bath temperature 260–280°, followed by crystallization of the distillate, gave VIII in 65% yield. In a few cases, the product could be crystallized directly after evaporating the solvent: the yield was then 78–85%. An analytical sample crystallized as square yellow plates, m. p. 115–116°.

Anal. Calcd. for $C_{17}H_{16}O_3N_2$: C, 68.91; H, 5.44. Found: C, 69.19; H, 5.85.

5-Phenoxy-6-methoxy-8-(γ-diethylaminopropylamino)-quinoline (IX).—29.4 grams VII (0.1105 mole), 17.6 g. (0.1173 mole) of γ-diethylaminopropyl chloride,[13] and 30 cc. of benzene were sealed into Pyrex tubes and heated for fourteen hours at 175–180°; 500 cc. of water was added and the mixture made basic with 10 g. of sodium hydroxide. The benzene was separated and the aqueous layer extracted with three 200-cc. portions of benzene. The combined benzene extracts were dried with potassium carbonate and evaporated. The residue was distilled at 10^{-5} mm. with a bath temperature of 200–210°. The product is a viscous red liquid which darkens on exposure to air; it may be stored under nitrogen. Three distillations gave pure material in approximately 60% yield.

Anal. Calcd. for $C_{23}H_{29}O_2N_3$: C, 72.79; H, 7.6. Found: C, 72.96; H, 7.55.

X was prepared similarly. Two distillations at 10^{-5} mm., bath temperature 220–230°, gave pure X as a dark red, viscous, easily oxidized oil. The yield was 58%.

Anal. Calcd. for $C_{24}H_{31}O_3N_3$: C, 70.40; H, 7.63. Found: C, 70.47; H, 7.47.

Attempts to prepare stable, non-hygroscopic salts of IX and X were unsuccessful.

(13) Prepared at Columbia University from $ClCH_2CH_2CH_2Br$.

Summary

Two new 5-aryloxy-6-methoxy-8-dialkylamino-alkylamino-quinolines have been prepared. A description of the preparation and properties of the intermediates is included.

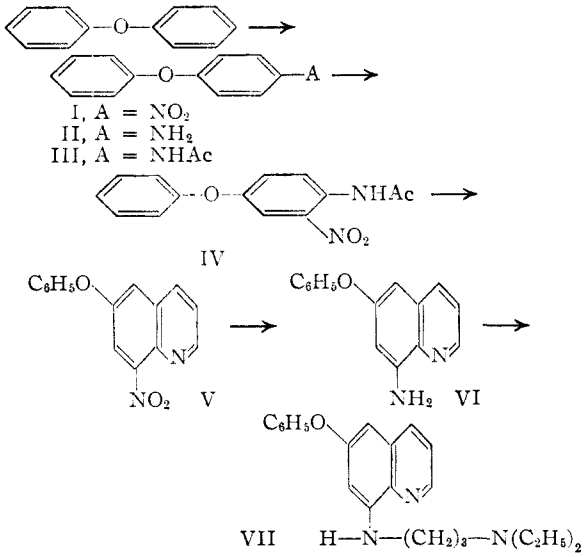
MINNEAPOLIS 14, MINNESOTA RECEIVED APRIL 5, 1946

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

Synthesis of 6-Phenoxy-8-(3′-diethylaminopropylamino)-quinoline[1]

BY W. M. LAUER, R. T. ARNOLD, BURRIS TIFFANY[2] AND C. O. WILSON

The presence of and the importance attached to the methoxyl group in position-6 of the quinoline nucleus in quinine and numerous other synthetic antimalarials stimulated interest in the corresponding 6-phenoxy derivatives having an appropriately alkylated amino group in position-8. A general synthetic route used for the preparation of compounds of this type was employed and is indicated in the sequence shown.



Although compound IV is mentioned in a journal article[3] and compounds V and VI[4] in a German patent no directions for the preparation of these substances have appeared.

