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Trichloromethylquinolines: Synthesis and Reaction with Trimethyl Phosphite

Tetsuzo Kato,* Nobuya Katagiri, and Akihiro Wagai

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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Heating of methylquinolines (**1**, **3**, **6**, and **12**) with phosphorus pentachloride in phosphoryl chloride gave the corresponding trichloromethylquinoline derivatives (**2**, **4**, **9**, and **14**). Similar treatment of 4-chloro-2-methyl-3-nitroquinoline (**16**) gave 4-chloro-2-dichloromethyl-3-nitroquinoline (**17**), 4-chloro-3-nitro-2-trichloromethylquinoline (**18**), and 3,4-dichloro-2-cyanoquinoline (**19**).

The reaction of 2-trichloromethylquinolines (**2**, **9**, and **18**) with trimethyl phosphite gave the corresponding methylated products, 2-(1,1-dichloroethyl)quinolines (**21**, **24**, and **27**). However, 4-trichloromethylquinolines (**4** and **14**) reacted with trimethyl phosphite under similar conditions to give 4-dichloromethylquinolines (**23** and **13**).

Keywords——chlorination; dichloromethylquinolines; trichloromethylquinolines; phosphorus pentachloride; phosphoryl chloride; trimethyl phosphite; methylation; phosphorylation; 2-(1,1-dichloroethyl)quinolines

Previously, we have reported that heating of methylpyridine derivatives with phosphorus pentachloride in phosphoryl chloride gives the corresponding trichloromethylpyridine derivatives.[1] Concerning methylquinoline homologs, chlorination using chlorine gas was reported to give trichloromethylquinolines.[2] They are also obtained by the reaction of phosphorus pentachloride with quinoline carboxylic acids[3] or their hydrazides.[4] In the present paper, we wish to report the reaction of methylquinoline derivatives with phosphorus pentachloride in phosphoryl chloride, and the reaction of the chlorinated products, trichloromethylquinolines with trimethyl phosphite.

Reaction of Methylquinoline Derivatives with Phosphorus Pentachloride in Phosphoryl Chloride

Heating of 2-methylquinoline (**1**) with phosphorus pentachloride in phosphoryl chloride gave 2-trichloromethylquinoline (**2**) in 61% yield. Similar treatment of 4-methylquinoline (**3**) gave 4-trichloromethylquinoline (**4**) and 3-chloro-4-trichloromethylquinoline (**5**) in 40% and 8% yields, respectively.

In 1888, Conrad *et al.*[5] reported that heating of 2-methyl-4(1*H*)-quinolone (**6**) with an equimolar amount of phosphorus pentachloride gave the monochloro- and trichloroquinoline derivatives, for which they proposed the structures 4-chloro-2-methylquinoline (**7**) and 4-chloro-2-dichloromethylquinoline (**8**), respectively. When this reaction was carried out by us in the presence of phosphoryl chloride, 4-chloro-2-trichloromethylquinoline (**9**) (60%) was obtained as well as 3,4-dichloroquinoline derivatives (**10** and **11**).

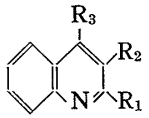
A similar reaction of 4-methyl-2(1*H*)-quinolone (**12**) gave 2-chloro-4-dichloromethylquinoline (**13**), 2-chloro-4-trichloromethylquinoline (**14**), and 2,3-dichloro-4-trichloromethylquinoline (**15**) in 10%, 27%, and 8% yields, respectively.

4-Chloro-2-methyl-3-nitroquinoline (**16**), under the same conditions, was transformed to 4-chloro-2-dichloromethyl-3-nitroquinoline (**17**), 4-chloro-3-nitro-2-trichloromethylquinoline (**18**), and 3,4-dichloro-2-cyanoquinoline (**19**) in 24%, 25%, and 3% yields, respectively. Physical and analytical data for the dichloro- and trichloromethylquinolines are summarized in Table I.

Upon catalytic reduction, compound **19** was readily reduced to 2-cyanoquinoline (**20**).

