Side-chain Chlorination of Methylquinolines

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Methylquinolines **1-4** were chlorinated by heating with phosphorus pentachloride in chlorobenzenes to side-chain halogen derivatives **5-14**. Methyl groups of compounds **1-4** can be chlorinated to chloromethyl, dichloromethyl or trichloromethyl groups depending on their positions and the reaction conditions.

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Relatively few examples have been reported for chlorination of methylquinolines despite the fact that side-chain halogenation of alkylquinolines is one of the most thoroughly investigated fields in the quinoline chemistry [1].

In the first paper of this field, Hammick [2] reported that 2-methylquinoline underwent chlorination to 2-trichloromethylquinoline with an excess of chlorine in a mixture of hot acetic acid and sodium acetate. This method was later applied for chlorination of 4-chloro-2-methylquinoline [3] and other methylquinolines with different substituents on the carbocyclic ring [4].

2-Methylquinoline can be converted to monochloromethylquinoline, accompanied with dichloromethylquinoline, with chlorine in carbon tetrachloride in the presence of sodium carbonate [5], or with *N*-chlorosuccinimide in chloroform in the presence of benzoyl peroxide [7].

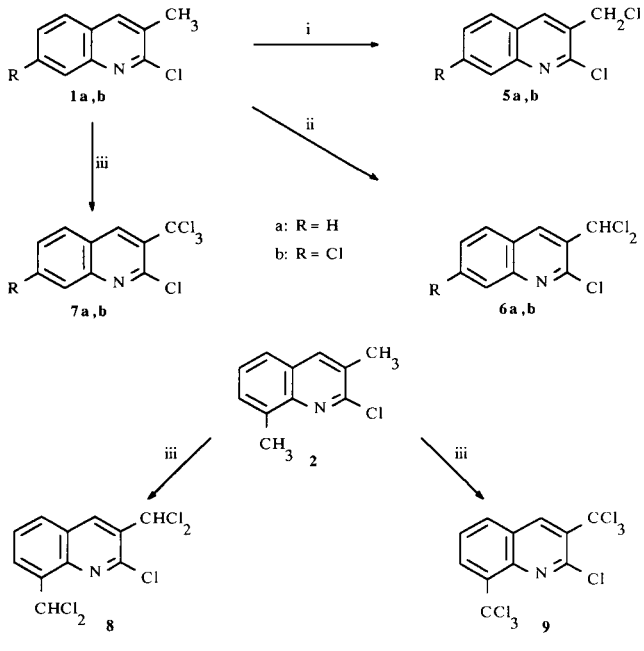
A detailed study has been made on chlorination of 4-chloro-2-methylquinolines, and phosphorus pentachloride as well as chlorine gas together with catalitical amount of phosphorus halides were claimed for preparation of differently substituted 4-chloro-2-halomethylquinolines [8].

Treatment of 2-methyl- and 4-methylquinolines with phosphorus pentachloride in phosphoryl chloride gives di- and trihalomethyl derivatives [9]. 2-Chloro-4-dichloromethyl- and 2-chloro-4-trichloromethylquinoline can be obtained by this procedure from 2-hydroxy-4-methylquinoline, but the chlorination of 2-chloro-4-methyl- or 2-chloro-3-methylquinolines has not been reported yet.

In this paper we wish to report on the reaction of 2-chloro-4-methyl- and 2-chloro-3-methylquinolines with phosphorus pentachloride in chlorobenzenes.

According to our investigation the chlorination of the methyl group on 2-chloro-3-methylquinolines **1** by means of phosphorus pentachloride leads, depending on the reaction conditions, to the monochloro- **5** or dichloro- **6** or trichloromethyl **7** derivative as the main product. Heating 2-chloro-3-methylquinolines **1** with phosphorus pentachloride in 1,2-dichlorobenzene at 150° gave mainly the 3-chloromethyl derivative **5**. When **1** was treated with phosphorus pentachloride in 1,2,4-trichlorobenzene at 180°, the 3-dichloromethyl derivative **6** was obtained, while at 200° with excess phosphorus pentachloride the 3-trichloromethyl derivative **7** was the main product. The desired product was in all cases accompanied with lower or higher chlorinated byproducts but after a crystallization they were available in pure form in good yields. It is essential to note here, that the optimum reaction time in every case was determined by gc monitoring of the reactions.

