**6-Phenoxy-8-(3-diethylaminopropylamino)-quinoline.**—6-Phenoxy-8-aminoquinoline (7.1 g.) was treated with 3-diethylaminopropyl chloride (4.5 g.) at 165° for sixteen hours in a sealed Carius tube. The contents of the cooled tube were placed in a separatory funnel and benzene was added. After shaking the benzene layer with several portions of aqueous potassium hydroxide, the benzene was evaporated at a pressure of 20 mm. Distillation of the residue in a molecular still at $10^{-5}$ mm. gave a liquid product boiling at 200°; yield 2.8 g.

*Anal.* Calcd. for $C_{22}H_{27}ON_3$: C, 75.45; H, 7.64. Found: C, 75.6; H, 7.7.

## Summary

A general route leading to the synthesis of 6-phenoxy-8-aminoquinolines is described.

MINNEAPOLIS, MINN. RECEIVED APRIL 5, 1946

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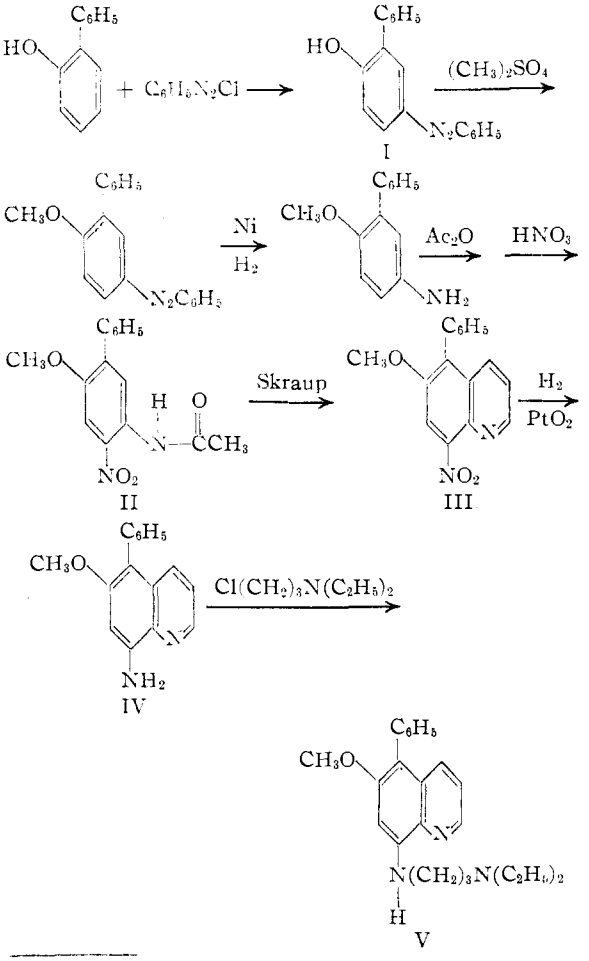
[CONTRIBUTION FROM THE NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

# Synthesis of 8-(3-Diethylaminopropylamino)-6-methoxy-5-phenylquinoline[1]

BY H. R. SNYDER AND NELSON R. EASTON

8-(3-Diethylaminopropylamino)-6-methoxy-5-phenylquinoline, an analog of pamaquine (plasmochin), has been prepared for testing as a possible therapeutic agent in the treatment of malaria. The reactions used in the synthesis are summarized below.




Benzenediazonium chloride and *o*-phenylphenol have been coupled previously[2] to give 2-hydroxy-5-phenylazobiphenyl (I). 5-Acetamido-2-methoxy-4-nitrobiphenyl (II) could be prepared from I without the purification of any of the intermediate compounds. The methylation with dimethyl sulfate, the reduction with Raney nickel as the catalyst, the acetylation with acetic anhydride and the nitration with nitric acid were very facile reactions and gave an 83% over-all yield of II. A Skraup reaction on II produced III, which was then reduced with hydrogen over platinum oxide catalyst to give IV. The amine IV was converted to the final product, V, by treatment with 3-diethylaminopropyl chloride. This material, SN-12,307,[3] was tested against avian malaria and found to be inactive.

Hydrolysis of II to the free amine and subsequent catalytic reduction and condensation with phenanthraquinone to form a phenazine established the position of the nitro group as *ortho* to the acetylamino group. Since nitration of 5-acetylamino-2-methoxytoluene occurs in the 4-position[4] it seems very unlikely that the present nitration could have given the 6-nitro isomer.

