[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY,
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THE SYNTHESIS OF 5-HYDROXY-8-NITROQUINOLINE AND CERTAIN OF ITS DERIVATIVES[1]

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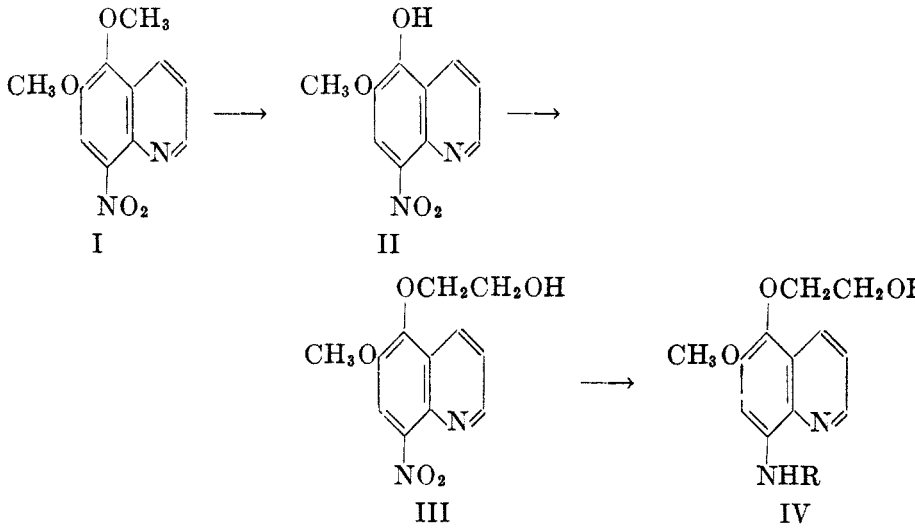
In a search for an antimalarial drug of the plasmochin type which would be less toxic than plasmochin, attention was directed to certain derivatives of 5-hydroxy-8-aminoquinoline. In particular, it was desired to introduce the 2-hydroxyethoxyl group into position 5 of the quinoline ring. Although this investigation was interrupted before any satisfactory candidate drug had been produced, certain of the intermediates had been made. The present paper is a report of this synthetic work.

The original plan for the synthesis of one of the drugs involved the following sequence of transformations.



By analogy with the results of Cardwell and Robinson (1) on the hydrolysis of 4-nitroveratrole, it was expected that cleavage of the 5-methoxyl group in 5,6-dimethoxy-8-nitroquinoline (I) could be effected by use of aqueous ethanolic potassium hydroxide and that acid catalysts would bring about preferential cleavage of the methoxyl group in the 6 position. Experiment showed, however, that when the dimethoxy compound was hydrolyzed by either alkaline or acidic reagents, cleavage occurred at the 5 position only. Heating in a closed tube with

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concentrated hydrochloric acid was necessary to cleave both methoxyl groups. The ease of cleavage of the 5-methoxyl group was such that it took place slowly when an aqueous methanol solution of the dimethoxyquinoline was boiled for an extended period during recrystallization. The most satisfactory method for obtaining the hydroxy compound (II) was to heat the dimethoxyquinoline with dilute hydrochloric acid.

The quinolinol (II) was a bright red solid, soluble in dilute acids or bases but insoluble in most organic solvents, and had the melting point 240°. It proved to be very difficult to alkylate, attempts at methylation with methyl sulfate and with diazomethane, for example, being unsuccessful. However, reconversion to the dimethoxyquinoline (I) was accomplished in low yield by the action of methyl iodide on the silver salt of the quinolinol.

In an effort to evaluate the influence of the methoxyl group on the quinolinol (II) the hitherto unknown 5-hydroxy-8-nitroquinoline (V) was synthesized. It was made from 5-chloro-8-nitroquinoline both by direct hydrolysis and by acid cleavage of the intermediate 5-methoxy-8-nitroquinoline. Preparation and hydrolysis of 2-nitro-5-chloroacetanilide was an essential step in the synthesis of 5-chloro-8-nitroquinoline. Better yields of 2-nitro-5-chloroacetanilide were obtained by nitrating *m*-chloroacetanilide with fuming nitric acid in glacial acetic acid and acetic anhydride than were possible with previous procedures (2, 3, 4). When 2-nitro-5-chloroacetanilide was treated with sodium ethoxide, an almost quantitative yield of the free amine was obtained. This catalytic exchange method was discovered by Verkade (5).