Experimental

3-Nitro-4-acetamidodiphenyl Ether.—4-Acetamidodiphenyl ether (78.6 g.) was dissolved in a mixture of acetic anhydride (150 cc.) and glacial acetic acid (300 cc.) at 60°. This solution was cooled rapidly to 10° and concentrated nitric acid (25 cc.) added dropwise at such a rate that the temperature of the reacting medium did not exceed 10°. After the addition of nitric acid was complete, the mixture was allowed to stand for four hours and then poured slowly onto chipped ice. Bright yellow crystals were removed by filtration and recrystallized from aqueous ethanol; yield 84.6 g. (90%); m. p. 101–102° (Brewster and Strain[3] report m. p. 103°).

6-Phenoxy-8-nitroquinoline.—Arsenic pentoxide (5.4 g.), dry glycerol (11.8 g.) and 3-nitro-4-acetamidodiphenyl ether (10 g.) were mixed thoroughly. To the pasty mass thus formed, concentrated sulfuric acid (12.7 g.) was added with vigorous stirring. Following the initial exothermic reaction, the mixture was heated at 140–145° for two and one-half hours. The cooled solution was poured slowly and with stirring into an excess of aqueous potassium hydroxide (20%).

Collection of the precipitate by filtration followed by recrystallization from ethanol (95%) gave a sharp melting product; yield 3.2 g.; m. p. 135–136°.[4]

6-Phenoxy-8-aminoquinoline.—In a one-liter three-necked flask were placed 6-phenoxy-8-nitroquinoline (32 g.) water (300 cc.) and glacial acetic acid (6 cc.). After this mixture was heated to boiling and kept in suspension by vigorous stirring, iron filings (33.5 g. of 40 mesh) were added over a period of several hours. Heating and stirring were continued over an eighteen-hour period. The aqueous layer was extracted with ether and the brown residue (remaining after decantation) was extracted repeatedly with small portions (amounting in all to 300 cc.) of hot ethanol (95%). The combined ether and alcohol soluble fractions were evaporated to a small volume and transferred to a sausage flask. Distillation gave a pale yellow oil which crystallized after being seeded; b. p. 200–210° (2 mm.); m. p. 65°; yield 21 g. (74%).

We have assumed that the melting point of 56° reported by Schönhöfer[4] is a typographical error.

(1) This study 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.

(2) Present address, Abbott Laboratories, North Chicago, Illinois.

(3) Brewster and Strain, THIS JOURNAL, **56**, 118 (1934).

(4) Schönhöfer, German Patent 550,327; *Frdl.*, **19**, 1417 (1932).

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.

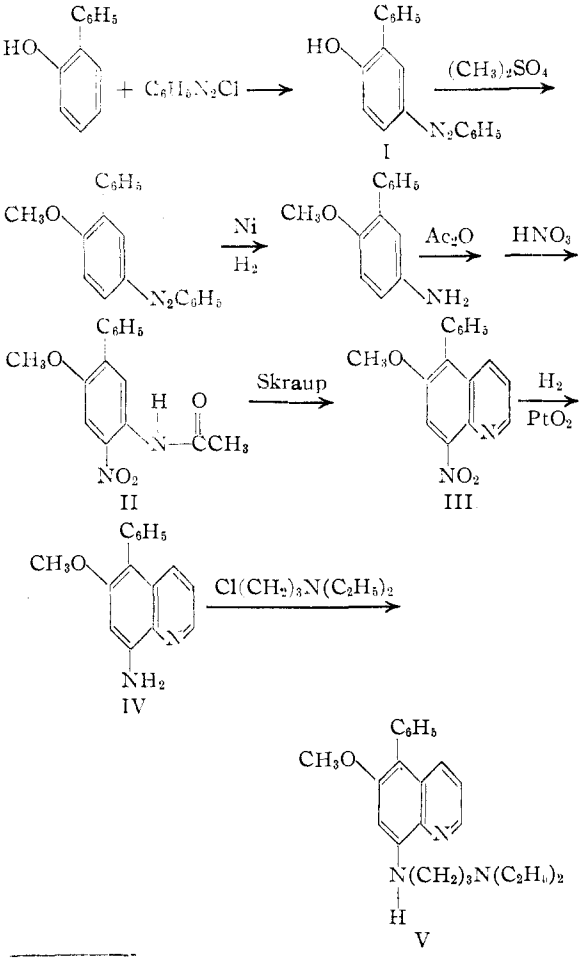
MINNEAPOLIS, MINN. RECEIVED APRIL 5, 1946

[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).