## Experimental

**Preparation of 2-Methoxy-5-phenylazobiphenyl (I).**—To a solution of 240 g. of sodium hydroxide in about 5 liters of water was added 204 g. of *o*-phenylphenol. The resulting solution was allowed to cool by standing overnight, and then a solution of benzenediazonium chloride (prepared from 120 ml. of aniline) was added slowly with vigorous stirring. The mixture was stirred for two to three hours. It was then filtered, and the precipitate was washed well with a 15% solution of sodium hydroxide and discarded. It probably consisted largely of the di-substituted product. The filtrate and washings were placed in a large crock containing about 500 g. of ice, and to this mixture 250 ml. of dimethyl sulfate was added slowly with continuous stirring. After all the dimethyl sulfate had been added the mixture was stirred for three to four hours and then allowed to stand overnight. The next day the precipitate was filtered and recrystallized from 95% ethanol. The yield of bright orange solid melting at 85–86° was 132 g. (38%).

(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 the University of Illinois.

(2) Borsche and Schotten, *Ber.*, **50**, 600–604 (1917).

(3) The Survey Number, designated SN-, refers to the number assigned a drug by the Survey of Antimalarial Drugs. The activities of these compounds will be tabulated in a forthcoming monograph.

(4) Arnold and McCool, THIS JOURNAL, **64**, 1316 (1942).

*Anal.* Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59. Found: C, 79.16; H, 5.72.

**Preparation of 5-Acetamido-2-methoxy-4-nitrobipher[-1] (II).**—A solution of 264 g. of I in 800 ml. of absolute alcohol was hydrogenated at 100° and 1800 lb. pressure of hydrogen. Raney nickel was used as the catalyst.

The catalyst was separated by filtration and the residue was concentrated under reduced pressure. The residue was steam-distilled until no more aniline was detectable in the distillate. The residue was cooled and the water layer decanted. The semi-solid material which remained was taken up in about 1200 ml. of glacial acetic acid and 140 ml. of acetic anhydride was added; the resulting solution was allowed to stand overnight. The crystals which had separated were redissolved by heating the mixture on a steam-bath, and the resulting solution was cooled in an ice-bath until a few crystals appeared. To this mixture 120 ml. of concentrated nitric acid was added in small portions with swirling. A precipitate soon appeared. The mixture was allowed to stand at room temperature for two hours and then added to three times its volume of water. The resulting precipitate was filtered and recrystallized from 95% ethanol.

The yield of recrystallized product was 203 g., with an additional 15 g. being obtained by concentrating the mother liquor to one-quarter of its volume. The total yield of yellow crystals which melted at 155–156° was 218 g. (83%).

*Anal.* Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.92; H, 4.93. Found: C, 62.97; H, 4.95.

The intermediate products were isolated in the initial run. The melting points and analyses are as follows:

2-Methoxy-5-aminobiphenyl hydrochloride, m. p. 220° (dec.).

*Anal.* Calcd. for $C_{13}H_{14}NOCl$: C, 66.24; H, 5.99. Found: C, 66.11; H, 6.16.

2-Methoxy-5-acetaminobiphenyl, m. p. 168–169°.

*Anal.* Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27. Found: C, 74.74; H, 6.23.

**Preparation of 6-Methoxy-8-nitro-5-phenylquinoline (III).**—A mixture of 61.5 g. of II, 92 g. of concentrated sulfuric acid, 50 g. of arsenic acid, and 105 g. of glycerol was refluxed, with stirring, in an oil-bath at 170° for three and one-half hours. While still hot the resulting mixture was poured into water and made basic with sodium hydroxide. The precipitate which formed was collected on a Büchner funnel and dried in an oven at 80°.

The dried, black precipitate was then placed in a Soxhlet extractor and continuously extracted with benzene for sixteen hours. The benzene solution was concentrated to dryness under reduced pressure. The residue was dissolved in hot 95% ethanol and the resulting solution was treated with Norit and filtered. When the mixture was cooled it deposited crystals.

The yield of solid was 19.6 g., with an additional 2.4 g. being obtained by concentrating the mother liquor as in the previous experiment. The total yield of compound melting at 175–176° was 22 g. (36.6%).

*Anal.* Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32. Found: C, 68.52; H, 4.51.

**Preparation of 8-Amino-6-methoxy-5-phenylquinoline (IV).**—In a 300-ml. Erlenmeyer flask were placed 5.2 g. of the nitro compound (III) and 150 ml. of glacial acetic acid. The mixture was heated on a steam bath until all of the solid had dissolved. The warm solution was then poured into a hydrogenation bottle and 0.1 g. of platinum oxide catalyst added. The hydrogenation was carried out under 30–40 lb. pressure. The calculated amount of hydrogen was absorbed in about ten minutes. The catalyst was separated by filtration and the filtrate was concentrated to dryness under reduced pressure. The residue was taken up in hot alcohol and enough concentrated ammonium hydroxide was added to make the solution basic to litmus. Water was then added until no more precipitation occurred.