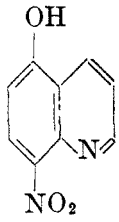
6-Hydroxy-8-nitroquinoline, likewise new, was obtained in low yield by the acid cleavage of the well-known 6-methoxy-8-nitroquinoline.

The melting points of all *bz*-hydroxy-8-nitroquinolines are high. 5-Hydroxy-8-nitroquinoline melts with decomposition at 261°, 6-hydroxy-8-nitroquinoline at 242°, and 7-hydroxy-8-nitroquinoline at 255° (6). All these nitroquinolinols are deeply colored; 5-hydroxy-8-nitroquinoline is brilliant yellow, 6-hydroxy-8-nitroquinoline is red-brown, and 7-hydroxy-8-nitroquinoline is bright yellow. Examination of the literature showed that, with many phenolic compounds that can be alkylated only with difficulty, success could be achieved by use of the silver salt and an alkyl iodide. Thus 5-hydroxy-6-methoxy-8-nitroquinoline appears to have properties that are similar to those of other nitroquinolinols of the same type.

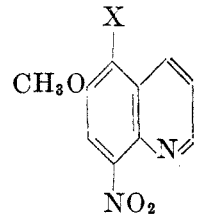
The conversion of the quinolinol (II) to the corresponding 2-hydroxyethoxy compound (III) by ethoxylation could not be effected. The action of benzyloxyethyl *p*-toluenesulfonate in ethanolic potassium hydroxide (7) on the quinolinol, of benzyloxyethyl iodide or ethylene bromohydrin on the silver salt of the quinolinol, and of ethylene oxide on the potassium salt of the quinolinol failed to yield the desired derivative.

Tetrakis (2-hydroxyethyl)ammonium hydroxide in 39% aqueous solution was tried also as an alkylating agent. Experiment showed that *p*-nitrophenol, employed as a model compound, could be converted to 2-(*p*-nitrophenoxy)ethanol

by use of this reagent. However, attempts to hydroxyethylate the quinolinol were unsuccessful.



V



VI (X = Cl)
VII (X = Br)

The hydroxyethoxy derivative (III) was finally obtained from 5-chloro-6-methoxy-8-nitroquinoline (VI). The chloro compound had been prepared from 4-amino-2-chloro-5-nitroanisole previously by the Skraup reaction (8). In the present work it was found possible to make it in high yields by treating the quinolinol (II) with phosphorus oxychloride. The conversion of the chloro compound to ethers by treatment with sodium alkoxides had been carried out earlier (9). The hydroxyethoxy compound (III) was made by treatment of the chloro derivative (VI) with the monosodium derivative of ethylene glycol. Actually, it was possible to effect this change simply by heating the chlorine derivative with ethylene glycol in the presence of potassium hydroxide and a small amount of water.

The same hydroxyethoxy derivative was obtained when the bromo compound (VII), prepared by the directions of Lauer, Rondestvedt, Arnold, Drake, Van Hook, and Tinker (10), was employed in place of the chloro compound. Since the structure of the bromo compound was known, the identity of the alkylation products from the two halogen compounds confirms the structures assigned to the chloro compound and the quinolinol, and proves that cleavage of the dimethoxy compound took place at position 5 rather than 6.

In the preparation of the hydroxyethoxy derivative it was observed that the two halogen compounds gave approximately the same yields and that the yield was not increased by the addition of potassium iodide. The presence of water was found to be necessary, although it caused a considerable amount of the halogen compound to revert to the quinolinol.

The hydroxyethoxy derivative was much more soluble in water than was the quinolinol. It could be reconverted to the hydroxy compound by hydrolysis with hot 50% aqueous ethylene glycol containing potassium hydroxide.

Reduction of the nitro compound (III) to the amine (IV, R = H) was effected in 84% yield by the use of platinum oxide and hydrogen under a few atmospheres pressure. The alkylation of the amine with 6-diethylamino-1-bromohexane was attempted by fusing the reactants in the absence of a solvent. The product was a yellow oil which when exposed to air rapidly developed a green color which soon turned brown. Attempts to convert the compound to a non-hygroscopic salt suitable for pharmacological testing were unsuccessful.