Formation of the 2-cyanoquinoline (**19**) might be rationalized as shown in Chart 2; namely, substitution of a chloro atom of $POCl_3$ for 3-nitro group of the quinoline (**16**) would give 3,4-

TABLE I. Physical and Analytical Data for Dichloro-and Trichloromethylquinolines



Compd. No.	R_1	R_2	R_3	mp (°C) or bp (°C)/mmHg	Appearance (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	NMR (CCl_4, ppm)
5	H	Cl	CCl_3	83—85	Colorless prisms (hexane)	$C_{10}H_5Cl_4N$	42.75 (42.87	1.79 1.70	50.47 50.38	4.99 4.99)	7.5—7.8 (2H, m, 6, 7-Hs), 8.0—8.2 (1H, m, 8-H),8.7—8.9 (1H, m, 5-H), 8.78 (1H, s, 2-H)
10	$CHCl_2$	Cl	Cl	109	Colorless needles (hexane)	$C_{10}H_5Cl_4N$	42.75 (42.64	1.79 1.75	50.47 50.37	4.99 4.82)	7.23 (1H, s, $-C\underline{H}Cl_2$), 7.6—8.3 (4H, m, 5, 6,7, 8-Hs)
11	CCl_3	Cl	Cl	134—135	Colorless needles (hexane)	$C_{10}H_4Cl_5N$	38.08 (38.19	1.28 1.22	56.20 56.36	4.44 4.58)	7.6—8.3 (4H, m, 5,6,7,8-Hs)
13	Cl	H	$CHCl_2$	96—100/0.005	Colorless oil	$C_{10}H_6Cl_3N$	48.72 (48.10	2.46 2.29	43.14 43.58	5.68 5.18)	7.20 (1H, s, $-C\underline{H}Cl_2$), 7.5—7.9 (2H, m, 6,7-Hs), 7.71 (1H, s, 3-H), 8.0—8.3 (2H, m, 5,8-Hs)
14	Cl	H	CCl_3	67—68	Colorless needles (hexane)	$C_{10}H_5Cl_4N$	42.75 (43.12	1.79 1.60	50.47 50.89	4.99 5.13)	7.4—7.9 (2H, m, 6,7-Hs), 7.98 (1H, s, 3-H), 8.04—8.2 (1H,m, 8-H), 8.5—8.8 (1H, m, 5-H)
15	Cl	Cl	CCl_3	59—61	Colorless needles (petroleum ether)	$C_{10}H_4Cl_5N$	38.08 (38.10	1.28 1.17	56.20 55.91	4.44 4.47)	7.5—8.15 (3H, m, 6,7,8-Hs), 8.65—8.90 (1H, m, 5-H)
17	$CHCl_2$	NO_2	Cl	156—158	Colorless needles (hexane)	$C_{10}H_5Cl_3N_2O_2$	41.20 (41.19	1.73 1.49	36.48 36.46	9.61 9.41)	7.09 (1H, s, $-C\underline{H}Cl_2$),[a] 7.8—8.6 (4H, m, 5,6,7,8-Hs)
18	CCl_3	NO_2	Cl	196	Colorless needles (hexane)	$C_{10}H_4Cl_4N_2O_2$	36.85 (36.81	1.24 1.02	43.50 43.08	8.59 8.38)	7.9—8.5 (4H, m, 5,[a] 6,7,8-Hs)

a) In $CDCl_3$.

