[CONTRIBUTION FROM THE RESEARCH LABORATORY OF LADY ESTHER, LTD.]

DERIVATIVES OF 6-METHOXY-8-NITROQUINOLINE. CHLORINATION WITH SULFURYL CHLORIDE

J. SCHULTZ,[1] M. A. GOLDBERG, G. CARSCH,[1a] AND E. P. ORDAS[1b]

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Since it was of interest, in connection with work on antimalarial drugs, to prepare derivatives of 6-methoxy-8-nitroquinoline containing chlorine in the hetero ring, it was decided to investigate the reaction between the N-oxide of this substituted quinoline and sulfuryl chloride. Unfortunately we were unable to isolate the N-oxide by the usual methods. However 6-methoxy-8-nitroquinoline itself was found to react with sulfuryl chloride to yield a mixture of chlorinated products. We were able to isolate five of these compounds; a dichloromethoxynitroquinoline, a trichloromethoxyquinoline, a trichlorohydroxyquinoline, a trichloromethoxynitroquinoline, and a tetrachloromethoxyquinoline.

The first of these was identified, by nitric acid oxidation to the known 5-chloronicotinic acid, as 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline.

The tetrachloromethoxyquinoline was also oxidized to 5-chloronicotinic acid with nitric acid. This indicates that three chlorine atoms enter the benzene ring, one replacing the nitro group, and the fourth enters the hetero ring in the 3-position. This compound is therefore 3,5,7,8-tetrachloro-6-methoxyquinoline. (Survey Number 13,480).[2]

The trichlorohydroxyquinoline, on the basis of its analysis, melting point, and melting point of its acetyl derivative appears to be identical with a compound prepared by Zincke and Müller (1). This compound was prepared by these investigators by a series of chlorinations starting with 6-hydroxyquinoline and was identified by them, mainly by analogy with the same reactions starting with β-naphthol, as 5,7,8-trichloro-6-hydroxyquinoline. Since this evidence appeared inconclusive, a sample of our trichlorohydroxyquinoline was oxidized by means of nitric acid to yield nicotinic acid (identified by melting point and melting point of its nitrate). Therefore this substance may be presumed to be 5,7,8-trichloro-6-hydroxyquinoline (SN 13,479).

By methylation of our trichlorohydroxyquinoline (SN 13,479) with dimethyl sulfate, we obtained a substance shown to be identical with our trichloromethoxyquinoline (SN 13,478). The latter is therefore identified as 5,7,8-trichloro-6-methoxyquinoline.

The remaining compound isolated from the sulfuryl chloride reaction was a trichloromethoxynitroquinoline whose structure we did not determine. This substance is accordingly designated x,y,z-trichloro-6-methoxy-8-nitroquinoline.

The 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline and the x,y,z-trichloro-

[1] Present address: New York Quinine and Chemical Works, Brooklyn, New York.

[1a] Present address: 600 S. Michigan Ave., Chicago 5, Ill.

[1b] Present address: Velsicol Corporation, Chicago 11, Ill.

[2] The Survey Number is the identification number assigned by the Malaria Survey Office of the National Research Council.

6-methoxy-8-nitroquinoline were reduced to the corresponding amines and several attempts were made by the usual methods for similar compounds to couple the dichloromethoxyaminoquinoline (SN 13,482) with 1-diethylamino-4-bromopentane. A portion of this dichloromethoxyaminoquinoline was also converted into the corresponding dichloromethoxyiodo compound (SN 13,483) and an attempt was made to couple this with 1-diethylamino-4-aminopentane. None of these coupling reactions succeeded, and will not be described. No attempt was made to couple the x,y,z-trichloro-6-methoxy-8-aminoquinoline (SN 13,481) with 1-diethylamino-4-bromopentane.