EXPERIMENTAL[3]

5-Hydroxy-6-methoxy-8-nitroquinoline (II). A. *Alkaline cleavage.* Five grams of 5,6-dimethoxy-8-nitroquinoline, 38 g. of potassium hydroxide, 125 g. of ethanol, and 110 g. of water were heated together at reflux temperature for eighteen hours. At the end of this time, the suspended material originally present had dissolved. When the reaction mixture was cooled, the orange-colored potassium salt of 5-hydroxy-6-methoxy-8-nitroquinoline was deposited. Extraction of the salt with ether and chloroform indicated the absence of 5,6-dimethoxy-8-nitroquinoline. The free 5-hydroxy compound was obtained as a bright red solid by acidification of the alkaline solution with concentrated hydrochloric acid (Congo Red). It was removed by filtration, washed, and dried in an oven. The yield was 3 g. or 64%. A sample was dissolved in alkali, reprecipitated with acid, washed with water and alcohol, and dried. It melted at 233°, with decomposition. The melting point 243–245° has been reported (11).

B. *Acid cleavage.* A mixture of 100 g. of crude 5,6-dimethoxy-8-nitroquinoline, 50 ml. of concentrated hydrochloric acid, and 1000 ml. of water was heated in an oil-bath at reflux temperature for six hours. A few drops of Aerosol-OS (10% solution) were added to prevent excessive foaming during the heating. After the reaction mixture had been cooled to room temperature, the dark red product was washed with water. The crude product was dissolved in a solution of 20 g. of sodium hydroxide in 3.5 l. of warm water, and the orange solution was filtered. The filtrate was made acid to litmus by adding a solution of about 40 ml. of concentrated hydrochloric acid in 500 ml. of water. The bright red product was washed with water, and dried in an oven. The yield was 89.6 g. (95%); m.p. 236–238°, with decomposition.

Alkylation of 5-hydroxy-6-methoxy-8-nitroquinoline. A. *With methyl iodide.* The silver salt of 5-hydroxy-6-methoxy-8-nitroquinoline was prepared by dissolving 3 g. of the 5-hydroxy compound in dilute sodium hydroxide and adding an aqueous solution containing 2.3 g. of silver nitrate. The red precipitate was washed well with water; the dry solid weighed 4 g. To a mixture of equal weights of the silver salt and methyl iodide was added 6 ml. of methanol, and the mixture maintained at reflux temperature for four hours. Excess methanol was added and the mixture filtered. The residue from the filtration was extracted several times with hot methanol; the extracts were combined with the above filtrate and evaporated to dryness under reduced pressure. The residue obtained by evaporation was taken up in ether; the ether solution was washed once with water, twice with 10% sodium hydroxide solution, and once again with water. Evaporation of the ether left light yellow needles; m.p. 123–125°. The melting point of a mixture of this product with authentic 5,6-dimethoxy-8-nitroquinoline was not depressed; the yield was 0.27 g. or 8.5%.

5-Chloro-6-methoxy-8-nitroquinoline. Phosphorus oxychloride (150 ml.) was heated in an oil-bath to 80° and 41 g. of 5-hydroxy-6-methoxy-8-nitroquinoline was added slowly with vigorous stirring. After the addition was complete, the mixture was brought to reflux temperature, and heating and stirring were continued one and one-half hours. The cooled mixture was poured into 700 ml. of concentrated ammonium hydroxide, sufficient ice being added to prevent the temperature from rising above 25°. The precipitate was washed with water, and dried in an oven. The cream-colored solid, m.p. 203.5–205°, weighed 42 g. (95%); the melting point 204° has been reported (8).

5-(2-Hydroxyethoxy)-6-methoxy-8-nitroquinoline. A. *By use of monosodium glycolate.* To a solution of 0.5 g. of sodium metal in 12 ml. of absolute ethanol was added 1.25 g. of ethylene glycol. The ethanol was removed *in vacuo*, and 50 ml. of ethylene glycol was added as solvent. The mixture was heated nearly to boiling, and 4.77 g. of 5-chloro-6-methoxy-8-nitroquinoline was added with stirring. After the heating had been continued for two hours, the reaction mixture was cooled and poured into 350 ml. of water. After filtration to remove a black solid, the solution was extracted with two 100-ml. portions of ether.

