[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

A Sulfur Analog of the Plasmochin Type: 8-(γ-Diethylaminopropylamino)-6-quinolyl Methyl Sulfide[1]

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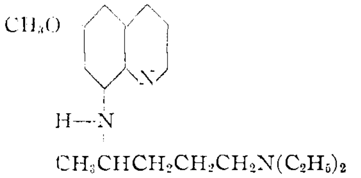
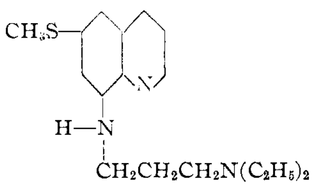
In connection with studies on experimental avian malaria it was desirable to prepare a type of the long-known plasmochin [I] in which the 6-methoxy group is replaced by a 6-methylmercapto group. The sulfur analog which has been prepared is 8-(γ-diethylaminopropylamino)-6-quinolyl methyl sulfide [II].

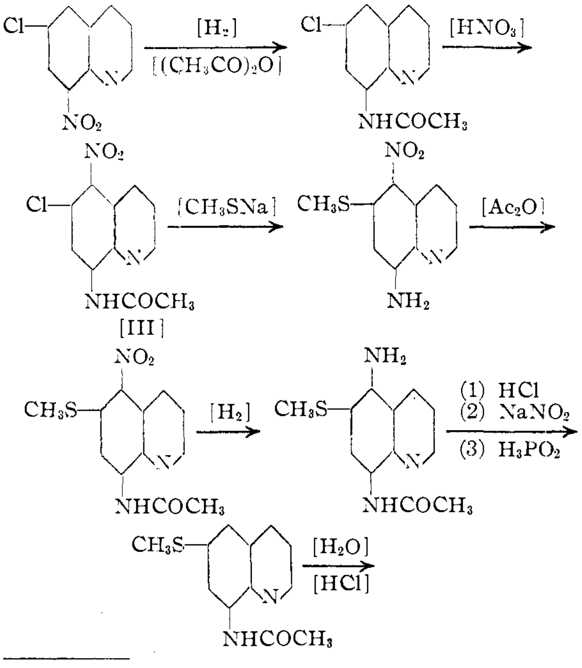


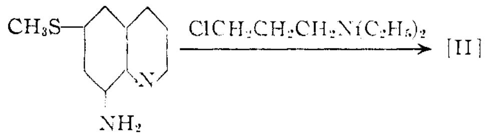
[I]



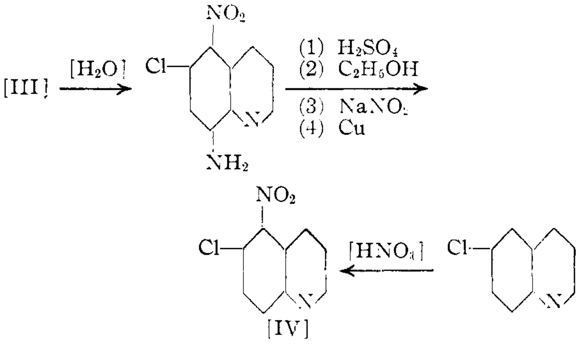
[II]

The following sequence of reactions was used in the synthesis of the sulfur analog.





The position of the nitro group in [III] was established as follows



Compound [IV] was shown to be identical with an authentic specimen prepared by the nitration of 6-chloroquinoline.

Some orienting experiments showed that it was not practicable to replace the chlorine in 6-chloro-8-nitroquinoline directly by an alkylmercapto group. It was for this reason that the synthesis started with a nitro group in the 5-position so that the adjacent chlorine would be activated for the reaction with sodium methylmercaptide.

Experimental

6-Chloro-8-nitroquinoline.—The general procedure of Richter and Smith[2a] was followed using one mole of 2-nitro-4-chloroaniline, four moles of dried glycerol, three-fourths mole of arsenic pentoxide and a weight of conc. sulfuric acid equal to 55% of the weight of the glycerol. In this manner, 193 g. (92.5%) of dry, crude product melting at 142–155° was obtained in a one mole run. The crude product was recrystallized from hot acetone containing decolorizing charcoal, and the yield of chloro-nitro compound melting at 158–159° was 140 g. (67%).

