was suitable for use in the next step after removal of catalyst and solvent. In one run the amine was purified by distillation, b. p. 100–105° (0.5 mm.). The distillate solidified; m. p. 59–60° (reported m. p. 59–59.5°[8]; 92–93°[7]).

3-Methyl-4-methoxyacetanilide.—The crude amine obtained by the hydrogenation of 88 g. of 2-methyl-4-nitroanisole as described above was warmed with 110 ml. of acetic anhydride for one and one-half hours on the steam-bath. The reaction mixture was allowed to stand in contact with dilute ammonium hydroxide overnight, during which the anilide crystallized. The pink solid was recrystallized from 30% alcohol (Norit); yield, 66.5 g. (70% from the nitro compound) of colorless plates, m. p. 103–104° (reported, plates, m. p. 103–103.5°[8]; needles, m. p. 158°[7]).

In another run 125.3 g. of distilled 3-methyl-4-methoxyaniline upon acetylation gave 140.2 g. (80%) of the anilide, m. p. 101–102.5°.

5-Methyl-6-methoxy-8-nitroquinoline.—Glycerol (100 ml.) was dried in an evaporating dish at 150–160° for fifteen minutes and, while still hot, was placed in a one-liter round-bottomed flask containing 25 g. (0.11 mole) of 2-nitro-4-methoxy-5-methylacetanilide and 17.5 g. (0.076 mole) of arsenic pentoxide. Concentrated sulfuric acid (37.5 ml.) was added during three to five minutes, with constant swirling. The temperature was then raised to 148–150° and held there for ten minutes by occasional application of heat. In some runs it was necessary to cool the reaction flask during the early stages of the reaction. The mixture was allowed to cool to 125° and was then poured into one liter of ice water, filtered, and the solution basified with 90 g. of sodium hydroxide dissolved in 150 ml. of water. The products from three such runs were combined and recrystallized from a mixture of approximately 400 ml. of dioxane and 500 ml. of 95% alcohol, giving 33 g. of light tan needles, m. p. 193.5–194°. Concentration of the filtrate to 35 ml. and addition of 100 ml. of 95% alcohol, followed by cooling, gave an additional 8.1 g. of brown crystalline product, m. p. 191–194°. The total yield was 57% of the theoretical.

5-Methyl-6-methoxy-8-aminoquinoline.—Sixty-three grams of 5-methyl-6-methoxy-8-nitroquinoline was hydrogenated in 150 ml. of absolute alcohol over Raney nickel at an initial pressure of 2000 lb. per sq. in. and at a temperature of 75–80°. To the reaction mixture was added 150 ml. of 95% alcohol; the mixture was then heated to boiling and filtered. From the filtrate 30.0 g. of light tan crystals, m. p. 138–139°, separated. An additional 14.1 g., m. p. 137–138.5°, was recovered from the filtrate, making a total yield of 81% of material suitable for use in the next step. A small sample was recrystallized from 75% alcohol for analysis, m. p. 139–140.5°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43. Found[11]: C, 70.03, 69.78; H, 6.81, 6.15.

5-Methyl-6-methoxy-8-(2′-diethylaminoethylamino)-quinoline (I, SN 14,008)[4].—Twenty-eight grams (0.15 mole) of 5-methyl-6-methoxy-8-aminoquinoline and 35.5 g. (0.2 mole) of diethylaminoethyl chloride hydrochloride (Sharples Chemicals, Inc.) were suspended in 20 ml. of alcohol, 20 ml. of water, 40 ml. of dioxane, and 40 ml. of ethylene glycol. The mixture was boiled under reflux for seventy-eight hours in an oil-bath at 120 ± 2°. During the heating period a total of 33 g. (0.24 mole) of sodium acetate trihydrate was added in four portions at intervals. The solution was cooled, diluted with two liters of water, and extracted with five 75-ml. portions of chloroform, a treatment which removed unreacted 5-methyl-6-methoxy-8-aminoquinoline. From the dried chloroform solution, removal of solvent and recrystallization from dilute alcohol gave 7.5 g. (26.8%) of the starting amine, m. p. 138–139°. The aqueous solution which had been extracted with chloroform was strongly basified with sodium hydroxide and extracted with five 75-ml. portions of chloroform. From the dried chloroform solution fractional distillation yielded 17.2 g. of drug, b. p. 150–154° (0.05–0.08 mm.), changing to a yellow solid; this corresponds to a 40% yield based upon the total starting amine, or 55% after making allowance for the recovered amine. The base (29.4 g.) was converted into the dihydrochloride by reaction with 9 g. of dry hydrogen chloride in 500 ml. of absolute alcohol. Addition of 350 ml. of ethyl acetate to the warm solution caused the separation of the orange crystalline dihydrochloride; yield, 34.2 g., m. p. 218–219° (dec.).