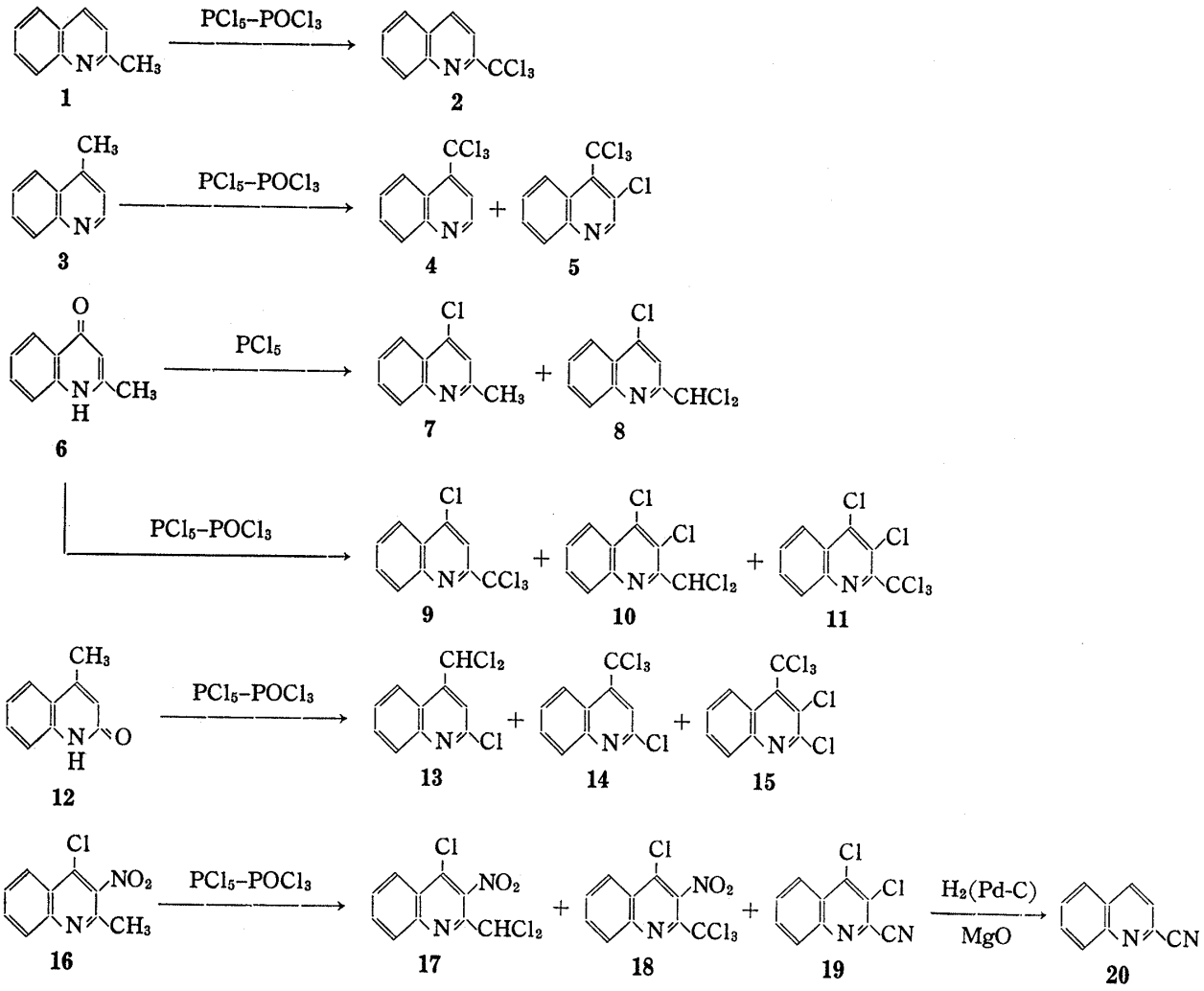


Chart 1

dichloro-2-methylquinoline (B) and nitroso phosphorodichloridate (A). The next stage might well involve nitrosation of the dichloroquinoline (B) with (A) to give the oxime (D) *via* the nitrosomethylquinoline intermediate (C). Dehydration of the oxime (D) with phosphorus pentachloride then gives the product (**19**).

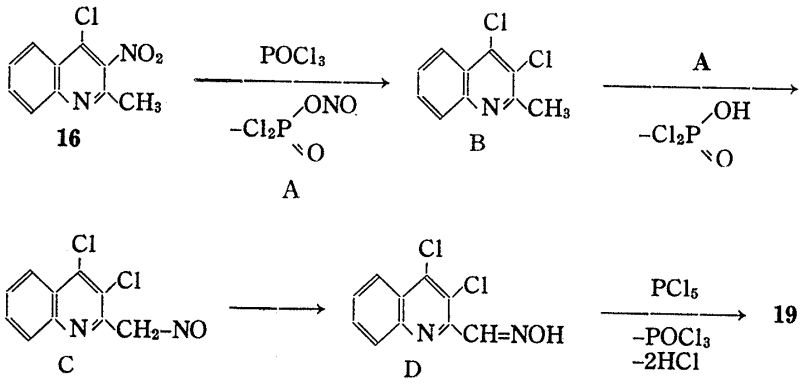


Chart 2

Reaction of Trichloromethylquinolines with Trimethyl Phosphite

It was reported[6] that benzotrichloride reacts with triethyl phosphite in the presence of cuprous chloride to give 1,1,2,2-tetrachloro-1,2-diphenylethane. A similar reaction in the

