Chlorination of 3,4-Quinolinediyl Bis-sulfides and 3-Thiosubstituted 4-Quinolinethiones with Phosphoryl Chloride#

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Transformation of some 4-quinolinyl sulfides **3** and 4-quinolinethiones **4** into 4-chloroquinolines **5** was performed in the reaction with phosphoryl chloride (alone or in *N,N*-dimethylformamide and ethanol). 3-Quinolinyl sulfides were stable in the reaction conditions.

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Introduction.

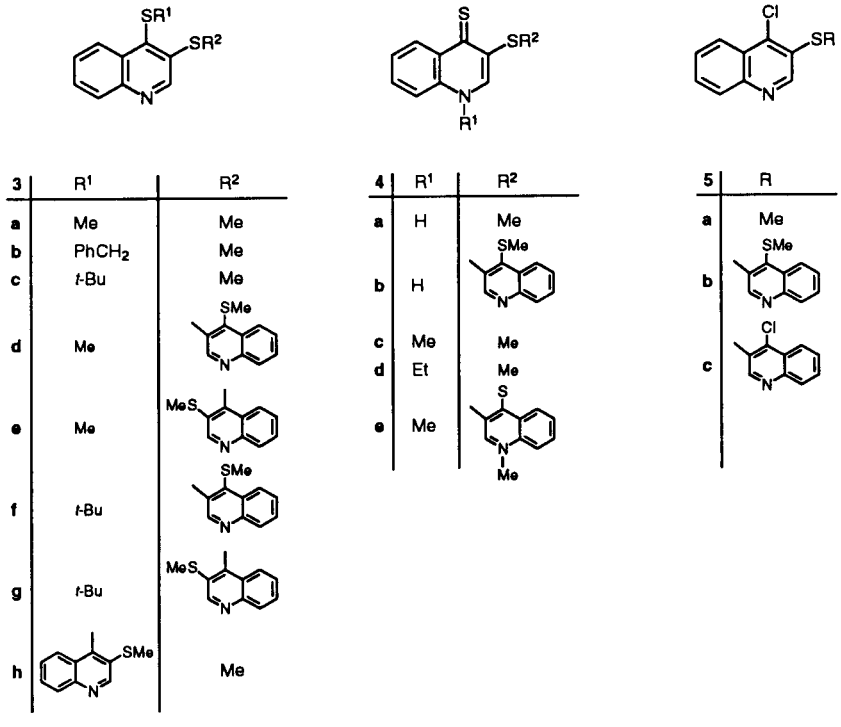
4-Quinolinyl sulfides (*i.e.* 4-alkylthio- and 4-arylthioquinolines) are mainly obtained by the nucleophilic substitution of chlorine atom in 4-chloroquinolines with alkanethiolate anions [1], arenethiols [2] or with thiourea followed by *S*-alkylation [3]. In our previous papers we found simple way to obtain various substituted 3,3'- and 3,4'-diquinolinyl sulfides [4-7], 3-alkylthioquinolines [4,7-10] and 4-quinolinethiones [8,11] in the opening reactions of the 1,4-dithiin ring in thioquinanthrene **1** (1,4-dithiino-[2,3-*c*;5,6-*c*']diquinoline), isothioquinanthrene **2** (1,4-dithiino-[2,3-*c*;6,5-*c*']diquinoline and in dialkylthioquinanthrenediinium bis-salts. Having in hand numerous β and γ-quinolinyl sulfides we considered reverse functionalization of such quinoline derivatives, *i.e.* transformation of thioquinolines to chloroquinolines. Encouraged by promising result of the reaction of 4-alkoxy-3,4'-diquinolinyl sulfides with phosphoryl chloride [8] and chlorinolysis of substituted 4-benzylthioquinolines with chlorine gas [12-14] we undertook further study of synthesis of chloroquinolines from quinolinyl sulfides.

Results and Discussion.

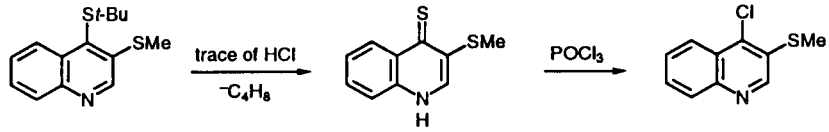
In the present paper we have investigated the stability of the sulfide-type and thione-type of $C_{quinolinyl}$-sulfur bonds in the reactions of 3,4-quinolinediyl bis-sulfides **3** and 3-thiosubstituted 4-quinolinethiones **4** with phosphoryl chloride as a chlorinating agent under selected conditions (phosphoryl chloride alone or in *N,N*-dimethylformamide [15,16] and ethanol).