6-Chloro-8-aminoquinoline.—The reduction of 6-chloro-8-nitroquinoline to 6-chloro-8-aminoquinoline by stannous chloride and hydrochloric acid[2b] was found to be somewhat unwieldy. Two other procedures were examined, and of these the catalytic method (using Raney nickel) is preferred. A solution of 15 g. (0.072 mole) of pure 6-chloro-8-nitroquinoline in 200 cc. of absolute ethanol was hydrogenated in the presence of Raney nickel under three atmospheres of hydrogen at a temperature of 95–100° in one hour. After filtration and removal of the ethanol the resultant oil was distilled at 125–130° (0.5 mm.) to yield 11.5 g. (90%) which melted at 72–73° after solidification.

In the other reduction, 15 g. (0.072 mole) of the crude

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[1] Most of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Iowa State College.

[2] (a) Richter and Smith, THIS JOURNAL, **66**, 396 (1944). (b) Richter and Smith, "Phenanthroline and Substituted Phenanthroline Indicators," published by the G. F. Smith Chemical Co., Columbus, Ohio.

6-chloro-8-nitroquinoline (m. p., 142–145°) was dissolved in 200 cc. of 95% ethanol; 1 cc. of concd. hydrochloric acid was added, and then 15 g. (0.27 g. atom) of iron powder. The mixture was refluxed for three hours, filtered, and distilled to yield 9 g. (70%) of 6-chloro-8-aminoquinoline boiling at 125–130° (0.5 mm.). The product from either reduction melts at 73° after crystallization from petroleum either.[2]

6-Chloro-8-acetaminoquinoline. After the initial reaction of 17.8 g. (0.1 mole) of 6-chloro-8-aminoquinoline in 13 cc. of benzene with 11.2 g. (0.11 mole) of acetic anhydride, the solution was refluxed for fifteen minutes. The weight of product obtained after washing the filtered crystals with petroleum ether (b. p., 60–68°) was 20 g. (91%), and the melting point was 145–147°. After recrystallization from benzene the chloro-acetamino compound melted at 146.5–147.5°.

Anal Calcd. for $C_{11}H_9ON_2Cl$: N, 12.68. Found: N, 12.80.

From 108 g. (0.6 mole) of 6-chloro-8-aminoquinoline, 300 cc. of benzene containing a few drops of ammonium hydroxide, 70.4 g. (0.69 mole) of acetic anhydride, there was obtained after refluxing for fifteen minutes 127 g. (96%) of acetamino compound as colorless needles melting at 144.5–145.5° subsequent to crystallization from a mixture of petroleum ether (b. p., 60–68°) and benzene.

5-Nitro-6-chloro-8-acetaminoquinoline.[3]—To 50 cc. of cold, stirred concd. sulfuric acid was added 9.8 g. (0.044 mole) of finely powdered 6-chloro-8-acetaminoquinoline. Then a cool solution of 5.6 g. (0.056 mole) of potassium nitrate in 20 cc. of concd. sulfuric acid was added during twenty minutes to the stirred mixture which was kept at a temperature of 20–25°. The mixture was allowed to stand at this temperature for four and one-half hours and then poured upon 700 g. of chopped ice. The lemon-yellow nitro compound was filtered, washed with water, and the suspension made slightly alkaline with ammonium hydroxide whereupon the color changed to olive green. Recrystallization from 95% ethanol in the presence of decolorizing charcoal gave 7 g. (60%) of pale yellow compound melting at 190–193°. The sample prepared for analysis melted at 195–196°.

Anal. Calcd. for $C_{11}H_8O_3N_3Cl$: N, 15.82. Found: N, 15.76.