presence of potassium iodide gives diethyl dichlorophenylmethylphosphonate.[6] The reaction of 3-methyl-5-trichloromethyl-1,2,4-oxadiazole with trimethyl phosphite was also reported to give 3-methyl-5-dichloromethyl-1,2,4-oxadiazole or 3-methyl-5-(1,1-dichloropropyl)-1,2,4-oxadiazole.[7] Such C-alkylation was first reported by Mark,[8] who obtained 1,2,3,4,5-pentachloroalkylcyclopentadiene by the reaction of hexachlorocyclopentadiene with trialkyl phosphite. In view of these results, we investigated the reaction of trimethyl phosphite with trichloromethylquinoline derivatives thus obtained.

When 2-trichloromethylquinoline (**2**) was heated with trimethyl phosphite, 2-(1,1-dichloroethyl)quinoline (**21**) and 2-dichloromethylquinoline (**22**) were obtained in 73% and 9% yields, respectively. A similar reaction of 4-trichloromethylquinoline (**4**) gave 4-dichloromethylquinoline (**23**) in 33% yield, but the methylated product corresponding to compound **21** was not detected.

Similarly, 4-chloro-2-trichloromethylquinoline (**9**) reacted with trimethyl phosphite to give the dichloroethyl (**24**) and the dichloromethyl derivative (**8**) in 54% and 14% yields, respectively.

The reaction of 2-chloro-4-trichloromethylquinoline (**14**) gave the dichloromethylquinoline derivative (**13**). A similar reaction of 4-chloro-2-dichloromethyl-3-nitroquinoline (**17**) with trimethyl phosphite afforded the phosphorylated product, $C_{14}H_{18}Cl_2N_2O_6P_2$, to which we assigned the structure dimethyl 2-dichloromethyl-4-dimethylphosphonoquinoline-3-phosphoramidate (**25**) on the basis of spectral data detailed in the experimental section. Hydrolysis of compound **25** gave dimethyl 3-amino-2-formylquinoline-4-phosphonate (**26**).

Similarly, 4-chloro-3-nitro-2-trichloromethylquinoline (**18**) was transformed to the methylated compound (**27**) and the phosphorylated product (**28**) in 51% and 8% yields, respectively. Physical and analytical data for 2-(1,1-dichloroethyl)quinolines are summarized in Table II.

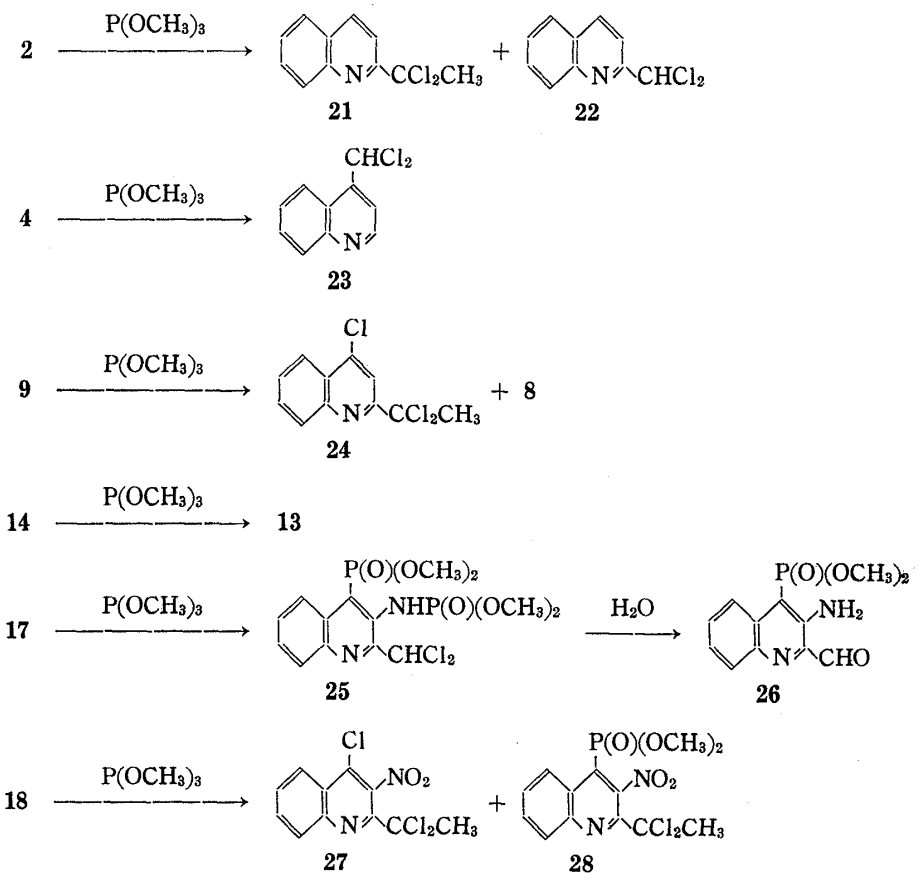
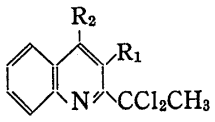