The results of chlorination of 3,4-quinolinediyl bis-sulfides and 3-thiosubstituted 4-quinolinethiones depend on the structure of the substrate. We obtained three types of

Scheme 1



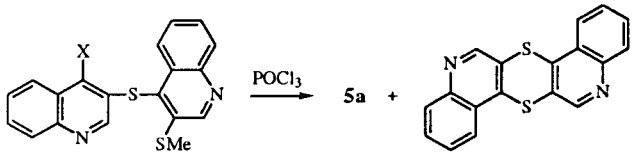
Scheme 2



3c **4a** **5a**

4-chloroquinolines **5a-5c**. Whereas we found the $C_{3\text{-quinolinyl}}$-SR bond completely unreactive to the chlorinating agent (as one could expect), the reactivity of the $C_{4\text{-quinolinyl}}$-SR bond depends strongly on the R substituent (*i.e.* methyl, benzyl, *t*-butyl and quinolinyl). When the substituent was methyl or benzyl group, we recovered 4-alkylthioquinolines **3a** and **3b**. It is worth noting that the $C_{4\text{-quinolinyl}}$-SR bond (R = benzyl) was cleaved easily by chlorine in chlorinolysis of 4-benzylthioquinoline [12-14].

Scheme 3



3e **1**

It is known that the mercapto group is protected as the *t*-butylthio group and the protecting group can be eliminated by an acid [17,18] . We observed that the reaction of 4-*t*-butylthioquinoline **3c** with phosphoryl chloride ran smoothly to 4-chloroquinoline **5a** in good yield (80%). In our opinion the reaction runs firstly as elimination of isobutene and secondly as chloro-desulfuration. This suggestion was confirmed by synthesis of 4(1*H*)-quinolinethione **4a** (in 97% yield) from 4-*t*-butylthioquinoline **3c** using hydrochloric acid and by reaction of 4(1*H*)-quinolinethione **4a** with phosphoryl chloride to give 4-chloroquinoline **5a** in good yield (82%).

In the cases of 3,4'- and 4,4'-diquinolinyl sulfides **3e, 3g** and **3h** we observed the cleavage of the $C_{4\text{-quinolinyl}}$-SR bond regardless if the R was 3- or 4-quinolinyl substituent. We isolated 4-chloroquinoline **5a** as the main product and thioquinanthrene **1** as the second product (from reaction of 3,4'-diquinolinyl sulfides **3e** and **3g**). It turned out the $C_{4\text{-quinolinyl}}$-SR bond (R = 3-quinolinyl) was more susceptible to cleavage by chloride anion that the $C_{4\text{-quinolinyl}}$-SR bond (R = *t*-Bu).

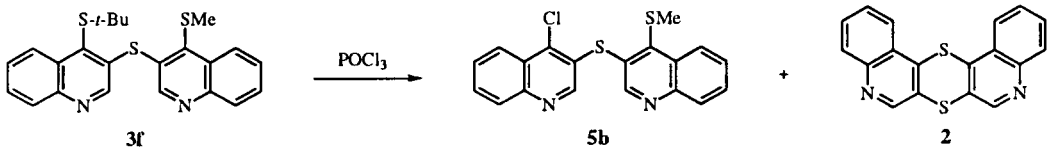
For methoxy analogue of sulfide **3e** (X = OMe) we observed the $C_{4\text{-quinolinyl}}$-OMe bond to be more susceptible to cleavage under Vilsmeier-Haack conditions than the $C_{4\text{-quinolinyl}}$-SR bond (R = 3-quinolinyl) [16] .

In the case of 3,3'-diquinolinyl sulfides **3f** we observed not only cleavage of the $C_{4\text{-quinolinyl}}$-SR bond (R = *t*-Bu) to give 4-chloroquinoline **5b** but also cyclization to isothioquinanthrene **2**. The tendency of sulfide **3f** to cyclization under acidic conditions was reported previously [5].