In other nitrations starting with 44 g. (0.2 mole) of 6-chloro-8-acetaminoquinoline, the yield of nitro compound melting at 192–194° was 22.6 g. (43%) and, in addition, there was recovered 19 g. (43%) of 6-chloro-8-acetaminoquinoline melting at 141–145°. In these particular nitrations the reaction temperature was 15–20°.

5-Nitro-6-chloro-8-aminoquinoline.—A suspension of 5 g. (0.0189 mole) of pure 5-nitro-6-chloro-8-acetaminoquinoline in 240 cc. of hydrochloric acid (two parts concd hydrochloric acid and one part water) was gently heated to boiling with rapid stirring, and then refluxed for ten minutes. After cooling to 0°, the solution was neutralized by a 20% solution of sodium hydroxide to give 4.2 g. (quantitative yield) of orange colored product melting at 190–194°. The melting point after crystallization from 95% ethanol was 198.5°.

Anal. Calcd. for $C_9H_6O_2N_3Cl$: N, 18.90. Found: N, 19.05.

Deamination of 5-Nitro-6-chloro-8-aminoquinoline.—To a cold, stirred mixture of 38 cc. of 95% ethanol and 9.6 cc. of concd. sulfuric acid was added 1.42 g. (0.0063 mole) of 5-nitro-6-chloro-8-aminoquinoline. After heating with stirring to 60° the finely divided lemon-yellow suspension was then cooled to 0°, and diazotized by the addition of 0.66 g. (0.0096 mole) of sodium nitrite in 12.4 cc. of water. The salmon-pink suspension was allowed to stand for one-half hour below 10°; then 0.44 g. of copper bronze was added, and the mixture was warmed gently under a reflux condenser until an energetic evolution of gas set in. Finally, the mixture was heated for ten minutes on a steam-bath, and the cooled solution was poured into ice water, neutralized with 20% sodium hydroxide, filtered, and the residue extracted with 95% ethanol. The ethanol was removed, after treatment with decolorizing charcoal, and from the ether extract of the residue there was obtained 0.3 g. (23%) of colorless crystals melting at 128–129°. A mixed m. p. with an authentic specimen of 5-nitro-6-chloroquinoline, prepared by nitration of 6-chloroquinoline in accordance with the procedure of Claus and Schedler,[4] showed no depression.

5-Nitro-8-amino-6-quinolyl Methyl Sulfide.—A 0.94 molar solution of sodium methyl mercaptide was prepared by dissolving 10.5 g. (0.45 g. atom) of sodium in 300 cc. of methyl cellosolve, chilling the solution below 0° by an ice–salt-bath, adding 25 g. (0.52 mole) of methyl mercaptan, and diluting to 450 cc. One hundred and fifty cc. (0.14 mole) of this sodium methyl mercaptide solution in methyl cellosolve was added to a refluxing solution of 32.5 g. (0.12 mole) of 5-nitro-6-chloro-8-acetaminoquinoline in 400 cc. of methyl cellosolve over a ten-minute period. A solid precipitated, and the mixture was refluxed for fifty minutes. Subsequent to cooling, filtration, washing with water, and drying there was obtained 24.8 g. (88%) of orange-colored product melting at 243–244°. The melting point was unchanged after recrystallization from methyl cellosolve. The amino compound is unusually insoluble in most organic solvents, but is soluble in dil. hydrochloric acid.

Anal. Calcd. for $C_{10}H_9O_2N_3S$: N, 17.87; S, 13.61. Found: N, 18.41 and 18.33; S, 13.49 and 13.31.

The condensation with sodium methyl mercaptide is quite rapid, for in a similar preparation in which the mixture was refluxed for five minutes the yield was 83%. The yield was not improved in other experiments with longer periods of refluxing.

5-Nitro-8-acetamino-6-quinolyl Methyl Sulfide.—From 6.8 g. (0.028 mole) of 5-nitro-8-amino-6-quinolyl methyl sulfide and 70 cc. of acetic acid and 7 cc. of acetic anhydride was obtained 7.1 g. (91%) of the acetamino compound as yellow needles which melted at 203–204° after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{11}O_3N_3S$: N, 15.16; S, 11.29. Found: N, 15.20; S, 11.19.