Scheme 1



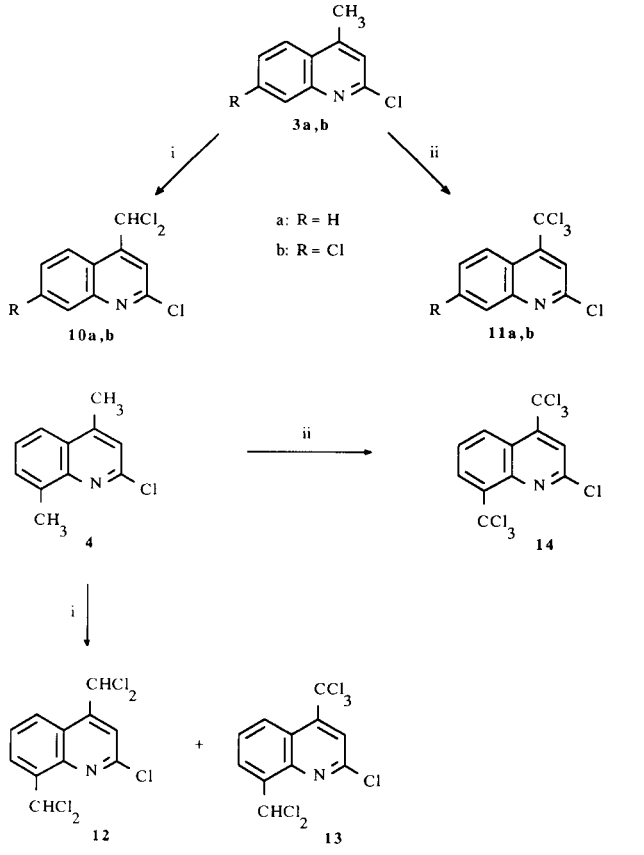
i: phosphorus pentachloride, 1,2-dichlorobenzene, 150°; ii: phosphorus pentachloride, 1,2,4-trichlorobenzene, 180°; iii: phosphorus pentachloride, 1,2,4-trichlorobenzene, 200°.

When another methyl group is present on the carbocyclic ring of 2-chloro-3-methylquinoline our attempts to prepare a monochloro derivative failed. For example, chlorination of 2-chloro-3,8-dimethylquinoline (**2**) at a temperature lower than 200° resulted in a reaction mixture with many components due to the simultaneous chlorination of both methyl groups. However, when **2** was treated with phosphorus pentachloride in 1,2,4-trichlorobenzene at 200°, occurance of a predominant amount of a product was observed by gc analysis. By processing the reaction mixture at this stage 2-chloro-3,8-bis(dichloromethyl)quinoline (**8**) can be prepared, but additional heating of the

reaction mixture after addition of excess phosphorus pentachloride leads to the formation of 2-chloro-3,8-bis(trichloromethyl)quinoline (**9**).

In the case of 2-chloro-4-methylquinolines we were unable to find such a reaction condition in which the 4-chloromethyl derivative was the main product. However, our procedure proved to be suitable for producing both 4-dichloromethyl- **10** and 4-trichloromethyl-2-chloroquinolines **11** from 2-chloro-4-methylquinolines **3** for lack of a homoaromatic methyl group. Similar reaction conditions but shorter reaction times are sufficient as it was described above for the preparation of the 2-chloro-3-dichloromethyl- or trichloromethylquinolines. These facts are in agreement with the literature [1], that a 4-methyl group undergoes halogenation more readily than a 3-methyl group because of its activation by the ring nitrogen atom.

Scheme 2



i: phosphorus pentachloride, 1,2,4-trichlorobenzene, 180°; ii: phosphorus pentachloride, 1,2,4-trichlorobenzene, 200°.