[3] All melting points are corrected.

After the combined ether extracts were dried over Drierite, the ether was removed and the yellow residue (m.p. 110–150°) was recrystallized three times from a benzene-ligroin mixture, Darco being used during the first recrystallization. The 5-(2-hydroxyethoxy)-6-methoxy-8-nitroquinoline was a bright yellow solid melting at 122–123°.

Anal. Calc'd for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58.
Found: C, 54.74; H, 4.36.

The acetyl derivative, prepared by treating the amine with acetic anhydride and pyridine and crystallized from dilute methanol, had a pale yellow color and melted at 70–71°.

Anal. Calc'd for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61.
Found: C, 55.20; H, 4.60.

B. *By use of ethylene glycol and potassium hydroxide.* To a suspension of 2.4 g. of 5-chloro-6-methoxy-8-nitroquinoline in 96 ml. of ethylene glycol was added a solution of 0.66 g. of 85% potassium hydroxide in 10 ml. of water. The mixture was heated for five hours at 165° and then concentrated nearly to dryness by distillation under water-pump pressure. Extraction with 100 ml. of boiling water removed the hydroxyethoxy derivative, leaving behind 0.41 g. (m.p. 197–200°) of starting material. After the water solution had been treated with Darco it was allowed to cool. The hydroxyethoxy derivative crystallized in greenish-yellow needles weighing 0.82 g.; m.p. 119–121°; yield 32%.

Similar results were obtained when the bromo compound (VII) was employed. The addition of potassium iodide did not affect the yield appreciably. In addition to the hydroxyethoxy compound and the unchanged halogen compound, some hydroxyquinoline (II) was formed.

8-Amino-5-(2-hydroxyethoxy)-6-methoxyquinoline. A mixture of 7.1 g. of 5-(2-hydroxyethoxy)-6-methoxy-8-nitroquinoline, 150 ml. of absolute ethanol, and 0.15 g. of platinum oxide catalyst was subjected to a hydrogen pressure of 40 lb. per sq. in. in an Adams apparatus. The theoretical amount of hydrogen was absorbed in thirty-five minutes. After removal of the catalyst, the hot alcohol solution was treated with Norit and a pinch of sodium hydrosulfite. The filtrate was concentrated by distillation and again treated with Norit and sodium hydrosulfite. Low-boiling petroleum ether (b.p. 30–60°) was added to incipient cloudiness, and the mixture was allowed to stand in an ice-box. The tan-colored needles which formed were washed with a benzene-petroleum ether mixture. The dry product, m.p. 103–104°, weighed 4.93 g. Concentration of the mother liquor and treatment as above yielded 0.34 g. of product; m.p. 103–106°. The total yield was 84%. A sample recrystallized from water had the melting point 104–105°.

Anal. Calc'd for $C_{12}H_{14}N_2O_3$: C, 61.54; H, 6.02.
Found: C, 61.63; H, 5.76.

The picrate was prepared by dissolving the amine in 95% ethanol and treating with a saturated ethanolic solution of picric acid. A sample recrystallized from absolute ethanol melted at 174–176°.

Anal. Calc'd for $C_{18}H_{17}N_5O_{10}$: C, 46.67; H, 3.69.
Found: C, 46.73; H, 3.49.

2-[8-(6-Diethylaminohexylamino)-6-methoxy-5-quinolyloxy]ethanol. An intimate mixture of 9.53 g. of 8-amino-5-(2-hydroxyethoxy)-6-methoxyquinoline and 12.9 g. of 6-diethylamino-1-bromohexane hydrobromide was heated in an oil-bath, with stirring, at 115–125° for twelve hours and at 125–135° for two hours, nitrogen being admitted continuously above the reaction mixture. The brittle, red solid obtained by cooling the reaction mixture was dissolved in approximately 150 ml. of warm water. After the aqueous solution had been cooled in ice, it was made strongly alkaline to litmus with 20% sodium hydroxide solution and extracted three times with chloroform (U.S.P.). The aqueous layer was partially saturated in the cold with potassium carbonate and extracted twice with chloroform. After the chloroform solution had been dried over magnesium sulfate, the solvent was removed and the residue subjected to distillation under the vacuum of an oil-pump and a liquid air-charcoal trap. A small forerun was collected as a yellow oil; b.p. 150–160° (0.1–0.3 mm.). A sample of the unstable oil was analyzed immediately.

