ated, reduced to the amine, acetylated and nitrated. The nitroacetylamino compound was submitted to the Skraup reaction and the product was hydrogenated and alkylated with 3-diethylaminopropyl chloride.

The intermediate nitration product was shown to have the nitro group in a position *ortho* to the acetylamino group by hydrolysis to the free amine, reduction to the diamine and condensation with phenanthraquinone to form a phenazine derivative.

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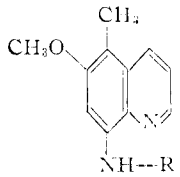
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

5-Methyl-6-methoxy-8-(2′-diethylaminoethylamino)-quinoline[1]

BY MARVIN CARMACK, L. W. KISSINGER[2] AND ISAIAH VON[3]

The synthesis of the potential antimalarial drug, 5 - methyl - 6 - methoxy - 8 - (2′ - diethylaminoethylamino) - quinoline (I),[4] was accomplished in a nine-step procedure starting with *o*-cresol. The drug and its parent base, 5-methyl-6-methoxy-8-aminoquinoline, have not been previously described, although most of the intermediates are known.



I, R = $-CH_2CH_2N(C_2H_5)_2$
II, R = $-(CH_2)_6N(C_2H_5)_2$

o-Cresol was nitrosated and the nitroso derivative oxidized to 2-methyl-4-nitrophenol in 75% yield by the procedure of Clemmence and Raiziss.[5] The phenol was methylated with methyl sulfate according to Gibson[6]; high yields (85–90%) were obtained in runs of a few grams, but the methylation was usually less complete in larger scale runs. In spite of the limitation on the scale of the methylation step, however, the method of Gibson was preferable to the procedure of Robinson,[7] since the latter gave a product which behaved in an anomalous manner in subsequent steps, indicating that it was contaminated with by-products of unknown structure.

2-Methyl-4-nitroanisole was hydrogenated over Raney nickel at 130 atmospheres to give 3-methyl-4-methoxyaniline. The melting points of the amine and its acetyl derivative agreed with the values reported by Heidelberger and Jacobs,[8] who prepared the compounds by a different method. The melting points were in disagreement with those ascribed by Robinson[7] to these compounds. Since Robinson gave few data on the sources of her starting materials, we believe that the agreement between our data and those of the well documented experiments of Heidelberger and Jacobs affords a confirmation of the correctness of the structures assigned to our products.

Nitration of the 3-methyl-4-methoxyacetanilide by the procedure of Arnold and McCool[9] gave 94–97% of 2-nitro-4-methoxy-5-methylacetanilide. The anilide was converted in 57% yield to 5-methyl-6-methoxy-8-nitroquinoline by a special modification of the Skraup synthesis devised by Elderfield and co-workers[10] for their preparation of 5,6-dimethoxy-8-nitroquinoline. The hydrogenation of the nitroquinoline took place smoothly over Raney nickel, giving 5-methyl-6-methoxy-8-aminoquinoline in 81% yield.

When the conventional procedure using a buffered solution in aqueous alcohol for the attachment of side chains was applied to the reaction of 5-methyl-6-methoxy-8-aminoquinoline and diethylaminoethyl chloride hydrochloride, only a small yield of drug was isolated and most of the starting amine was recovered. A modified procedure involving the addition of dioxane and diethylene glycol to the aqueous alcoholic solution greatly increased the yield of drug, probably by increasing the solubility of the reactants in the reaction mixture.

Even the modified procedure failed, however, to give the compound II from diethylaminohexyl chloride and 5-methyl-6-methoxy-8-aminoquinoline. Apparently this halide was not sufficiently reactive, since the starting material was largely recovered even after a long period of heating.

Experimental

3-Methyl-4-methoxyaniline.—2-Methyl-4-nitroanisole (m. p. 64–65°) was hydrogenated in absolute alcohol over Raney nickel at 95–100° and an initial pressure of approximately 2000 lb. per sq. in. The crude amine (yield, 81%)

(1) The work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the University of Pennsylvania and the Office of Scientific Research and Development.

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(4) This compound was submitted for tests of its antimalarial activity under the Survey Number 14,008. Results of the tests will be reprinted in a forthcoming publication entitled Antimalarial Drugs 1941–45.

(5) Clemmence and Raiziss, *J. Am. Pharm. Assoc.*, **23**, 536 (1934).

(6) Gibson, *J. Chem. Soc.*, **127**, 42 (1925).

(7) G. M. Robinson, *J. Chem. Soc.*, **109**, 1078 (1916).

(8) Heidelberger and Jacobs, THIS JOURNAL, **41**, 1453 (1919).

(9) Arnold and McCool, THIS JOURNAL, **64**, 1317 (1942).

(10) Elderfield, *et al.*, *ibid.*, **68**, 1584 (1946).

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.

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