In the presence of an additional methyl group on the homoaromatic ring of the quinoline, both methyl groups undergo chlorination at the same time, and our procedure is suitable most of all for the preparation of bis(trichloromethyl)quinolines. Thus, 2-chloro-4,8-bis(trichloromethyl)-quinoline (**14**) can be obtained in good yield from 2-chloro-4,8-dimethylquinoline (**4**) under similar reaction conditions described for the appropriate 3-methyl derivative **2**. However, when this reaction was carried out at 180° and was interrupted after 1 hour, a mixture of 2-chloro-4,8-bis-(dichloromethyl)quinoline (**12**) and 2-chloro-8-dichloromethyl-4-trichloromethylquinoline (**13**) was obtained and then separated by column chromatography.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. The ^{1}H-nmr spectra were recorded on a Bruker WP-200 SY instrument at 200 MHz in deuteriochloroform solution using tetramethylsilane as internal standard and chemical shifts are expressed in ppm. Mass spectra were scanned on a VG TRIO-2 spectrometer in the EI mode at 70 eV. A Fractovap 2300 chromatograph (Carlo-Erba) was used for gc and DC-Allurole Kieselgel 60 F 254 (Merck) silica gel plates for tlc analysis. The purification or separation of some products was performed by column chromatography using Kieselgel 60 (0.063-0.2 mm) (Reanal, Hungary) packing.

2-Chloro-3-chloromethylquinoline (**5a**).

A mixture of 2-chloro-3-methylquinoline (**1a**) (8.8 g, 50 mmoles), phosphorus pentachloride (20.8 g, 100 mmoles) and 1,2-dichlorobenzene (25 ml) was stirred at 150° for 4 hours. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in chloroform (10 ml) then hexane (30 ml) was added to give the product **5a**, 6.30 g (59%), mp 111-113°; ^{1}H-nmr: δ 4.85 (s, 2H, CH_2), 7.60 (m, 1H, 6-H), 7.75 (m, 1H, 7-H), 7.85 (m, 1H, 5-H), 8.05 (m, 1H, 8-H), 8.30 (s, 1H, 4H); ms: m/e 211 (M^+, 33), 176 (100).

Anal. Calcd. for $C_{10}H_7Cl_2N$: C, 56.64; Cl, 33.43. Found: C, 56.52; Cl, 33.35.

2,7-Dichloro-3-chloromethylquinoline (**5b**).

2,7-Dichloro-3-methylquinoline (**1b**), treated in the same way and in the same scale described above for the preparation of **5a**, afforded **5b**, 8.40 g (68%), mp 114-116°; ^{1}H-nmr: δ 4.85 (s, 2H, CH_2), 7.55 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2 Hz, 6-H), 7.80 (d, 1H, J = 8.5 Hz, 5-H), 8.05 (d, 1H, J = 2 Hz, 8-H), 8.30 (s, 1H, 4-H); ms: m/e 245 (M^+, 22), 210 (100).

Anal. Calcd. for $C_{10}H_6Cl_3N$: C, 48.72; Cl, 43.14. Found: C, 48.89; Cl, 43.10.

2-Chloro-3-dichloromethylquinoline (**6a**).

A mixture of compound **1a** (8.88 g, 50 mmoles), phosphorus pentachloride (31.2 g, 150 mmoles) and 1,2,4-trichlorobenzene (25 ml) was heated with stirring at 180° for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in chloroform (15 ml). Ethanol (45 ml) was added to this solution to give **6a**, 7.89 g (64%), mp 88-90°; ^{1}H-nmr: δ 7.22 (s, 1H, CH), 7.65 (m, 1H, 6-H), 7.80 (m, 1H, 7-H), 7.95 (m, 1H, 5-H), 8.05 (m, 1H, 8-H), 8.75 (s, 1H, 4-H); ms: m/e 245 (M^+, 16), 210 (100).

Anal. Calcd. for $C_{10}H_6Cl_3N$: C, 48.72; Cl, 43.14. Found: C, 48.76; Cl, 43.20.