Anal. Calc'd for $C_{22}H_{25}N_3O_3$: C, 67.83; H, 9.06.
Found: C, 68.93; H, 8.21.

5,6-Dihydroxy-8-nitroquinoline hydrochloride. A solution of 2 g. of crude 5,6-dimethoxy-8-nitroquinoline in 30 ml. of concentrated hydrochloric acid in a sealed tube was heated at 150° for six hours. The dark red crystals which were obtained were washed with concentrated hydrochloric acid; weight 1.4 g. A sample was prepared for analysis by recrystallizing four times from 95% ethanol to which ethyl ether had been added after filtration. The bright orange, water-soluble hydrochloride melted with decomposition at 233–238° in a sealed tube.

Anal. Calc'd for $C_9H_6N_2O_4.HCl$: C, 44.35; H, 2.91.
Found: C, 43.85; H, 2.73.

2-Nitro-5-chloroacetanilide. A solution of 17 g. of *m*-chloroacetanilide in a mixture of 20 g. of acetic anhydride and 9 g. of acetic acid was cooled to 0°. The temperature was held carefully within the limits 0° to −5° while a mixture of 9 g. of acetic acid and 10 g. of nitric acid (sp. gr. 1.52) was added slowly. The clear liquid, after being allowed to stand overnight at room temperature, was poured on 400 g. of crushed ice. The precipitate was washed thoroughly with water, and dried *in vacuo*. The dry solid was triturated with two 100-ml. portions of dry benzene and the insoluble 3-chloro-4-nitroacetanilide removed. The 2-nitro-5-chloroacetanilide, obtained by evaporating the benzene solution to dryness was recrystallized from 95% ethanol. The yield was 11.0 g. or 60%; m.p. 117–118°. The melting point 117–118° has been reported for this compound (4).

2-Nitro-5-chloroaniline. A solution of 0.04 g. of metallic sodium in 150 ml. of absolute methanol was added to 12.8 g. of 2-nitro-5-chloroacetanilide and the solution was boiled under reflux for three hours, after which 125 ml. of solvent was removed by distillation. The free amine crystallized in golden leaflets; evaporation of the mother liquor produced a second crop of crystals. The yield of pure amine (m.p. 127.5–128°) was 10 g. or 96%. The melting point 124–125° has been reported for this compound (3).

5-Chloro-8-nitroquinoline. This compound was prepared from 2-nitro-5-chloroaniline by the Skraup reaction according to the directions of Fourneau, Trefoul, Trefoul, and Wancolle (2).

5-Methoxy-8-nitroquinoline. A solution of 3 g. of 5-chloro-8-nitroquinoline and 3 g. of sodium methoxide in 125 ml. of absolute methanol was maintained at 55–60° for six hours and then allowed to stand at room temperature overnight. A yellow, crystalline product was removed from the cold solution, and the filtrate evaporated to dryness in a stream of dry air. The residue was extracted with 10 ml. of distilled water and the insoluble portion combined with the first crop of crystals. After recrystallization from methanol the yellow crystals melted at 119.5–120°. The yield of 5-methoxy-8-nitroquinoline was 2.5 g. or 85%.

Anal. Calc'd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95.
Found: C, 59.06; H, 3.77.

5-Hydroxy-8-nitroquinoline. A. *By cleavage of 5-methoxy-8-nitroquinoline.* A solution of 1 g. of 5-methoxy-8-nitroquinoline in 50 ml. of distilled water and 3 ml. of concentrated hydrochloric acid was boiled under reflux for six hours, and then allowed to stand overnight at room temperature. Enough dilute sodium hydroxide solution was added to make the solution weakly acid to Congo Red paper, the solid precipitate was dissolved in dilute sodium carbonate solution, and the insoluble 5-methoxy-8-nitroquinoline removed. In this way 0.25 g. of starting material was recovered unchanged. The yellow sodium carbonate solution was acidified with acetic acid; the light yellow precipitate, 5-hydroxy-8-nitroquinoline, m.p. 261° (decomp.), weighed 0.61 g.; yield 89% (based on the 5-methoxy-8-nitroquinoline utilized). It crystallized from absolute ethanol as compact orange crystals.

