heated for two days in an oil-bath at 110–115°. The mixture was poured into 250 ml. of water, made strongly basic with sodium hydroxide solution, and extracted with ether. After drying the ether solution over potassium carbonate, the ether was removed, and the residue was distilled *in vacuo*. Some quinoline nucleus (5.3 g. after recrystallization) was recovered. The coupled product (14.9 g., 48%) was obtained as a viscous yellow oil, b. p. 180–195° at 0.006 mm.

The free base (0.04 mole) was converted to the monohydroiodide by dissolving in 50 ml. of absolute ethanol and adding 21.8 g. of 47% hydriodic acid solution in 50 ml. of absolute ethanol. This solution was heated to 60° and cooled overnight. The crystallized hydroiodide salt was filtered off, a second crop being obtained by adding ether to the filtrate. After two recrystallizations from absolute ethanol, the yield of lemon-yellow monohydroiodide, m. p. 147–148° (cor.), was 13.6 g.

Anal.[15] Calcd. for $C_{19}H_{28}N_3Br \cdot HI$: C, 45.07; H, 5.77; I^-, 25.06. Found: C, 45.15; H, 5.82; I^-, 24.97.

Some higher melting salt (tan color) was isolated from a second crop in one case. This may have been the dihydroiodide; after recrystallization from water, the product melted at 147–148° (cor.).

Summary

1. Two plasmochin analogs having variations in the side-chain have been prepared.

2. 3 - Bromo - 8 - (6′ - diethylaminohexylamino)-quinoline has been synthesized.

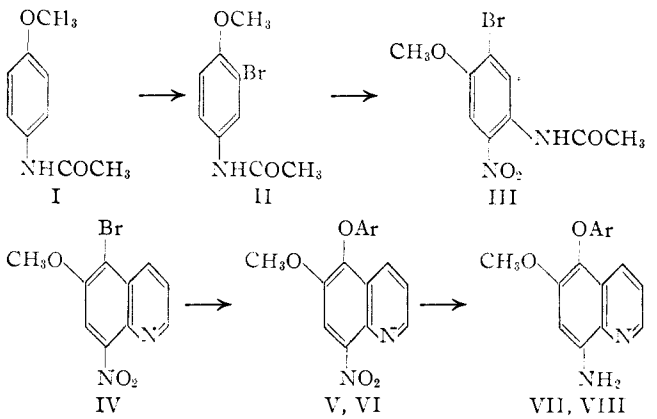
DURHAM, NORTH CAROLINA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Some Derivatives of 8-Aminoquinoline[1]

BY WALTER M. LAUER,[2] CHRISTIAN RONDESTVEDT,[2,4] RICHARD T. ARNOLD,[2] NATHAN L. DRAKE,[3] JOHN VAN HOOK[3] AND JOHN TINKER[2]

In the twenty-two years which have elapsed since the discovery of plasmochin, numerous derivatives of 8-aminoquinoline have been prepared in an effort to modify the toxic properties of the parent compound without sacrificing its anti-malarial properties. The workers at the I. G. Farbenindustrie have been especially active in this field. Attention was focused on 8-aminoalkylamino derivatives of 5,6-dimethoxyquinoline by Schönhöfer and his co-workers. In several patents issued in 1930 and later,[5,6] they reported the preparation and properties of a number of these derivatives. Subsequent work in this country has established their activity as antimalarials. In view of this, it was desirable to prepare compounds in which the nucleus was further modified by replacing the methoxyl group in the 5-position by aryloxyl. Accordingly, 5-phenoxy-6-methoxy-8-aminoquinoline (VII) and 5-(*p*-anisyloxy)-6-methoxy-8-aminoquinoline (VIII) were synthesized according to the following plan.



V, VII, Ar = C_6H_5; VI, VIII, Ar = p-$CH_3OC_6H_4$

The reactions leading to IV were carried out according to previously published procedures, modified as indicated in the experimental section to permit rapid operation on a larger scale. The replacement of the bromine atom in IV by aryloxyl was not successful if a large excess of phenol was used as solvent. However, when commercial butyl cellosolve (b. p. 171°) was substituted as the solvent, the reaction gave satisfactory yields of easily purified material. The use of ethylene glycol as solvent, in an effort to achieve more rapid reaction at the higher reflux temperature, gave a tarry product; operation at lower temperatures required an unduly long time, and the product was contaminated with unchanged IV.

Reduction of V (or VI) to VII (or VIII) could not be accomplished with hydrogen and Adams catalyst or palladium–charcoal catalyst. The only product obtained was the hydroxylamine, and this could not be reduced further without its isolation and unnecessary losses. Reduction was effected with iron filings and water containing a small amount of acetic acid.