We found recently [19] sulfide **3d** to be easily hydrolysed in the mixture of hydrochloric acid-ethanol (1:1). Next the oxo-function was readily transformed into the chlorine atom in the reaction with phosphoryl chloride. In this paper we decided to obtain the chloro compound in one-pot synthesis from 4-quinolinyl sulfide. With the purpose of chloro-desulfuration sulfide **3d** was refluxed in the mixture of phosphoryl chloride-ethanol (1:1). After one hour the reaction mixture became very viscous. Heating the mixture furthermore for half an hour gave the desired dichloroquinolinyl sulfide **5c** in 70 % yield.

The cleavage of the thiocarbonyl $C_{4\text{-quinolinyl}}$=S bond in 4-quinolinethiones **4a, 4c** and **4d** depends strongly on the substituent attached to the nitrogen atom. For *N*-non-substituted 4(1*H*)-quinolinethiones **4a** and **4b** the cleavage of the $C_{4\text{-quinolinyl}}$=S bond proceeded very smoothly to give 4-chloroquinolines **5a** in good yield. Chlorodesulfurization of *N*-alkyl-substituted 4-quinolinethiones **4c** and **4d** required prolonged time (even to 72 hours) and gave the 4-chloroquinoline **5a** with decreasing yield even

Scheme 4



3f **5b** **2**

Scheme 5

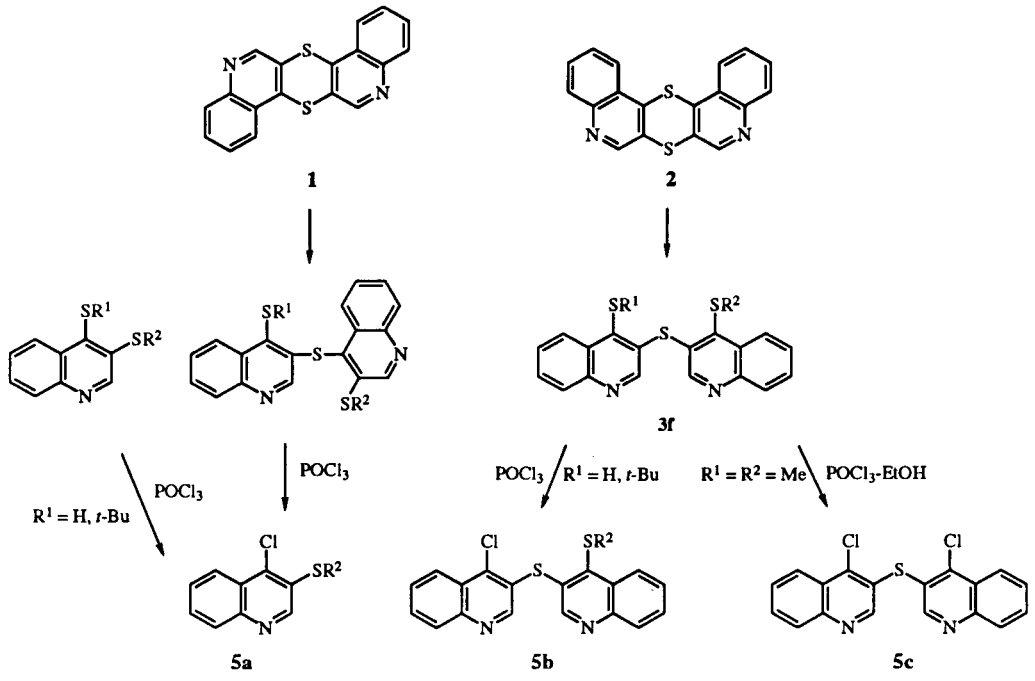


Table 1

Reactions of 3,4-Quinolinediyl Bis-sulfides 3 and 4-Quinolinethiones 4 with a Chlorinating Agent