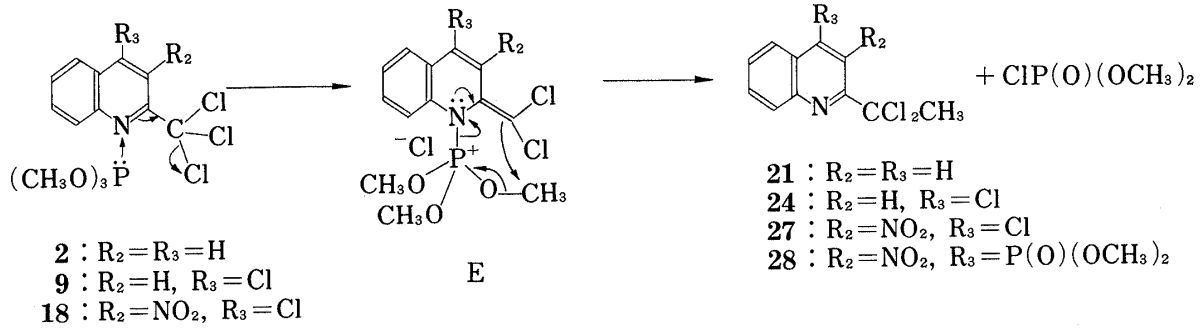
Chart 3

TABLE II. Physical and Analytical Data for 2-(1,1-dichloroethyl)quinolines



Compd. No.	R_1	R_2	mp (°C) or bp (°C)/mmHg	Appearance (Recrystn. solvent)	Formula
21	H	H	130—131/5	Colorless oil	$C_{11}H_9Cl_2N$
24	H	Cl	43—44	Colorless needles (petroleum ether)	$C_{11}H_8Cl_3N$
27	NO_2	Cl	165—166	Colorless needles (hexane)	$C_{11}H_7Cl_3N_2O_2$
28	NO_2	$P(O)(OCH_3)_2$	138—140	Pale yellow pillars (hexane)	$C_{13}H_{13}Cl_2N_2O_5P$

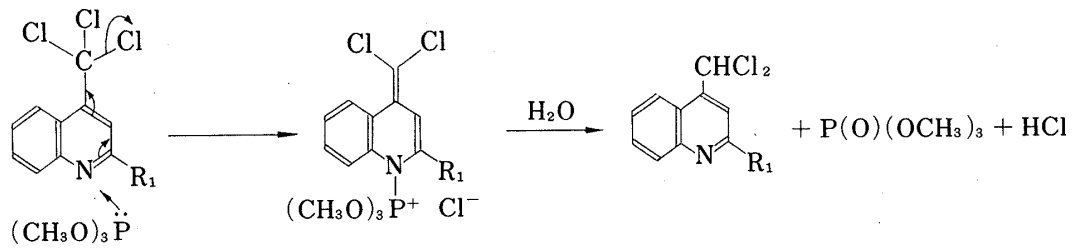
Compd. No.	Analysis (%) Calcd (Found) C	H	Cl	N	NMR ($CDCl_3$, ppm)
21	58.43 (58.13	4.01 4.19	31.36 31.33	6.19 6.20)	2.77 (3H, s, CH_3), 7.45—8.4 (6H, m, ring-Hs)
24	50.71 (50.43	3.09 3.05	40.82 40.92	5.38 5.47)	2.72 (3H, s, CH_3), 7.6—7.9 (2H, m, 6,7-Hs), 8.0—8.45 (2H, m, 5,8-Hs), 8.20 (1H, s, 3-H)
27	43.24 (43.33	2.31 2.35	34.81 34.81	9.17 9.04)	2.79 (3H, s, CH_3), 7.75—8.5 (4H, m, 5,6,7,8-Hs)
28	41.18 (41.04	3.46 3.41	18.70 18.79	7.39 7.46)	2.82(3H, s,CH_3), 3.91 (6H, d, $J=12$ Hz, $2\times POCH_3$), 7.5—8.4 (4H, m, 5,6,7,8-Hs)