2,7-Dichloro-3-dichloromethylquinoline (**6b**).

Using the same treatment described in the foregoing preparation of **6a**, **1b** (10.6 g, 50 mmoles) gave **6b**, 9.80 g (70%), mp 89-91°; ^{1}H-nmr: δ 7.20 (s, 1H, CH), 7.60 (dd, 1H, J_1 = 8.5 Hz, J_2

= 2 Hz, 6-H), 7.87 (d, 1H, J = 8.5 Hz, 5-H), 8.05 (d, 1H, J = 2 Hz, 8-H), 8.72 (s, 1H, 4-H); ms: m/e 279 (M^+, 12), 244 (100).

Anal. Calcd. for $C_{10}H_5Cl_4N$: C, 42.75; Cl, 50.47. Found: C, 42.56; Cl, 50.59.

2-Chloro-3-trichloromethylquinoline (**7a**).

Compound **1a** (8.88 g, 50 mmoles), phosphorus pentachloride (31.5 g, 150 mmoles) and 1,2,4-trichlorobenzene (25 ml) were heated with stirring at 200°. After the 3rd and the 6th hours additional portions of phosphorus pentachloride (10.4 g, 50 mmoles each) were added and the heating was continued up to the 9th hour. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in chloroform (15 ml), hexane was added to precipitate **7a**, 7.83 g (56%), mp 158-160°; ^{1}H-nmr: δ 7.67 (m, 1H, 6-H), 7.85 (m, 1H, 7-H), 7.95 (m, 1H, 5-H), 8.07 (m, 1H, 8-H), 8.95 (s, 1H, 4-H); ms: m/e 279 (M^+, 12), 244 (100).

Anal. Calcd. for $C_{10}H_5Cl_4N$: C, 42.75; Cl, 50.47. Found: C, 42.87; Cl, 50.28.

2,7-Dichloro-3-trichloromethylquinoline (**7b**).

This compound was produced from **1b** (10.6 g, 50 mmoles) just as **7a** was produced from **1a**, yield of **7b**, 9.80 g (62%), mp 98-100°; ^{1}H-nmr: δ 7.62 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2 Hz, 6-H), 7.90 (d, 1H, J = 8.5 Hz, 5-H), 8.05 (d, 1H, J = 2 Hz, 8-H), 8.92 (s, 1H, 4-H); ms: m/e 313 (M^+, 7), 280 (100).

Anal. Calcd. for $C_{10}H_4Cl_5N$: C, 38.08; Cl, 56.20. Found: C, 38.10; Cl, 56.11.

2-Chloro-3,8-bis(dichloromethyl)quinoline (**8**).

A mixture of 2-chloro-3,8-dimethylquinoline (**2**) (9.58 g, 50 mmoles), phosphorus pentachloride (62.4 g, 300 mmoles) and 1,2,4-trichlorobenzene (25 ml) was heated with stirring at 200° for 2 hours. The reaction mixture was evaporated under reduced pressure, the residue was dissolved in chloroform (10 ml) then the product was precipitated with hexane (30 ml). The precipitated product was isolated with suction and was recrystallized from chloroform-ethanol (1:3, v/v) to afford **8**, 8.1 g (49%), mp 110-111°; ^{1}H-nmr: δ 7.22 (s, 1H, CH), 7.75 (m, 1H, 6-H), 8.00 (dd, 1H, J_1 = 8 Hz, J_2 = 2 Hz, 5-H), 8.07 (s, 1H, CH), 8.40 (dd, 1H, J_1 = 8 Hz, J_2 = 2 Hz, 7-H), 8.77 (s, 1H, 4-H); ms: m/e 327 (M^+, 32), 294 (100).

Anal. Calcd. for $C_{11}H_6Cl_5N$: C, 40.10; Cl, 53.80. Found: C, 39.95; Cl, 53.86.

2-Chloro-3,8-bis(trichloromethyl)quinoline (**9**).