The amines VII and VIII were converted to diamines by alkylation with γ-diethylaminopropyl chloride in a sealed tube at 175° in the presence of benzene as solvent.

(1) This work was carried out under contracts, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Universities of Minnesota and Maryland.

(2) School of Chemistry, University of Minnesota.

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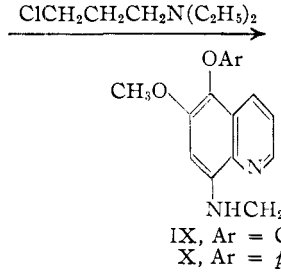
(5) German Patent 531,083, in *Frdl.*, **18**, 2717 (1931).

(6) German Patent 536,447, *ibid.*, p. 2718.



IX, Ar = C_6H_5
X, Ar = p-$CH_3OC_6H_4$

Experimental[7,8]

p-Acetoanisidide (I).—Commercial p-anisidine was acetylated in hot water with 25% excess acetic anhydride. The crude material, obtained in 96% yield (m. p. 123–126°), was satisfactory for the next step. It could be purified by crystallization from 45% ethanol; m. p. 127–128°.

2-Bromo-4-acetaminoanisole (II).—462 g. (2.80 moles) of crude I was dissolved in 1300 cc. of glacial acetic acid, and 455 g. (2.82 moles) of bromine was added at such a rate that the internal temperature did not exceed 50°. About an hour was required, during which time a yellow solid separated. Stirring was continued for an additional hour. The mixture was poured into 14 liters of ice water containing 50 g. of sodium bisulfite and stirred until the yellow or red color was discharged. After standing overnight, the dark oil solidified and was filtered. After drying at 70°, it was used directly in the nitration. An average yield of 70% of crude dry II was obtained.

If desired, the crude material may be further purified by recrystallization from 25% ethanol. The over-all yield from I to III is not improved, however, if pure II is used. The once crystallized material may be distilled in a sausage flask at 2 mm. with a bath temperature of 190°.

2-Bromo-4-acetamino-5-nitroanisole (III).—449 g. of crude II was dissolved in 500 cc. of acetic anhydride and 1000 cc. of glacial acetic acid. After cooling below 5°, 77 cc. of fuming nitric acid (density 1.49) was added at such a rate that the internal temperature did not exceed 5°. About an hour was required. After stirring for an additional three hours at 5°, the mixture was poured into 12 liters of ice water. After stirring thoroughly, the crude III was filtered, washed twice with 4-liter portions of cold water by slurrying in a beaker, and dried at 100°. (The partially dried lumps must be broken up periodically to achieve complete drying.) The crude III weighed 271 g., m. p. 165–6°. Crystallization from chloroform yields pure III, 170–200 g., m. p. 171–173. This corresponds to a yield of 32%, based on technical p-anisidine.

The structure of III was proved by deacetylating a portion, then deaminating according to the directions of Kornblum.[9] The deaminated product melted at 102–103°; the reported melting point of 2-bromo-5-nitroanisole is 104°.[10]

Concentration of the chloroform mothers liquors and removal of additional III gave a 1% yield of another compound, apparently an isomer of III, which melted at 158–160° after repeated crystallization. This compound gave the following analytical results but was not further investigated.

Anal. Calcd. for $C_9H_9O_4N_2Br$: C, 37.4; H, 3.11. Found: C, 36.7; H, 3.16.

5-Bromo-6-methoxy-8-nitroquinoline (IV).—100 grams (0.346 mole) of III was mixed with 40 g. of arsenic pentoxide and 85 cc. of U. S. P. glycerol and stirred to a stiff paste.[11] While vigorous stirring was maintained, 52 cc. of concentrated sulfuric acid was added in one portion, and the mixture was cautiously heated to 135°, using an oil-bath. The internal temperature was maintained between 130–140° for four and one-half hours, with vigorous stirring. While still hot, the dark brown viscous liquid was poured into a solution of 160 g. of sodium hydroxide in 2 l. of water containing 1500 g. of ice. After thorough stirring, the solid was allowed to settle. The dark brown aqueous layer was decanted through a filter, and the product washed three times by decantation with cold water. After sucking the product dry, it was slurried with 250 cc. of cold alcohol, filtered and dried thoroughly at 100°. If larger quantities of IV are desired, several runs may be combined during the washing process.