2 : $R_2=R_3=H$
9 : $R_2=H$, $R_3=Cl$
18 : $R_2=NO_2$, $R_3=Cl$

E

21 : $R_2=R_3=H$
24 : $R_2=H$, $R_3=Cl$
27 : $R_2=NO_2$, $R_3=Cl$
28 : $R_2=NO_2$, $R_3=P(O)(OCH_3)_2$



4 : $R_1=H$
14 : $R_1=Cl$

F

23 : $R_1=H$
13 : $R_1=Cl$

Chart 4

The mechanism of the reaction can be explained as shown in Chart 4; namely, coordination of phosphorus to the ring nitrogen of 2-trichloromethylquinolines gives the 2-dichloromethylene intermediate (E). *Via* a six-membered transition state, the intermediate (E) undergoes fission between nitrogen and phosphorus, accompanied by transmethylation to give the methylated products (**21**, **24**, **27**, and **28**). Meanwhile, the 4-trichloromethylquinolines (**4** and **14**) would be transformed to the 4-dichloromethylene intermediate (F), which is hydrolyzed to the 4-dichloromethylquinolines (**23** and **13**).

Since the dichloroalkyl group is equivalent to a carbonyl group, this reaction should be useful for the preparation of 2-acylquinoline derivatives. We are currently studying the reaction of 2-trichloromethylquinolines with other trialkyl phosphites.

Experimental

Infrared (IR) spectra were taken on a JASCO IR-S spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured with a Hitachi R-20 instrument using tetramethylsilane as an internal standard. PLC plates of silica gel 60 F_{254} (Merck) were used for preparative thin-layer chromatography. Melting and boiling points are uncorrected.

2-Trichloromethylquinoline (**2**)——A mixture of 2-methylquinoline (**1**) (2.15 g, 0.015 mol), phosphorus pentachloride (PCl_5) (15.6 g, 0.075 mol), and phosphoryl chloride ($POCl_3$) (11.5 g, 0.075 mol) was refluxed at 130° for 60 hr. The reaction mixture was concentrated under reduced pressure. The residue was poured into ice-water, and the mixture was extracted with chloroform. The chloroform extract was subjected to silica gel column chromatography with hexane as an eluent to give the product (**2**) as colorless pillars (petroleum ether), mp 60—62°, 2.24 g (61%) (lit.[2a] mp 56°). *Anal.* Calcd for $C_{10}H_6Cl_3N$: C, 48.72; H, 2.46; Cl, 43.14; N, 5.68. Found: C, 48.26; H, 2.61; Cl, 43.42; N, 5.32. The aqueous layer was neutralized with sodium carbonate, and the mixture was extracted with ether. The ether extract was concentrated, and the residue was purified by distillation to give the starting quinoline (**1**), bp 126—129° (17 mmHg), 0.35 g (16%).

Reaction of 4-Methylquinoline (**3**) **with PCl_5 in $POCl_3$**——A mixture of compound **3** (2.15 g), PCl_5 (15.6 g), and $POCl_3$ (11.5 g) was refluxed at 130° for 60 hr. The reaction mixture was treated as described above, and the chloroform extract was purified by silica gel column chromatography with benzene as an eluent to give 3-chloro-4-trichloromethylquinoline (**5**), 0.33 g (8%). Elution was continued to give the product (**4**) as colorless pillars (hexane) of mp 83—84° (lit.[4] mp 80—81°), 1.49 g (40%). *Anal.* Calcd for $C_{10}H_6Cl_3N$: C, 48.72; H, 2.46; Cl, 43.14; N, 5.68. Found: C, 48.93; H, 2.52; Cl, 43.25; N, 5.56. The aqueous layer was neutralized with sodium carbonate, and the mixture was extracted with ether. The ether extract provided the compound **3**, bp 130—132° (15 mmHg), 0.32 g (15%).

