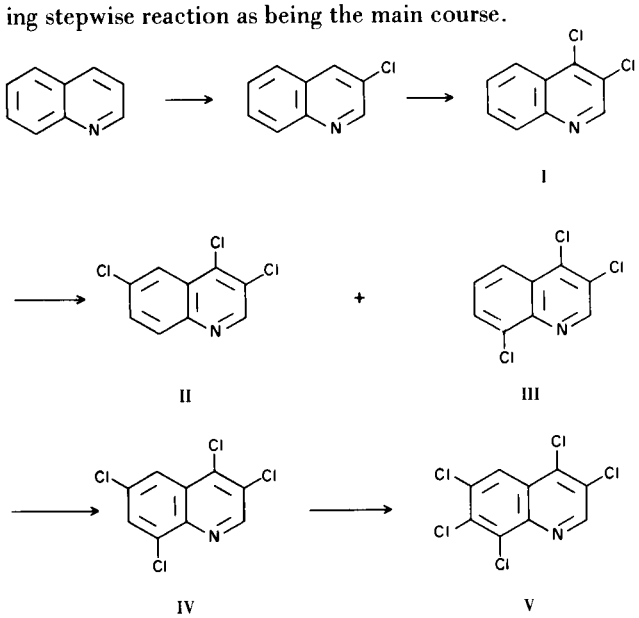
From 2,4,5-trichloroaniline and 3,4,5-trichloroaniline, by the same route, were prepared the 3,4,5,6,8- and 3,4,5,6,7-pentachloroquinolines, VIII and IX. They were found to be different from the component corresponding to peak 10.



VIII IX

Since the unknown showed two H^1-signals at 8.88 and 8.20 ppm, the presence of a hydrogen at 2-porition was suggested. Since the proton at 8.20 would be too low for a hydrogen atom at the 6-position, structure V with hydrogen at 5-position was proposed. The NMR data are summarized in Table II.

When chlorination was carried out in a very short time, 3-chloroquinoline was obtained. The formation of 3-chloroquinoline at the early stage of the reaction and the isolation of 3,4-dichloro-, 3,4,6- and 3,4,8-trichloro-, 3,4,6,8-tetrachloro- and 3,4,5,6,8-pentachloroquinolines in the more advanced stage of reaction, suggests the following stepwise reaction as being the main course.



I II III IV V

TABLE II

Chemical Shifts of Chlorinated Quinolines in p.p.m.

Quinolines	2	3	4	5	6	7	8	Notes
Unsubstituted	8.90	7.47	8.28	7.92	7.54	7.73	8.06	Acetone (a)
5,7-Dichloro-	8.82	7.34	8.39	---	7.50	---	7.95	Carbon tetrachloride (b)
5,6,8-Trichloro-	9.1	7.6	8.6	---	---	8.3	---	Methylene chloride (c)
3,4,6-Trichloro- (II)	8.85	---	---	8.18	---	7.74	8.08	Deuteriochloroform
3,4,7-Trichloro (VII)	8.90	---	---	8.23	7.7	---	8.16	Deuteriochloroform (d)
3,4,8-Trichloro (III)	8.86	---	---	8.0	7.48	7.76	---	Deuteriochloroform
3,4,6,8-Tetrachloro (IV)	8.95	---	---	8.07	---	7.79	---	Deuteriochloroform
3,4,6,7-Tetrachloro-	8.95	---	---	8.42	---	---	8.35	Dueteriochloroform (e)
3,4,5,6,7-Pentachloro-(IX)	8.86	---	---	---	---	---	8.21	Deuteriochloroform
3,4,5,6,8-Pentachloro- (VIII)	8.94	---	---	---	---	7.98	---	Carbon tetrachloride
3,4,6,7,8-Pentachloro- (V)	8.88	---	---	8.20	---	---	---	Deuteriochloroform

(a) W. Brugel, Nuclear Magnetic Resonance Spectra and Chemical Structure, Vol. I, Academic Press, N. Y., 1967, p. 166. (b) F. A. L. Anet, *J. Chem. Phys.*, 32, 1274 (1960). (c) M. Gordon, H. J. Hamilton, C. A. Adkins, J. Hay, and D. E. Pearson, *J. Heterocyclic Chem.*, 4, 410 (1967). (d) Synthesized by the method of Surrey and Cutler, *J. Am. Chem. Soc.*, 68, 2570 (1946). (e) By-product in the synthesis of 3,4,7-trichloroquinoline due to over-chlorination. Identified by mass spectrum and NMR only.

TABLE III

		Calcd.			Found		
Quinolines	M.p.	C	H	N	C	H	N
3,4-Cl_2	68-69° (69-70) (a)	54.56	2.54	7.07	54.6	2.4	7.0
3,4,6-Cl_3	113-114° (108-109) (b)	46.49	1.73	6.03	46.6	1.7	5.9
3,4,8-Cl_3	118-119° (121-122) (b)				46.5	1.7	6.4
3,4,6,8-Cl_4	190-192° (202-203) (b)	40.49	1.13	5.24	40.47	1.04	4.99
3,4,6,7,8-Cl_5	202-203°	35,86	.67	4.65	36.1	.8	4.7

(a) Ref. 9. (b) For individual synthesis, see Experimental.

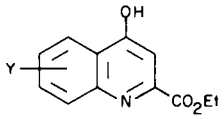
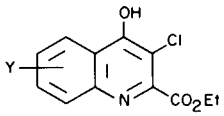
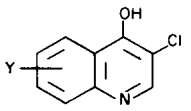
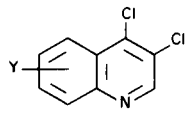
The introduction of the 4-chlorine atom is markedly different from the general course of bromination, which takes place at the 3-, 6- or 8-positions (11), and it probably takes place through addition-elimination similar to that of the formation of 4-bromoquinoline (12). In fact, the whole reaction may be an orderly sequence of addition-elimination reactions.