From a preparation involving 41.2 g. (0.175 mole) of 5-nitro-8-amino-6-quinolyl methyl sulfide in 120 cc. of glacial acetic acid, and 45 g. (0.44 mole) of acetic anhydride with a fifteen-minute period of refluxing there was obtained 48.1 g. (99%) of product melting at 202–203°.

The acetamino compound (0.5 g.) was hydrolyzed to 5-nitro-8-amino-6-quinolyl methyl sulfide by heating for two minutes in 15 cc. of conc. hydrochloric acid and 15 cc. of ethanol.

5-Amino-8-acetamino-6-quinolyl Methyl Sulfide.—A solution of 3.5 g. (0.0126 mole) of 5-nitro-8-acetamino-6-quinolyl methyl sulfide in 100 cc. of absolute ethanol was reduced with Raney nickel at a pressure of about 40 pounds of hydrogen. The ethanol was completely removed by distillation at reduced pressure; then the residue was washed out with petroleum ether (b. p., 60–68°) and filtered to give 2.9 g. (91%) of product melting at 139–140°. Recrystallization from ethanol gave material melting at 141–143°. It appears that recrystallization from a mixture of benzene and petroleum ether is to be preferred for a product with the same melting point (141–143°) is obtained without the discoloration noted when ethanol was used. Traces of water in the presence of air appear to cause darkening of the product; but the dried compound is apparently quite stable.

Anal. Calcd. for $C_{12}H_{13}ON_3S$: N, 17.0; S, 12.95. Found: N, 16.90; S, 12.66.

Deamination of 5-Amino-8-acetamino-6-quinolyl Methyl Sulfide.—To a suspension of 10 g. (0.04 mole) of the amine in 200 cc. of water and 20 cc. of concd. hydrochloric acid was added dropwise a solution of 2.8 g. (0.04 mole) of

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(3) This preparation was adapted from the procedure of Keilin and Cass THIS JOURNAL, **64**, 2442 (1942).

(4) Claus and Schedler, *J. prakt. Chem.*, **49**, 359 (1894).

sodium nitrite in 30 cc. of water at 0°. Then to the clear solution was added 15 g. of 50% hypophosphorous acid, and the solution was allowed to stand in an ice box for twenty hours. After making basic with sodium hydroxide, the mixture was extracted[5] with ether, the ether was removed by distillation, and the residue was dissolved in a solution of 70 cc. of benzene and one cc. of acetic anhydride. After removing some benzene and adding some petroleum ether (b. p. 60-68°), 4 g. (43%) of product melting at 130-132° was obtained. Recrystallization from a mixture of benzene and absolute ethanol gave an analytical sample melting at 133-134°.

Anal. Calcd. for $C_{12}H_{12}ON_2S$: N, 12.05; S, 13.74. Found: N, 12.26; S, 13.79.

From another deamination (of 22 g. or 0.089 mole of the amine) in which chloroform and ether were used in the extraction[5] the yield of product melting at 123-128° was 13 g. (65%). This material was hydrolyzed by refluxing for twenty minutes with 100 cc. of concd. hydrochloric acid. Neutralization and extraction with a large volume of benzene gave 8 g. (47%) of amine distilling at 152-153° (0.7 mm.), and melting at 76-78°. The same **8-amino-6-quinolyl methyl sulfide** was obtained by hydrochloric acid hydrolysis of some pure 8-acetamino-6-quinolyl methyl sulfide.

Anal. Calcd. for $C_{10}H_{10}N_2S$: N, 14.72. Found: N, 14.92.

In some subsequent preparations the acetamino compound was not isolated. Instead the chloroform and carbon tetrachloride (the mixture used in the later extractions) was removed, and the residue was hydrolyzed by 1:1 hydrochloric acid to give 51% of 8-amino-6-quinolyl methyl sulfide distilling at 143-145° (0.4 mm.) and melting at 78° (with softening at 74°).