Reaction of 2-Methyl-4(1*H*)-quinolone (**6**) **with PCl_5 in $POCl_3$**——A mixture of compound **6**[9] (1.59 g, 0.01 mol), PCl_5 (10.4 g, 0.05 mol), and $POCl_3$ (7.7 g, 0.05 mol) was refluxed for 12 hr. The reaction mixture was treated as described above, and the chloroform extract was purified by silica gel column chromatography. Elution with hexane gave 3,4-dichloro-2-trichloromethylquinoline (**11**), 0.12 g (4%). Elution was continued to give 4-chloro-2-trichloromethylquinoline (**9**) of mp 67—68° (lit.[2b] mp 63.5—65°), 1.69 g (60%). Subsequent elution with benzene gave 3,4-dichloro-2-dichloromethylquinoline (**10**), 0.07 g (2%).

Reaction of 4-Methyl-2(1*H*)-quinolone (**12**) **with PCl_5 in $POCl_3$**——A mixture of compound **12**[10] (1.59 g), PCl_5 (10.4 g), and $POCl_3$ (7.7 g) was refluxed for 60 hr. The reaction mixture was treated as described above. The chloroform extract was subjected to silica gel column chromatography. The column was developed with hexane to give 2,3-dichloro-4-trichloromethylquinoline (**15**), 0.26 g (8%). Elution was continued to give 2-chloro-4-trichloromethylquinoline (**14**), 0.77 g (27%). Subsequent elution with hexane–benzene (1: 1) gave 2-chloro-4-dichloromethylquinoline (**13**), 0.24 g (10%).

Reaction of 4-Chloro-2-methyl-3-nitroquinoline (**16**) **with PCl_5 in $POCl_3$**——A mixture of compound **16**[11] (2.23 g), PCl_5 (10.4 g), and $POCl_3$ (7.7 g) was refluxed for 5 hr. The reaction mixture was treated as described above, and the chloroform-soluble part was subjected to silica gel column chromatography. The column was developed with hexane–benzene (4: 1) to give 4-chloro-3-nitro-2-trichloromethylquinoline (**18**), 0.82 g (25%). Subsequent elution with benzene gave 4-chloro-2-dichloromethyl-3-nitroquinoline (**17**), 0.7 g (24%). Elution was continued to give 3,4-dichloro-2-cyanoquinoline (**19**) of mp 97—98° as colorless needles (hexane), 0.07 g (3%). *Anal.* Calcd for $C_{10}H_4Cl_2N_2$: C, 53.85; H, 1.81; Cl, 31.79; N, 12.56. Found: C, 53.45; H, 1.53; Cl, 31.25; N, 12.87. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2280, 1563. NMR ($CDCl_3$) δ: 7.68—8.4 (4H, m, ring Hs).

Catalytic Reduction of Compound 19 over Pd-C——A mixture of compound **19** (100 mg), MgO (60 mg), and 10% Pd-C (40 mg) in H_2O–MeOH (2: 1) (12 ml) was shaken under hydrogen. After the hydrogen uptake had ceased, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was subjected to preparative silica gel thin-layer chromatography, and development with benzene gave 2-cyanoquinoline (**20**) of mp 92—94°; its IR spectrum was identical with that of an authentic sample.[12]

Reaction of 2-Trichloromethylquinoline (**2**) **with Trimethyl Phosphite**——A mixture of compound **2** (0.5 g) and trimethyl phosphite (6 ml) was heated at 140° for 15 hr. The reaction mixture was concentrated under

reduced pressure (30 mmHg) at 130°. The residue was subjected to silica gel column chromatography. Elution with hexane gave 2-(1,1-dichloroethyl)quinoline (**21**), 0.33 g (73%). Subsequent elution with benzene gave 2-dichloromethylquinoline (**22**) of mp 82° (lit.[13] mp 82°), 40 mg (9%).

4-Dichloromethylquinoline (23)——A mixture of compound **4** (0.5 g) and trimethyl phosphite (6 ml) was heated at 140° for 2 hr. The reaction mixture was treated as described above. The residue was subjected to silica gel column chromatography. Elution with benzene gave a colorless oil (**23**) of bp 109—110° (3 mmHg), 0.14g (33%). *Anal.* Calcd for $C_{10}H_7Cl_2N$: C, 56.63; H, 3.33; Cl, 33.43; N, 6.60. Found: C, 56.52; H, 3.48; Cl, 33.21; N, 6.36. NMR ($CDCl_3$) δ: 7.34 (1H, s, $-C\underline{H}Cl_2$), 7.6—8.0 (3H, m, 3,6,7-Hs), 8.1—8.4 (2H, m, 5,8-Hs), 9.2 (d, $J=5$ Hz, 2-H).