No	Substrate	Chlorinating agent	Temp. [°C]	Time [h]	The products (yield, %) 4-Chloroquinoline	Dithiin
1	**3a**	A	reflux	24	– [a]	–
2	**3b**	A	reflux	24	– [a]	–
3	**3c**	A	reflux	24	**5a** (80)	–
4	**3d**	A	reflux	24	– [a]	–
5	**3d**	C	reflux	1.5	**5c** (70)	–
6	**3e**	A	reflux	120	**5a** (72)	**1** (75)
7	**3f**	A	reflux	24	**5b** (57)	**2** (20)
8	**3g**	A	reflux	24	**5a** (86)	**1** (50)
9	**3g**	B	20	72	– [a]	–
10	**3g**	B	100	1	**5a** (76)	**1** (31)
11	**3h**	A	reflux	24	**5a** (81)	–
12	**4a**	A	reflux	24	**5a** (82)	–
13	**4b**	B	100	1	**5b** (35)	**2** (34)
14	**4c**	A	reflux	36	**5a** (67)	–
15	**4d**	A	reflux	72	**5a** (38)	–
16	**4e**	A	reflux	72	– [a]	–

A - $POCl_3$ (neat), B - $POCl_3$ in DMF, C - $POCl_3$ and ethanol. [a] The substrate recovered in at least 90% yield.

with use of triethylamine hydrochlorides as an alkyl group acceptor [20] (67% and 38% for *N*-methyl- and *N*-ethyl-4-quinolinethiones, respectively). Furthermore, compound **4e** possessing double *N*-methyl-thione functions turned out to be unreactive in the same reaction conditions. Reaction of 4-quinolinethione **4b** with phosphoryl chloride in dimethylformamide reagent gave the same result as we observed for sulfide **3f**: *i.e.* 4-chloroquinoline **5b** and isothioquinanthrene **2**.

Conclusion.

In conclusion we would emphasize that 3,4-quinolinediyl bis-sulfides possessing labile $C_{4\text{-quinolinyl}}$-SR bonds (R = *t*-Bu, 3- or 4-quinolinyl) and 4(1*H*)-quinolinethiones can be readily transformed into 4-chloroquinolines in the reaction with phosphoryl chloride (alone or in solvents). This novel preparation of 4-chloroquinolines with the sulfide substituents at postion 3 from thioquinolines (obtained from quinoline in three or four steps *via* thioquinanthrene **1** and isothioquinanthrene **2**) compares favorably in ease and yield with methods based mainly on the reactions of 4(1*H*)-quinolinones [21].

EXPERIMENTAL

Melting points were determined in open and sealed capillary tubes on a Boetius melting point apparatus and are uncorrected. The ^1H nmr spectra were recorded on a Bruker MSL 300 (300 MHz) spectrometer in deuteriochloroform solutions. Mass spectra were run on a LKB spectrometer using the electron impact method. Thin layer chromatography was performed on aluminium oxide (type E) and silica gel 60 254F plates (Merck) using methylene chloride and benzene-ethyl acetate (1:1) solution as eluents. Silica gel (100-200 mesh) Merck Kiesel gel 60 was employed for column chromatography. Sodium 2-methylpropanethiolate was commercial (Aldrich Chemical Co.) and sodium phenylmethanethiolate was prepared from phenyl-

methanethiol (Merck) and sodium hydride in anhydrous benzene.

Thioquinanthrene **1** was obtained by exhaustive sulfuration of quinoline with elemental sulfur [22]. Isothioquinanthrene **2** was prepared as described in reference [5]. 4,4'-Dimethylthio-3,3'-diquinolinyl sulfide **3d**, 3',4-dimethylthio-3,4'-diquinolinyl sulfide **3e** and 4-*t*-butylthio-4'-methylthio-3,3'-diquinolinyl sulfide **3f** were obtained directly from thioquinanthrene **1** or isothioquinanthrene **2** as described in references [5,6]. 3,3'-Dimethylthio-4,4'-diquinolinyl sulfide **3h** was obtained according to the procedure [23]. 1-Methyl- and 1-ethyl-3-methylthio-4-thioxo-1,4-dihydroquinoline **4c** and **4d** and 3,3'-bis(1-methyl-3-methylthio-4-thioxo-1,4-dihydroquinolinyl) sulfide **4e** were obtained from dialkylthioquinanthrenediinium and dialkylisothioquinanthrenediinium salts [11,24].

3,4-Dimethylthioquinoline **3a** and 3-methylthio-4-benzylthioquinoline **3b**.