Anal. Calcd. for $C_{17}H_{25}N_3O\cdot 2HCl$: C, 56.66; H, 7.55; N, 11.66. Found[12]: C, 56.15, 55.94; H, 7.39, 7.42; N, 11.80, 11.88.

Another run which was similar except for the use of the conventional procedure utilizing 50% alcohol as solvent gave only 11% of the final drug, and 76% of the starting amine was recovered.

Summary

5-Methyl-6-methoxy-8-aminoquinoline was prepared and converted into 5-methyl-6-methoxy-8-(2′ - diethylaminoethylamino) - quinoline (SN 14,008).

(11) Analyses by Dr. Liebe Cavalieri.

(12) Analyses by Dr. Carl Tiedcke, Laboratory of Microchemistry, New York, N. Y.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

8-(3-Diethylamino-2-hydroxypropylamino)-5,6-dimethoxyquinoline[1] and Some of its Homologs[2]

BY WALTER M. LAUER, RICHARD T. ARNOLD AND ROBERT E. BUCKLES[3]

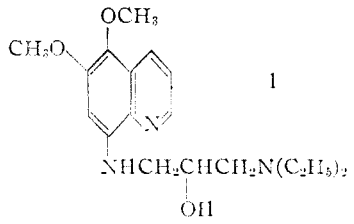
The threat of toxic reactions has imposed restrictions on the use of plasmochin as an antimalarial drug. However, Schönhöfer[4] has reported that the introduction of a methoxyl group in the 5-position of plasmochin decreased the toxicity to approximately one-fourth that of plasmochin without appreciably changing the antimalarial activity. In view of this study it was considered desirable to prepare 8-(3-diethylamino - 2 - hydroxypropylamino) - 5,6 - dimethoxyquinoline (I) for pharmacological examination. Accordingly, 5,6-dimethoxy-8-aminoquinoline was condensed with 1-diethylamino-2,3-epoxypropane. Similarly, 1-di-*n*-butylamino-2,3-epoxypropane was condensed with the same nucleus and 8-(3-

(1) SN 12,516. The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. The activities of these drugs will be tabulated in a forthcoming monograph.

(2) This work was carried out under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Minnesota.

(3) Present address: Department of Chemistry, University of Iowa, Iowa City, Ia.

(4) F. Schönhöfer, *Z. physiol. Chem.*, **274**, 1 (1942).



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diethylamino-2-hydroxypropylamino)-6-methoxyquinoline was prepared.

Experimental

8-(3-Diethylamino-2-hydroxy-propylamino)-5,6-dimethoxyquinoline.[5]—To molten 5,6-dimethoxy-8-aminoquinoline (20.4 g.) was added dropwise over a period of three hours, 1-diethylamino-2,3-epoxypropane (14.0 g.). The temperature was maintained at 175–180° and the mixture was stirred continuously. Heating and stirring was continued for one-half hour after the addition of the oxide was completed. The warm reaction mixture was then dissolved in 1 *N* hydrochloric acid (200 ml.). A solution of sodium citrate (40 g. of citric acid in 200 ml. of 1 *N* sodium hydroxide), was added and the tarry material which separated was removed by filtration and extraction with ether. Sodium hydroxide (300 ml., 1 *N*) was then added and some 5,6-dimethoxy-8-aminoquinoline (2.5 g.) was recovered. The further addition of 1 *N* sodium hydroxide (300 ml.) yielded a black tarry material (20 g.). Purification of this material by crystallization was exceedingly difficult and therefore it was subjected to distillation under low pressures (*ca.* 10^{-4} mm.). During this distillation most of the remaining 5,6-dimethoxy-8-aminoquinoline sublimed into the neck of the distillation apparatus. The distillate solidified on standing overnight, but a considerable residue remained in the distillation apparatus. Repeated crystallization of the distillate gave a yellow crystalline product melting at 88–90°.