A number of these compounds were tested for antimalarial activity by the Malaria Research Group at the National Institute of Health. The following compounds tested showed no antimalarial action against *P. gallinaceum* in the chick when administered orally in the highest tolerated dose (Test A-1 of the Malaria Survey):

5,7,8-trichloro-6-methoxyquinoline (SN 13,478)
5,7,8-trichloro-6-hydroxyquinoline (SN 13,479)
3,5,7,8-tetrachloro-6-methoxyquinoline (SN 13,480)
x,y,z-trichloro-6-methoxy-8-aminoquinoline (SN 13,481)
3,5 (or 7)-dichloro-6-methoxy-8-aminoquinoline (SN 13,482)
3,5 (or 7)-dichloro-6-methoxy-8-iodoquinoline (SN 13,483)

EXPERIMENTAL[3, 4]

Chlorination of 6-methoxy-8-nitroquinoline. (Experiment I). To 40 g. of 6-methoxy-8-nitroquinoline in a 2-liter, round bottomed flask equipped with a reflux condenser, the top of which was protected by a calcium chloride tube and led to a gas absorber, was added 800 cc. of redistilled sulfuryl chloride (b.p. 68.5–70°). The mixture was refluxed gently (large quantities of SO_2 and HCl were evolved) for 15 minutes. It was then allowed to cool and divided between two 4-liter beakers, each containing about 500 g. of ice and 500 cc. of water. The mixture was stirred frequently until a vigorous reaction set in. The reaction was kept under control by the addition of ice. Finally precipitation was completed by adding more water to bring the total volume to approximately 7.5 liters. The mixture was then heated on the steam-bath for 1.5 hours, cooled, and filtered. This procedure was repeated with 40 g. then 20 g. of starting material, combining all filtrates and all precipitates.

5,7,8-Trichloro-6-hydroxyquinoline. The above filtrate was heated to about 80°, made alkaline with 40% sodium hydroxide, and filtered while hot from the precipitated starting material, which amounted to 20 g. The alkaline filtrate was acidified to *p*H about 5 and 16 g. of 5,7,8-trichloro-6-hydroxyquinoline filtered off. After recrystallization from dilute alcohol, then from methanol it was obtained as colorless needles m.p. 241–241.5° after slight sintering at 235°; lit. 244° (1).

Oxidation of 5,7,8-trichloro-6-hydroxyquinoline. A solution of 1.0 g. of 5,7,8-trichloro-6-hydroxyquinoline in 40 cc. of concentrated nitric acid was boiled gently for one hour. The solution was then evaporated almost to dryness on the water-bath in a current of air. The residue was dissolved in a small volume of hot water and allowed to cool. Light yellow crystals (0.37 g. 50%) of nicotinic acid nitrate, m.p. 189–191° were obtained.

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[3] We are indebted to the Winthrop Chemical Co. for the 6-methoxy-8-nitroquinoline used in this work.

[4] All C, H, and N analyses were done by Dr. T. S. Ma.

The nicotinic acid nitrate was dissolved in about 10 cc. of water, the solution neutralized to methyl red with dilute sodium hydroxide solution and an excess of copper sulfate solution added. The precipitated nicotinic acid copper salt was filtered off, washed free of sulfate with water and then suspended in about 25 cc. of water containing 0.10 g. of ammonium nitrate. H_2S was passed into the suspension to precipitate the copper, the solution of nicotinic acid was filtered off and concentrated to small volume. On cooling, about 0.2 g. (40%) of colorless nicotinic acid crystals, m.p. 229–231°, separated. Recrystallization from water raised the melting point to 231–232°.

5,7,8-Trichloro-6-acetoxyquinoline. Acetylation of the 5,7,8-trichloro-6-hydroxyquinoline with acetic anhydride gave colorless needles m.p. 138.5–139.5°; lit. 139° (1).

x,y,z-Trichloro-6-methoxy-8-nitroquinoline. The original precipitate was extracted with 1500 cc. of hot concentrated hydrochloric acid, leaving a residue of about 20 g. From this material there was obtained by recrystallization from benzene, then dioxane, about 10 g. of a trichloro-6-methoxy-8-nitroquinoline in the form of pale yellow needles, m.p. 203.5–204°.