Compound **2** (9.58 g, 50 mmoles), phosphorus pentachloride (62.4 g, 300 mmoles) and 1,2,4-trichlorobenzene (25 ml) were heated with stirring at 200°. After the 3rd and 6th hours fresh portions of phosphorus pentachloride (20.8 g, 100 mmoles each) were added and heating was continued up to the 9th hour. The reaction mixture was evaporated under reduced pressure, the residue was dissolved in chloroform (30 ml) and the product was precipitated with ethanol (90 ml), yield of **9**, 11.0 g (55%), mp 239-241°; ^{1}H-nmr: δ 7.67 (m, 1H, 6-H), 8.07 (dd, 1H, J_1 = 8 Hz, J_2 = 2 Hz, 5-H), 8.55 (dd, 1H, J_1 = 8 Hz, J_2 = 2 Hz, 7-H), 8.95 (s, 1H, 4-H); ms: m/e 395 (M^+, 5), 362 (100).

Anal. Calcd. for $C_{11}H_4Cl_7N$: C, 33.17; Cl, 62.30. Found: C, 33.05; Cl, 62.30.

2-Chloro-4-dichloromethylquinoline (**10a**).

A mixture of 2-chloro-4-methylquinoline (**3a**) (8.88 g, 50 mmoles), phosphorus pentachloride (26.0 g, 125 mmoles) and 1,2,4-trichlorobenzene (25 ml) was heated with stirring at 180° for 30 minutes, then was evaporated under reduced pressure. The residue was purified by silica gel column chromatography with chloroform:hexane (1:1, v/v) eluent to give the product **10a** as a colorless oil, 6.96 g (57%) which was crystallized from hexane, yield, 3.88 g (32%), mp 59-61° (lit [9] oil); ^{1}H-nmr: δ 7.27 (s, 1H, CH), 7.67 (m, 1H, 6-H), 7.75-7.87 (m, 2H, 3-H + 7-H), 8.07-8.20 (m, 2H, 5-H + 8-H); ms: m/e 245 (M^+, 26), 210 (100).

Anal. Calcd. for $C_{10}H_6Cl_3N$: C, 48.72; Cl, 43.14. Found: C, 48.50; Cl, 43.25.

2,7-Dichloro-4-dichloromethylquinoline (**10b**).

2,7-Dichloro-4-methylquinoline (**3b**) (10.6 g, 50 mmoles) was treated in a manner similar to that described above for the preparation of **10a**. The evaporation residue was crystallized from hexane, then was recrystallized from chloroform-hexane (1:3, v/v) to provide **10b**, 6.42 g (46%), mp 100-102°; ^{1}H-nmr: δ 7.18 (s, 1H, CH), 7.62 (dd, 1H, J_1 = 9 Hz, J_2 = 2 Hz, 6-H), 7.75 (s, 1H, 3-H), 8.07 (d, 1H, J = 2 Hz, 8-H), 8.13 (d, 1H, J = 9 Hz, 5-H); ms: m/e 279 (M^+, 24), 244 (100).

Anal. Calcd. for $C_{10}H_5Cl_4N$: C, 42.75; Cl, 50.47. Found: C, 42.65; Cl, 50.36.

2-Chloro-4-trichloromethylquinoline (**11a**).

Compound **3a** (8.88 g, 50 mmoles), phosphorus pentachloride (31.5 g, 150 mmoles) and 1,2,4-trichlorobenzene were heated with stirring at 200°. After the 2nd and 4th hours fresh portions of phosphorus pentachloride (10.4 g, 50 mmoles each) were added and the heating was continued up to the 6th hour. The reaction mixture was evaported then the residue was distilled (150-160°, 1 mm Hg) to give **11a** as an oil, 8.96 g (64%) which was crystallized from hexane, yield, 5.32 g (38%), mp 68-70° (lit [9] mp 67-68°; ^{1}H-nmr: δ 7.70 (m, 1H, 6-H), 7.80 (m, 1H, 7-H), 8.05 (s, 1H, 3-H), 8.12 (m, 1H, 8-H), 8.70 (m, 1H, 5-H); ms: m/e 279 (M^+, 5), 244 (15).