The mixture was allowed to stand until the precipitate had coagulated. The mixture was then filtered and the precipitate washed with water. The precipitate was dissolved in hot petroleum ether (b. p. 90–110°) and treated with Norit. On cooling the product crystallized.

The yield of light yellow crystals which melted at 105° was 3.8 g. (76%).

*Anal.* Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64. Found: C, 76.51; H, 5.83.

**Preparation of 8-(3-Diethylaminopropylamino)-6-methoxy-5-phenylquinoline (V).**—A mixture of 20 g. of IV and 14 g. of 3-diethylaminopropyl chloride was dissolved in 100 ml. of 95% ethanol. Two crystals of potassium iodide were added and the mixture was refluxed on a steam-bath for twenty-four hours. Refluxing for forty-eight hours gave a slightly lower yield, 51% instead of 55%.

The mixture was diluted with water and made basic with a 10% solution of sodium hydroxide. It was then extracted several times with ethyl ether; the ether solution was dried over magnesium sulfate and concentrated to dryness. The residue was taken up in hot petroleum ether (30–60°) and filtered. The filtrate was cooled in a Dry-Ice bath. The product precipitated and was filtered. This purification was found later to be unnecessary.

The yield of crude product melting at 44–46° was 16 g.

The crude product was dissolved in hot ethanol and added to a hot alcoholic solution of picric acid (four equivalents of picric acid). A heavy oil separated immediately; this became crystalline when it was cooled and scratched. The *picrate* was purified by boiling with absolute ethanol and filtering the hot solution. The red product melted at 179–181°.

*Anal.* Calcd. for dipicrate $C_{35}H_{35}N_9O_{15}$: C, 51.16; H, 4.29. Found: C, 51.43; H, 4.42.

A 43-g. portion of the picrate was decomposed by shaking with concentrated hydrochloric acid. The picric acid was extracted with benzene and the hydrochloric acid solution was made basic with a 10% solution of sodium hydroxide. This mixture was extracted with ethyl ether. The ether solution was dried over magnesium sulfate and concentrated. The residue weighed 20 g., and after one recrystallization from petroleum ether (b. p. 30–60°) gave 16.6 g. of bright yellow platelets which melted at 49–50°.

*Anal.* Calcd. for $C_{23}H_{29}N_3O$: C, 76.00; H, 8.04. Found: C, 75.84; H, 8.24.

**Preparation of 12-Methoxy-11-phenyldibenzo[a,c]-phenazine.**—A mixture of 7 g. of II, 200 ml. of water, and 50 ml. of concentrated hydrochloric acid was refluxed until the solid went into solution; however, a small amount of oily material remained undissolved. The mixture was cooled and neutralized with a concentrated solution of ammonium hydroxide. The red solid which precipitated was collected on a filter and was recrystallized from 95% ethanol. The yield of 5-amino-2-methoxy-4-nitrobiphenyl (VI), melting at 105°, was 4 g. An additional 1.5 g. was obtained from the alcoholic mother liquor. The total yield was 5.5 g. (91%).

A solution of 4.9 g. of the amine (VI) in 150 ml. of ethanol was hydrogenated under 30–40 lb. pressure of hydrogen using 0.1 g. of platinum oxide as the catalyst. The calculated amount of hydrogen was absorbed in thirty minutes. The catalyst was separated by filtration and to one-third of the filtrate was added 1.3 g. of phenanthraquinone; this mixture was refluxed for thirty minutes. The hot mixture was filtered and the precipitate was recrystallized from ethyl Cellosolve and then from ethyl acetate. The solid melted at 213–215°.

*Anal.* Calcd. for $C_{27}H_{18}N_2O$: C, 83.91; H, 4.68. Found: C, 83.82; H, 4.64.

## Summary

The synthesis of 8-(3-diethylaminopropylamino)-6-methoxy-5-phenylquinoline has been accomplished.

*o*-Phenylphenol was condensed with benzenediazonium chloride and the product was methyl-

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.

URBANA, ILLINOIS RECEIVED APRIL 5, 1946

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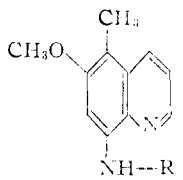
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

# 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.

(2) Present address: Naval Ordnance Laboratory, Washington, D. C.

(3) Present address: Calco Chemical Division, American Cyanamide Company, Bound Brook, New Jersey.

(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).