Anal. Calc'd for $C_{10}H_5Cl_3N_2O_3$: C, 39.0; H, 1.62; N, 9.10.
Found: C, 38.44; H, 1.81; N, 8.90.

x,y,z-Trichloro-6-methoxy-8-aminoquinoline. To a solution of 70 g. of stannous chloride in 130 cc. of hydrochloric acid and 130 cc. of water was added a solution of 18 g. of the x,y,z-trichloro-6-methoxy-8-nitroquincline in 450 cc. of dioxane, with cooling so that the temperature did not exceed 50°. The mixture was allowed to stand 24 hours at room temperature, and the precipitated complex filtered off and washed with dilute hydrochloric acid. The complex was decomposed with aqueous sodium hydroxide and the amine extracted with ether. The ethereal solution was evaporated to dryness and the residue recrystallized from alcohol to yield about 9 g. of yellow needles; m.p. 212.5–213°.

Anal. Calc'd for $C_{10}H_7Cl_3N_2O$: N, 10.10. Found: N, 10.24.

3,5 (or 7)-Dichloro-6-methoxy-8-nitroquinoline. The hot, concentrated hydrochloric acid filtrate from extraction of the trichloromethoxyquinoline was diluted with a large amount of water and yielded a precipitate of 31.6 g. Crystallization from isopropanol gave 12.5 g. of yellow needles, m.p. 213–219°. Recrystallization raised the m.p. to 223.5–224.5°.

Anal. Calc'd for $C_{10}H_6Cl_2N_2O_3$: C, 44.00; H, 2.20; Cl, 26.0.
Found: C, 43.98; H, 2.34; Cl, 25.95.

Oxidation of 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline. A solution of 8 g. of 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline in 300 cc. of concentrated nitric acid was refluxed for 20 hours, when a small sample showed no precipitation with dilute sodium hydroxide. The solution was then evaporated to dryness and the residue taken up in 200 cc. of water. The *p*H was adjusted to 2 with sodium hydroxide solution; crystallization at 0° overnight yielded 1.32 g. (28.5%) of yellow crystals, m.p. 168–169.5°. Two recrystallizations from water raised the melting point to 170–171°. This corresponds to the reported melting point of 5-chloronicotinic acid (2).

Anal. Calc'd for $C_6H_4ClNO_2$: Cl, 22.5; Neutral Equiv., 157.5.
Found: Cl, 22.6; Neutral Equiv., 157.5.

3,5 (or 7)-Dichloro-6-methoxy-8-aminoquinoline. To a solution of 94 g. of stannous chloride in 170 cc. of hydrochloric acid and 250 cc. of water was added a solution of 24 g. of 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline in 500 cc. of hydrochloric acid. The mixture was cooled during the addition to maintain the temperature at about 45°. The mixture was allowed to stand for 24 hours at room temperature and the resulting complex filtered off and washed with dilute hydrochloric acid. The complex was decomposed with aqueous sodium hydroxide and the amine extracted with ether. The ethereal solution was evaporated to dryness and the residue crystallized from alcohol to yield 17.5 g. of pale yellow needles; m.p. 130.5–131.5°.

Anal. Calc'd for $C_{10}H_8Cl_2N_2O$: N, 11.5. Found: N, 11.39.

3,5 (or 7)-Dichloro-6-methoxy-8-iodoquinoline. A solution of 10 g. of 3,5 (or 7)-dichloro-6-methoxy-8-aminoquinoline in 100 cc. of concentrated sulfuric acid was diazotized at 5–10° with 3.4 g. of sodium nitrite in 40 cc. of sulfuric acid and 500 cc. of glacial acetic acid.

The solution was allowed to stand 20–25 minutes and then diluted with 500 cc. of ice and water. A solution of 3.5 g. of urea in a little water was then added and the solution allowed to stand 20 minutes longer. A solution of 8.2 g. of potasium iodide in 80 cc. of water was then added. The mixture was allowed to stand for 30 minutes, then heated on the steam-bath till evolution of nitrogen ceased.

The precipitate was filtered off and thoroughly washed with water and dried. The solid was crystallized from benzene (using carbon) to yield 9.7 g. of pale buff colored needles, m.p. 218–219°.

Anal. Calc'd for $C_{10}H_6Cl_2INO$: I, 35.9. Found: I, 35.8.