Anal. Calcd. for $C_{10}H_5Cl_4N$: C, 42.75; Cl, 50.47. Found: C, 42.59; Cl, 50.58.

2,7-Dichloro-4-trichloromethylquinoline (**11b**).

Compound **3b** (10.6 g, 50 mmoles) was subjected to the same procedure as described above for the preparation of **11a**. The evaporated reaction mixture was crystallized from hexane to give **11b**, 11.67 g (74%), mp 127-129°; ^{1}H-nmr: δ 7.65 (dd, 1H, J_1 = 9 Hz, J_2 = 2 Hz, 6-H), 8.05 (s, 1H, 3-H), 8.12 (d, 1H, J = 2 Hz, 8-H), 8.62 (d, 1H, J = 9 Hz, 5-H); ms: m/e 313 (M^+, 11), 280 (100).

Anal. Calcd. for $C_{10}H_4Cl_5N$: C, 38.08; Cl, 56.20. Found: C, 37.90; Cl, 56.10.

2-Chloro-4,8-bis(dichloromethyl)quinoline (**12**) and 2-Chloro-8-dichloromethyl-4-trichloromethylquinoline (**13**).

A mixture of 2-chloro-4,8-dimethylquinoline (**4**) (9.58 g, 50 mmoles), phosphorus pentachloride (62.4 g, 300 mmoles) and 1,2,4-trichlorobenzene (25 ml) was heated with stirring at 180° for 1 hour. The reaction mixture was evaporated under reduced pressure and the residue was subjected to silica gel column chromatography using hexane as eluent. The first of two main products from the column was 2-chloro-8-dichloromethyl-4-trichloromethylquinoline (**13**), 3.24 g (30%) which was crystallized from hexane to give **13**, 2.60 g (24%), mp 93-95°; ^{1}H-nmr: δ 7.80

(m, 1H, 6-H), 8.12 (s, 1H, CH), 8.15 (s, 1H, 3-H), 8.42 (dd, 1H, J_1 = 9 Hz, J_2 = 1 Hz, 7-H), 8.75 (dd, 1H, J_1 = 9 Hz, J_2 = 1 Hz, 5-H); ms: m/e 361 (M^+, 22), 328 (100).

Anal. Calcd. for $C_{11}H_5Cl_6N$: C, 36.31; Cl, 58.46. Found: C, 36.35; Cl, 58.73.

The elution was continued to give 4.08 g (37%) of 2-chloro-4,8-bis(dichloromethyl)quinoline (**12**) which was crystallized from hexane, yield, 3.40 g (31%), mp 67-69°; ^{1}H-nmr: δ 7.22 (s, 1H, CH), 7.80 (m, 1H, 6-H), 7.85 (s, 1H, 3-H), 8.12 (s, 1H, CH), 8.25 (dd, 1H, J_1 = 9 Hz, J_2 = 1 Hz, 5-H), 8.40 (dd, 1H, J_1 = 9 Hz, J_2 = 1 Hz, 7-H); ms: m/e 327 (M^+, 32), 294 (100).

Anal. Calcd. for $C_{11}H_6Cl_5N$: C, 40.10; Cl, 53.81. Found: C, 40.24; Cl, 53.70.

2-Chloro-4,8-bis(trichloromethyl)quinoline (**14**).

This compound was prepared from **4** (9.58 g, 50 mmoles) just as **9** was prepared from **2**, yield of **14**, 11.17 g (56%), mp 180-182°; ^{1}H-nmr: δ 7.70 (m, 1H, 6-H), 8.15 (s, 1H, 3-H), 8.55 (dd, 1H, J_1 = 8 Hz, J_2 = 1 Hz, 7-H), 8.82 (dd, 1H, J_1 = 8 Hz, J_2 = 1 Hz, 5-H); ms: m/e 395 (M^+, 5), 362 (100).

Anal. Calcd. for $C_{11}H_4Cl_7N$: C, 33.17; Cl, 62.30. Found: C, 33.13; Cl, 62.05.

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