Reaction of 4-Chloro-2-trichloromethylquinoline (9) with Trimethyl Phosphite——A mixture of compound **9** (0.56 g) and trimethyl phosphite (6 ml) was heated at 140° for 4 hr. The reaction mixture was treated as described above, and the residue was subjected to silica gel column chromatography. Elution with hexane gave 4-chloro-2-(1,1-dichloroethyl)quinoline (**24**), 0.28 g (54%). Elution was continued to give 4-chloro-2-dichloromethylquinoline (**8**) of mp 100—101° (lit.[5] mp 102°) as colorless needles (petroleum ether), 70 mg (14%).

2-Chloro-4-dichloromethylquinoline (13)——A mixture of compound **14** (0.56 g) and trimethyl phosphite (6 ml) was heated at 140° for 2 hr. The reaction mixture was treated as described above, and the residue was subjected to silica gel column chromatography. Elution with hexane–benzene (1: 1) gave compound **13**, 0.23 g (47%).

Dimethyl 2-Dichloromethyl-4-dimethylphosphonoquinoline-3-phosphoramidate (25)——A mixture of compound **17** (3.5 g) and trimethyl phosphite (36 ml) was heated at 100° for 1 hr. The reaction mixture was treated as described above, and the residue was subjected to silica gel column chromatography. Elution with ethyl acetate gave a crystalline substance, which was recrystallized from ether to give compound **25** of mp 112—113° as pale yellow prisms, 1.77 g (33%). *Anal.* Calcd for $C_{14}H_{18}Cl_2N_2O_6P_2$: C, 37.94; H, 4.09; Cl, 16.00; N, 6.32. Found: C, 37.99; H, 4.10; Cl, 15.92; N, 5.89. NMR (CCl_4) δ: 3.77 (6H, d, $J=12$ Hz, $2\times POC\underline{H}_3$), 3.79 (6H, d, $J=12$ Hz, $2\times POC\underline{H}_3$), 7.45—7.8 (2H, m, 6,7-Hs), 7.9—8.3 (2H, m, 5,8-Hs), 7.99 (1H, s, $C\underline{H}Cl_2$), 8.65 (1H, d, $J=6$ Hz, NH, exchangeable with D_2O).

Hydrolysis of Compound 25——A suspension of compound **25** (0.4 g) in H_2O–EtOH (1: 1) (16 ml) was refluxed for 15 hr. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with chloroform. The chloroform-soluble part was subjected to silica gel column chromatography. Elution with benzene–chloroform (2: 1) gave dimethyl 3-amino-2-formylquinoline-4-phosphonate (**26**) of mp 175—176° as orange pillars (hexane). *Anal.* Calcd for $C_{12}H_{13}N_2O_4P$: C, 51.44; H, 4.68; N, 10.00. Found: C, 51.52; H, 4.70; N, 9.87. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 3360, 1690. NMR ($CDCl_3$) δ: 3.75 (6H, d, $J=$ 12 Hz, $2\times POC\underline{H}_3$), 7.25—7.7 (2H, m, 6,7-Hs), 7.85—8.6 (4H, m, 5,8-Hs and NH_2, exchangeable with D_2O), 10.16 (1H, d, $J=2$ Hz, C<u>H</u>O).

Reaction of 4-Chloro-3-nitro-2-trichloromethylquinoline (18) with Trimethyl Phosphite——A mixture of compound **18** (0.63 g) and trimethyl phosphite (6 ml) was heated at 100° for 1 hr. The reaction mixture was concentrated under reduced pressure (30 mmHg) at 130°, and the residue was subjected to silica gel column chromatography. Elution with benzene gave 4-chloro-2-(1,1-dichloroethyl)-3-nitroquinoline (**27**), 0.31 g (51%). Further elution gave dimethyl 2-(1,1-dichloroethyl)-3-nitroquinoline-4-phosphonate (**28**), 60 mg (8%).

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