Anal. Calcd. for $C_{18}H_{27}O_3N_3$: C, 64.85; H, 8.16. Found: C, 64.87; H, 8.57.

8-(3-Di-*n*-butylamino-2-hydroxy-propylamino)-5,6-dimethoxyquinoline.—This substance was prepared in essentially the same way as the above-described diethylamino compound.

5,6-Dimethoxy-8-aminoquinoline (17.5 g., 0.087 mole) and 1-di-*n*-butylamino-2,3-epoxypropane (16.0 g., b. p. 105–110 at 22 mm.) were heated together at 180°. The reaction mixture was worked up as in the previous case using a citrate buffer to separate the major portion of unreacted 5,6-dimethoxy-8-aminoquinoline. Addition of 1 *N* sodium hydroxide, followed by ether extraction and evaporation of solvent, gave a dark residue which was distilled under low pressure (*ca.* 10^{-4} mm.). There was obtained a dark viscous liquid (22.7 g.). The distillate could not be obtained in crystalline form. Redistillation gave a liquid product (18.5 g.) of the expected composition.

Anal. Calcd. for $C_{22}H_{35}O_3N_3$: C, 67.83; H, 9.06. Found: C, 68.08; H, 9.01.

Further distillation failed to give a crystallizable product.

8-(3-Diethylamino-2-hydroxy-propylamino)-6-methoxyquinoline.—This compound was prepared from 6-methoxy-8-aminoquinoline (17.4 g.) and 1-diethylamino-2,3-epoxypropane (14.0 g.). The procedure followed that already described for the 5,6-dimethoxy homolog. On distillation a yield of 12.3 g. was obtained. Further purification by redistillation and extraction from a phosphate buffer followed by a third distillation gave a liquid product which showed the following composition.

Anal. Calcd. for $C_{17}H_{25}O_2N_3$: C, 67.16; H, 8.29. Found: C, 67.18; H, 8.58.

Summary

The preparation of 8-(3-diethylamino-2-hydroxypropylamino)-5,6-dimethoxyquinoline and two homologs is described.

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(5) We are indebted to Robert Elderfield of Columbia University for 5,6-dimethoxy-8-aminoquinoline used in this preparation.

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY No. 1038]

The Synthesis of Potential Antimalarials. Some 2-Substituted 8-(3-Diethylaminopropylamino)-quinolines[1]

BY KURT MISLOW AND J. B. KOEPFLI

This investigation was part of a general program to develop a drug with the desirable antimalarial properties of pamaquine but without its high toxicity.

The possibility suggested itself of reducing the toxicity of pamaquine by preparing an analog with a carbostyril or 2-alkoxyquinoline nucleus, because an *in vitro* degradation product of quinine[2] which was less toxic although less active than quinine itself, was found to possess a carbostyril structure.[3] The preparation of certain 2-hydroxy-4-methyl-8-(dialkylaminoalkyl)-quinolines as potential antimalarials had been previously reported[4]; however, the compounds had a 4-methyl substituent not present in the pamaquine nucleus.

In the present investigation, it had originally been intended that the side chain of pamaquine (4-diethylamino-1-methylbutyl) would be attached to the 8-aminoquinoline nucleus. Since, however, recent evidence[5] indicates that the use of this side chain may be accompanied by the formation of isomers, it is the preparation of the 8-(3-diethylaminopropylamino)-quinolines VIIIa, VIIIb, IXa and IXb which is described here.

The final compounds were prepared as indicated in the accompanying general scheme. 2-Methoxy-8-aminoquinoline (VIIa) was obtained by reduction of the known 2-methoxy-8-nitroquinoline

(1) This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

(2) Kelsey, Ceiling, Oldham and Dearborn, *J. Pharmacol.*, **80**, 391 (1944).

(3) Mead and Koepfli, *J. Biol. Chem.*, **154**, 507 (1944).

(4) Johnson and Hamilton, THIS JOURNAL, **63**, 2867 (1911).

(5) R. C. Elderfield, private communication.