EXPERIMENTAL (13)

General Procedure for Chlorination.

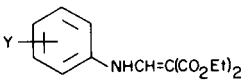
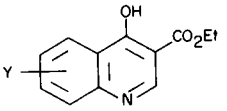
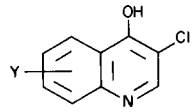
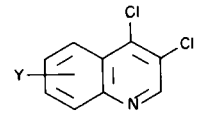
Quinoline was placed in a 100 ml. resin pot fitted with a condenser, gas inlet, thermometer attached to Lab-stat-heat lamp and magnetic stirrer. Chlorine was bubbled in after the temperature of the reactant had been brought to the desired range. The heavy paste-like material obtained from the reaction was dissolved in

TABLE IV

Compounds	M.p.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
	Y = 6-Cl 214-220°	57.26	4.01	5.57	57.5	3.7	6.1
	8-Cl 144-147°				57.2	3.9	5.6
	Y = 6-Cl 250-253°	50.39	3.17	4.90	50.7	3.0	5.0
	8-Cl 115-116°				50.5	3.2	4.9
	Y = 6-Cl 340°	50.48	2.35	6.54	50.52	2.37	6.57
	8-Cl 297-300°				50.8	2.5	6.7
	Y = 6-Cl 108-109° (a)						
	8-Cl 121-122°						

(a) No attempt was made to reach the highest m.p. by repeated recrystallization. Comparisons and identification with compounds obtained from direct chlorination were made by IR (carbon disulfide, Nujol mull), and NMR (in deuteriochloroform).

TABLE V

Compounds	M.p.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
	Y = 2,4-Cl_2 107-109°	50.60	4.55	4.22	50.56	4.78	4.11
	3,4,5-Cl_3 91-92°	45.87	3.85	3.82	45.81	3.68	3.69
	2,4,5-Cl_3 114-115°				46.3	3.86	3.6
	Y = 6,8-Cl_2 305°	50.39	3.17	4.90	50.18	2.96	5.25
	5,6,7-Cl_3 318°	44.97	2.52	4.37	44.91	2.36	4.31
	5,6,8-Cl_3 273-275°				45.4	2.6	4.4
	Y = 6,8-Cl_2 342-345°	43.52	1.62	5.64	43.37	1.67	5.79
	5,6,7-Cl_3 (a)						
	5,6,8-Cl_3 (a)						
	Y = 6,8-Cl_2 202-203° (b)						
	5,6,7-Cl_3 143-144° (b) (c)	35.86	0.67	4.65	35.57	.3	(d)
	5,6,8-Cl_3 (c) (c)						

(a) Chlorination of the trichloro-4-quinolinols were not complete and products were not separated from starting material. The mixtures were reacted with phosphorus oxychloride to give the corresponding 4-chloro compounds. (b) Comparisons and identifications with compounds obtained from direct chlorination were made by IR (carbon disulfide, Nujol mull), and NMR (in deuteriochloroform). (c) Identification by mass-spectroscopy. (d) Not enough sample for nitrogen analysis.

dichloromethane and the solution was washed with potassium carbonate solution, dried, and concentrated.

When the reaction was carried out at 100° for 10 minutes, only a small amount of 3-chloroquinoline was produced. When the reaction was carried out at 160-190° for 10 hours, a mixture was obtained from which the five major products were isolated.

A 10' - ¼" column of 3% Silicone 710 on ABS was used for GLC analysis. Products were isolated by a combination of distillation and crystallization followed by GLC. Structure assignments were based on data from elementary analyses, mass spectroscopic, NMR, IR and comparison with known compounds or compounds synthesized by unequivocal routes. Data for the major products are summarized in Table III.

3,4,6-Trichloroquinoline and 3,4,8-Trichloroquinoline.

From *p*-chloroaniline, or *o*-chloroaniline, and the sodium salt of diethyl oxalacetate, using the procedure of Surrey and Cutler (9), the above compounds were prepared. Data for the intermediates and final products are summarized in Table IV.

3,4,6,8-Tetra, 3,4,5,6,7- and 3,4,5,6,8-Pentachloroquinolines.

Using the method of Riegel *et.al.* (10), condensation of diethyl ethoxymethylenemalonate with 2,4-dichloroaniline, 3,4,5-trichloroaniline or 2,4,5-trichloroaniline, followed by ring closure, hydrolysis and decarboxylation, the corresponding 4-quinolinols were obtained. Chlorination and replacement of the hydroxyl group with the chloro group gave the above compounds. Data for the intermediates and final products are summarized in Table V.

REFERENCES

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(4) W. H. Taplin III, U. S. Patent 3,420,833, September 8, 1967.

(5) A. Edinger and H. Lubberger, *J. Prakt. Chem.*, **162**, 340 (1896); R. H. Baker, C. J. Albisetti, Jr., R. M. Dodson, G. R. Lappin, and B. Riegel, *J. Am. Chem. Soc.*, **68**, 1532 (1946). *inter alia.*

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(9) A. R. Surrey and R. A. Cutler, *ibid.*, **68**, 2570 (1946).

(10) B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson, and R. H. Baker, *ibid.*, **68**, 1264 (1946).

(11) Ref. (1), p. 7, Table III.

(12) J. J. Eisch and B. Jaselskis, *J. Org. Chem.*, **28**, 2865 (1963).

(13) Melting points are uncorrected. NMR spectra were obtained in deuteriochloroform - TMS with Varian A-60 or T-60 spectrometer. Chemical shifts were reported in ppm downfield from TMS.

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