5,8-Diacetamino-6-quinolyl Methyl Sulfide.— This diacetamino compound, prepared in benzene from 5-amino-8-acetamino-6-quinolyl methyl sulfide and acetic anhydride, melted at 242-248°.

Anal. Calcd. for $C_{14}H_{15}O_2N_3S$: N, 14.50. Found: N, 15.0 and 15.0.

8-(γ-Diethylaminopropylamino)-6-quinolyl Methyl Sulfide, Dihydrochloride.—Four grams of 8-amino-6-quinolyl methyl sulfide (0.021 mole), 3.75 g. (0.025 mole) of freshly distilled γ-diethylaminopropyl chloride and 5.4 g. (0.02 mole) of sodium citrate were added to 25 cc. of commercial absolute ethanol and the mixture was refluxed for forty-eight hours. It was then cooled, poured into 250 cc. of water, and made strongly basic with solid sodium hydroxide. The solution was extracted with ether, and after drying the ether layer over sodium sulfate it was filtered. Ethanolic hydrogen chloride was added to precipitate a yellow dihydrochloride. After several recrystallizations from a 95% ethanol-ether mixture, 3.0 g. (38%) of yellow needles were obtained melting at 214-218° in a rapidly heated bath, but with some preliminary softening. The analytical sample melted at 217-220°.

Anal. Calcd. for $C_{17}H_{25}N_3S.2HCl$: Cl, 18.9; S, 8.5. Found: Cl, 18.8; S, 8.3.

Summary

In connection with studies on experimental avian malaria, 8-(γ-diethylaminopropylamino)-6-quinolyl methyl sulfide has been prepared. This compound is a sulfur analog of plasmocid.

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[5] The extractions were somewhat tedious due to the emulsions nd the large quantity of solvent needed.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of 1-Alkylamino-4-bromopentane Derivatives and of Other Amino Halides[1]

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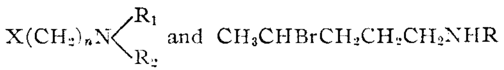
In a subsequent paper[2] the synthesis of a number of 8-(substituted aminoalkylamino)-quinoline derivatives is described. In the present paper we wish to present a description of the syntheses used for the preparation of the intermediate aminoalkyl halides required for the 8-aminoquinoline derivatives. The majority of the amino halides fall into two main structural groups, namely, those represented by the type formulas



$$X(CH_2)_nN\begin{matrix}R_1\\R_2\end{matrix} \quad \text{and} \quad CH_3CHBrCH_2CH_2CH_2NHR$$

I II

Variations in group I involved for the most part changes in R_1, representing an alkyl group, while R_2 remained constant as hydrogen, in the cases where n = 3 and 6. Bromides with n = 5 and 7 and $R_1 = R_2$ = ethyl were also prepared. Variations in group II involved variations of R.

For the synthesis of 3-*n*-propylamino-1-chloropropane advantage was taken of the greater reactivity of the bromine as compared to the chlorine in trimethylene chlorobromide,[3] and the desired aminochloride was thus prepared by condensation of trimethylene chlorobromide with *n*-propylamine. A similar synthesis with isopropylamine did not give favorable results, so that 3-isopropylamino-1-chloropropane was prepared by reaction of isopropylamine with trimethylene bromohydrin followed by replacement of the hydroxyl group in the intermediate 3-isopropylaminopropanol-1 by chlorine.

The general method used for preparing the aminohalides of Type I where n = 5, 6, and 7, R_1 is an alkyl group and R_2 is an alkyl group or hydrogen was based on a reaction originally used by Clarke[4] and extended by Drake, *et al.*,[5] for the synthesis of 6-diethylamino-1-bromohexane according to the following equations

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[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

[2] Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946).

[3] Drake *et al.*, *ibid.*, **68**, 1540 (1946).

[4] Clarke, *J. Chem. Soc.*, **103**, 1689 (1913).

[5] Drake, *et al.*, THIS JOURNAL, **68**, 1536 (1946).