A solution of sulfide **3e** (0.76 g, 2 mmoles) in 20 ml of dry DMSO at 70° was stirred with sodium phenylmethanethiolate (0.31 g, 2.1 mmoles) for 30 minutes. The mixture was cooled down to room temperature, poured into 60 ml of 15% aqueous sodium hydroxide and extracted with chloroform (3 x 20 ml). The combined extracts were washed with water, dried with anhydrous sodium sulfate and evaporated to give a crude product. The product was purified by column chromatography (silica gel 60, chloroform) to give 0.48 g of sulfide **3b** (81%) mp 106-107°; ^{1}H nmr (deuteriochloroform): δ 2.63 (s, 3H, SCH_3); 4.08 (s, 2H, SCH_2); 7.13 (s, 5H, C_6H_5), 7.47-8.37 (m, $4H_{arom}$); 8.76 (s, 1H, H-2); ms: (15 eV) m/z (relative intensity) 297 (M^+, 94.7), 282 (M-CH_3, 30.2), 206 (M-$C_6H_5CH_2$, 9.6), 91 ($C_6H_5CH_2^+$, 100)

Anal. Calcd. for $C_{17}H_{15}NS_2$: C, 68.65; H, 5.08; N, 4.71; S, 21.56. Found: C, 68.41; H, 5.21; N, 4.52; S, 21.32.

The water layer was stirred with methyl iodide (0.46 g, 3.3 mmoles) and then extracted with chloroform (3 x 20 ml). The combined extracts were worked-up as described above to give 0.36 g of sulfide **3a** (82%), m. 93-94° lit.[25] mp 93-94°.

3-Methylthio-4-*t*-butylthioquinoline **3c**.

A solution of sulfide **3g** (0.84 g, 2 mmoles) in 20 ml of dry DMSO at 70° was stirred with sodium 2-methyl-2-propanethiolate (0.25 g, 2.2 mmoles) for 20 minutes. The mixture was cooled down to room temperature, poured into 60 ml of 15% aqueous sodium hydroxide and stirred with methyl iodide (0.46 g, 3.3 mmoles). The resulting solid was filtered off, washed with water and air-dried. The crude product was purified by column chromatography (silica gel 60, chloroform) to give 0.88 g of sulfide **3c** (84%), mp 105-106°; ^{1}H nmr (deuteriochloroform): δ 1.37 (s, 9H, $C(CH_3)_3$), 2.62 (s, 3H, SCH_3), 7.54-8.59 (m, $4H_{arom}$), 8.80 (s, 1H, H-2); ms: (15 eV) m/z (relative intensity) 263 (M^+, 16.4), 207 (M-C_4H_8, 100), 192 (M-C_4H_8 and CH_3, 23.5).

Anal. Calcd. for $C_{14}H_{17}NS_2$: C, 63.83; H, 6.50; N, 5.32; S, 24.34. Found: C, 63.61: H, 6.67; N, 5.23; S, 24.07.

4-*t*-Butylthio-3'-methylthio-3,4'-diquinolinyl Sulfide **3g**.

To a suspension of thioquinanthrene **1** (1.6 g, 5 mmoles) in 20 ml of dry DMSO at 20° sodium 2-methyl-2-propanethiolate (0.85 g, 7.5 mmoles) was added. The mixture was stirred for 2 hours and then poured into 60 ml of 15% aqueous sodium hydroxide. Possibly residual thioquinanthrene **1** was filtered off and the filtrate was stirred with methyl iodide (1.0 g, 7 mmoles). The resulting solid was filtered off, washed with water and air-dried. The crude product was purified by column chromatography (silica gel 60, chloroform) to give 1.80 g of sulfide **3g** (85%), mp 175-176°; ^{1}H nmr (deuteriochloroform): δ 1.54 (s, 9H, $C(CH_3)_3$), 2.62 (s, 3H, SCH_3), 7.58-8.66 (m, $8H_{arom}$), 7.85 (s, 1H, H-2), 8.88 (s, 1H, H-2'); ms: (15 eV) m/z (relative intensity) 422 (M^+, 28.9), 366 (M-C_4H_8, 48.1), 333 (M-C_4H_7S, 91.7), 319 (M-C_4H_8 and CH_3S, 100), 318 (M-C_4H_8 and CH_3S, 42.2).

Anal. Calcd. for $C_{23}H_{22}N_2S_3$: C, 65.36; H, 5.25; N, 6.63; S, 22.76. Found: C, 65.18; H, 5.37; N, 6.28; S, 22.48.