Anal. Calc'd for $C_9H_6N_2O_3$: C, 56.85; H, 3.18.
Found: C, 56.60; H, 3.26.

B. *By hydrolysis of 5-chloro-8-nitroquinoline.* A mixture of 0.5 g. of 5-chloro-8-nitroquinoline, 1.5 g. of potassium hydroxide, 10 ml. of 95% ethanol, and 15 ml. of distilled water was boiled under reflux for seven hours. The clear solution was added to 25 ml. of 95%

ethanol and cooled in the refrigerator. The potassium salt of 5-hydroxy-8-nitroquinoline, obtained as long orange needles, was redissolved in distilled water and treated with acetic acid. The brilliant yellow product was dried in air; the yield was 0.21 g. or 45%; m.p. 258–260° (decomp.).

Acetate of 5-hydroxy-8-nitroquinoline. A solution of 0.61 g. of 5-hydroxy-8-nitroquinoline, 0.5 g. of acetic anhydride, and 25 ml. of dry pyridine was maintained at 70° for four hours and allowed to stand at room temperature overnight. The pyridine and acetic acid were removed by distillation *in vacuo*, and the residue was taken up in ether. Evaporation of the ether produced a fluffy, yellow solid which was recrystallized from petroleum ether (b.p. 80–100°). The acetate, in the form of white needles, was obtained in nearly quantitative yield; m.p. 114–114.5°. It was found to be sensitive to moisture.

Anal. Calc'd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.46.
Found: C, 57.10; H, 3.36.

6-Hydroxy-8-nitroquinoline. One gram of 6-methoxy-8-nitroquinoline, 15 ml. of 42% hydrobromic acid, and 7.5 ml. of glacial acetic acid were heated in an oil-bath at 140° for forty hours. The dark brown solution was cooled in the refrigerator and the brown crystals isolated on a filter. The filtrate was made neutral to Congo Red paper with 10% sodium hydroxide solution and the brown precipitate collected. When the two solids were combined and extracted with 10% sodium hydroxide solution, an insoluble portion (starting material) weighing 0.25 g. remained. The solution was made acid with acetic acid and the brown powder recrystallized from ethanol; brown needles, m.p. 242° (decomp.); weight 0.28 g.; yield 40% (based on the 6-methoxy-8-nitroquinoline utilized).

Anal. Calc'd for $C_9H_6N_2O_3$: C, 56.85; H, 3.18.
Found: C, 57.12; H, 3.35.

Acetate of 6-hydroxy-8-nitroquinoline. A mixture of 0.15 g. of 6-hydroxy-8-nitroquinoline, 5 ml. of dry pyridine, and 10 drops of acetic anhydride was allowed to stand overnight at room temperature. The pyridine and acetic acid were removed by distillation *in vacuo*, and the product was recrystallized from a benzene-petroleum ether (b.p. 80–100°) mixed solvent. A nearly quantitative yield of white, needle-like crystals of the acetate was obtained; m.p. 111.5–112°.

Anal. Calc'd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.46.
Found: C, 56.88; H, 3.56.

SUMMARY

5-Hydroxy-6-methoxy-8-nitroquinoline has been prepared by the hydrolysis of 5,6-dimethoxy-8-nitroquinoline and converted to 5-chloro-6-methoxy-8-nitroquinoline by the action of phosphorus oxychloride. The chloride and the analogous bromide were converted to the corresponding 2-hydroxyethoxy derivative by treatment with ethylene glycol in the presence of potassium hydroxide. Reduction of the resulting nitro compound yielded 8-amino-5-(2-hydroxyethoxy)-6-methoxyquinoline. Alkylation of the amine with 6-diethylamino-1-bromohexane yielded a compound which appeared to be an impure sample of 2-[8-(6-diethylaminohexylamino)-6-methoxy-5-quinolyloxy]ethanol.

For purposes of comparison, 5- and 6-hydroxy-8-nitroquinoline were synthesized.

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