3,5,7,8-Tetrachloro-6-methoxyquinoline. From the isopropanol mother liquors (crystallization of the 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline) was obtained by fractional crystallization from acetone about 1.8 g. of fine colorless needles, m.p. 188–188.5°.

Anal. Calc'd for $C_{10}H_5Cl_4NO$: C, 40.4; H, 1.68; M.W., 297.
Found: C, 40.38; H, 2.07; M.W. (Rast), 292.

Oxidation with nitric acid yielded 5-chloronicotinic acid, which did not depress the melting point of the chloronicotinic acid obtained from 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline.

Experiment II. To 50 g. of 6-methoxy-8-nitroquinoline in a 1-liter round bottomed flask with a distilling head, condenser, and receiver was added 350 cc. of sulfuryl chloride. The flask was placed in a water-bath at 60° and the temperature was raised gradually to keep up a rapid distillation. After about 10 minutes, the lumps of solid which had formed were broken up, after which distillation was continued. After 35 minutes, the mixture had become practically dry. The solid cake which remained was extracted with about 700 cc. of conc'd hydrochloric acid in several portions, the mixture being heated to boiling with each portion of acid, cooled, and filtered.

A residue of 9.5 g. of acid-insoluble matter was obtained. Crystallization from benzene or isopropanol gave about 4.5 g. of the same x,y,z-trichloro-6-methoxy-8-nitroquinoline isolated in Experiment I (m.p. 202.5–204°).

The hydrochloric acid solution at this point had a volume of about 750 cc. and was 11 *N* in HCl. Water (180 cc.) was added, the solution left in the refrigerator overnight and a small gummy precipitate filtered off. One hundred twenty cc. of water was added to the filtrate and 2.24 g. of precipitate m.p. 150–188° removed. The solution was now diluted to about 2500 cc. with water and 19 g. of precipitate melting at 190–217° obtained. One crystallization from benzene-hexane yielded 10.3 g. of 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline, melting at 223.5–224.5° with sintering at 219°. The mother liquor from this crystallization was evaporated to dryness. Fractional crystallization of the residue from acetone yielded 1 g. of 3,5,7,8-tetrachloro-6-methoxyquinoline, m.p. 183–186°. Recrystallization from ethyl acetate raised the melting point to 188–188.2°.

The acid solution from the precipitation of the crude 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline was concentrated to about 60 cc. *in vacuo*, diluted, made alkaline with sodium hydroxide solution, and extracted with benzene. At this point, 14.2 g. of material insoluble in alkali or benzene was filtered off. By extraction with boiling dilute alkali, a residue of 5.4 g. of 6-methoxy-8-nitroquinoline was obtained, together with an alkaline solution which on adjusting the *p*H to 5 precipitated about 7 g. of 5,7,8-trichloro-6-hydroxyquinoline, m.p. 225–235°. The benzene solution was evaporated to dryness leaving a residue of 10.7 g. Fractional precipitation from hydrochloric acid followed by crystallizations from benzene, then methanol yielded about 1.5 g. of 5,7,8-trichloro-6-methoxyquinoline, m.p. 144.5–145.0° (slight sintering at 144.0°). About 3 g. of 6-methoxy-8-nitroquinoline was also recovered in the course of the fractional precipitations.

Anal. Calc'd for $C_{10}H_6Cl_3NO$: C, 45.7; H, 2.38; N, 51.33; Cl, 40.6; M.W., 262.5.
Found: C, 45.64; H, 2.69; N, 5.23; Cl, 39.2; M.W. (Rast), 257.

A sample of the 5,7,8-trichloro-6-hydroxyquinoline on methylation with dimethyl sulfate, gave 5,7,8-trichloro-6-methoxyquinoline, which did not depress the melting point of the above material.

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SUMMARY

1. A study of the reaction between 6-methoxy-8-nitroquinoline and sulfuryl chloride has been made.

2. A number of chlorinated quinoline derivatives not previously described have been prepared.

3. A number of chlorinated quinoline derivatives have been evaluated as antimalarials.

CHICAGO (38), ILL.

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