3-Methylthio-4-thioxo-1,4-dihydroquinoline **4a**.

Sulfide **3c** (0.53 g, 2 mmoles) was refluxed in 20 ml of hydrochloric acid (1:1) for 20 minutes. After cooling the reaction mixture was diluted with 80 ml of water and neutralized with 10% aqueous sodium hydroxide to *p*H = 3. The resulting orange solid was filtered off, washed with water and dried over phosphorus pentoxide to give 0.40 g of thione **4a** (97%), mp 225-226° (lit [8] mp 228°).

1,4-Dihydro-4-thioxo-4'-methylthio-3,3'-diquinolinyl Sulfide **4b**.

This compound was obtained from aqueous sodium 3-(4'-methylthio-3'-quinolinyl)-thio-4-quinolinethiolate solution [5] by careful addition of 5% hydrochloric acid to *p*H = 9. The resulting orange solid was filtered off, washed with water and dried over phosphorus pentoxide to give thione **4b** (95%), mp 235-237°.

Anal.. Calcd. for $C_{19}H_{14}N_2S_3$: C, 62.26; H, 3.85; N, 7.64; S, 26.24. Found: C, 61.90; H, 4.10; N, 7.49; S, 26.01.

Chlorination of Sulfides **3** and Thiones **4**. General Procedure.

a) Method A. With Phosphoryl Chloride.

Sulfide **3** or thione **4** (2 mmoles) and in some cases (thiones **4c-4e**) triethylamine hydrochloride (0.83 g, 6 mmoles) were refluxed in 15 ml of phosphoryl chloride for 24-120 hours (Table 1). The progress of the reaction was monitored by tlc. Then the excess of phosphoryl chloride was evaporated in vacuo. The residue was stirred with ice (30 g) and neutralized with concentrated ammonia. The resulting solid was filtered off, washed with water and air-dried. The solid was dissolved in chloroform (5 ml). Possibly the insoluble solid was filtered off and crystallized from DMF to give dithiins **1** or **2**. The chloroform filtrate was purified by column chromatography (silica gel 60, chloroform) to give 4-chloroquinolines **5**.

b) Method B. With Phosphoryl Chloride in *N,N*-Dimethylformamide.

Sulfide **3** or thione **4** (2 mmoles) was stirred in the mixture of phosphoryl chloride (0.92 g, 6 mmoles) and *N,N*-dimethylformamide (10 ml) at 20° or 100° under nitrogen atmosphere for 1 or 72 hours (Table 1). The progress of the reaction was monitored by tlc. The reaction mixture was worked-up as described above.

The isolated dithiins had following mps: thioquinanthrene **1** mp 310-311°, lit [22] mp 314-315°; isothioquinanthrene **2** mp 270-271°, lit [26] mp 269-270°.

4-Chloro-3-methylthioquinoline **5a**.

This compound had mp 104-105°, lit [8] mp 104-105°.

4-Chloro-4'-methylthio-3,3'-diquinolinyl Sulfide **5b**.

This compound had mp 117-118°; ^{1}H nmr (deuteriochloroform): δ 2.56 (s, 3H, SCH_3), 7.61-8.56 (m, $8H_{arom}$), 8.40 (s, 1H, H-2,), 8.79 (s, 1H, H-2); ms: (15 eV) m/z (relative intensity) 368 (M^+, 57.6), 370 (M+2, 24.2), 318 (M-CH_3 and Cl, 100), 333 (M-Cl, 63.9).

Anal. Calcd. for $C_{19}H_{13}N_2S_2Cl$: C, 61.86; H, 3.55; N, 7.59; S, 17.38; Cl, 9.61. Found: C, 61.66; H, 3.68; N, 7.41; S, 17.20; Cl, 9.48.

c) Method C. With Phosphoryl Chloride and Ethanol.

To a solution of sulfide **3d** (0.76 g, 2 mmoles) in 20 ml of ethanol 20 ml of phosphoryl chloride was added very carefully (drop by drop) through a condenser. The mixture was refluxed about one hour until it became very viscous. Heating was continued for half an hour. After cooling the reaction mixture was worked up as described above. The crude product was purified by column chromatography (silica gel 60, chloroform) to give 0.50 g of 4-chloroquinoline **5c** (70%), mp 129-130°, lit [26] mp 129°.

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