The dry solid from four such runs was powdered and refluxed for two hours each with two 4-liter portions of benzene. The benzene extracts were filtered through a fluted filter, combined and cooled, and the product separated 155 g., m. p. 203–205°, was obtained. Concentration of the benzene mother liquors yielded an additional 31 g., m. p. 201–205°, which on recrystallization from dioxane weighed 24 g., m. p. 204–205°. A number of similar runs gave an average yield of 45% of pure IV, after reworking all mother liquors. A fully purified sample crystallized from dioxane as clusters of pale yellow needles, m. p. 205–206° (reported[6a] 205–206°).

5-Phenoxy-6-methoxy-8-nitroquinoline (V).—113.2 g. (0.40 mole) of IV was dissolved in a boiling solution of potassium phenoxide prepared by dissolving 113 g. of pure phenol and 36 g. of potassium hydroxide in butyl cellosolve and diluting with the same solvent to 1200 cc. After refluxing vigorously for two hours, the mixture was poured into 8 liters of cold water. After standing overnight, the orange aqueous layer was decanted through a filter and the residue washed twice by decantation with 4 liter portions of cold water. After filtering and drying, the solid was extracted with 6 liters of refluxing ether for two hours. The undissolved material (largely unchanged IV and some amorphous charred substance) was separated, and the ether extract was washed twice with 10% sodium hydroxide solution and twice with water. After drying over sodium sulfate, the solution was partially decolorized by stirring with 10 g. of Norite for ten minutes, and the ether was evaporated. After standing for several hours at room temperature, the residue was filtered to remove some dark oil and washed with ice-cold alcohol. Crystallization from 95% ethanol gave 59 g. (51%) of V, m. p. 137–139°. By combining the oil with the mother liquors, an additional amount of V could be obtained. The average yield from several runs was 53%. An analytical sample separated from alcohol as bright yellow plates.

Anal. Calcd. for $C_{16}H_{12}O_4N_2$: C, 65.00; H, 4.06. Found: C, 64.92; H, 3.90.

By a similar procedure, using hydroquinone monomethyl ether,[12] and refluxing for three hours, a 58% yield of VI was obtained, m. p. 121–2°.

Anal. Calcd. for $C_{17}H_{14}O_5N_2$: C, 62.6; H, 4.3. Found: C, 62.84; H, 4.16.

5-Phenoxy-6-methoxy-8-aminoquinoline (VII).—29.6 grams (0.1 mole) of V was stirred for sixteen hours on the steam-bath with 300 cc. of water, 5 cc. of glacial acetic acid and 35 g. of iron filings. The water was filtered off and extracted with ether. The solid residue in the flask was stirred vigorously with three 400-cc. portions of ether and one 200-cc. portion of acetone. The combined extracts were dried with sodium sulfate and evaporated on the steam-bath. The residue was distilled in a sausage flask at 3 mm. or less, at a bath temperature of 240–260°. The crude distillate, 24.0 g., was crystallized from 95% alcohol, giving 22 g. (84%), m. p. 121–2°. A fully purified sample crystallized from alcohol as square yellow plates, m. p. 124.0–124.5°.

Anal. Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.30. Found: C, 72.02; H, 4.97.

VIII was prepared similarly. Distillation at 1 mm.,

(7) All melting points are uncorrected.

(8) The analyses reported in this paper were performed by Mrs. Doris Barnes and Mr. James Kerns at the University of Minnesota.

(9) Kornblum, "Organic Reactions," Vol. II, p. 294.

(10) Adams, THIS JOURNAL, **57**, 1592 (1935).

(11) The yield depends considerably on thorough mixing here. With larger runs, the percentage yield is reduced.

(12) Obtained from the Tennessee Eastman Company.

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.

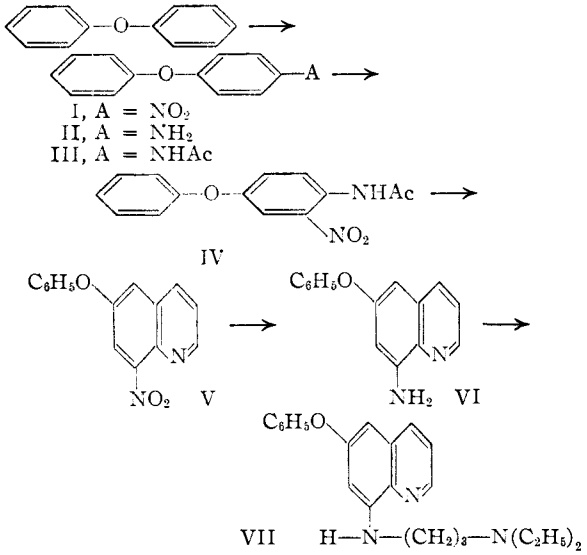
MINNEAPOLIS 14, MINNESOTA RECEIVED APRIL 5, 1946

[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).