Merck) were suspended in a solution of 6.7 ml. of 6 *N* hydrochloric acid in 670 ml. of 96% ethanol. The suspension was stirred and refluxed for six hours, filtered, and the filtrate evaporated. The residual oil gave 45.3 g. (82%) of crude product. Distillation under nitrogen gave a light yellow oil, b. p. 210–212° (0.2 mm.), which crystallized to give 35.2 g. (64%) of colorless needles. A sample for analysis, recrystallized from 70% ethanol, melted at 86–87°.

Anal. Calcd. for $C_{17}H_{16}O_2N_2$: C, 72.83; H, 5.75; N, 9.99. Found: C, 72.95; H, 5.90; N, 10.58.

2-Benzyloxy-6-methoxy-8-(3-diethylaminopropylamino)-quinoline (VIIIc).—This compound was prepared in the same manner as VIIIa, by condensing VIIc with 1-diethylamino-3-chloropropane hydrochloride.[18] The base came over as a yellow, viscous oil, b. p. 244–246° (0.06 mm.), in 81% yield. VIIIc was analyzed as the dihydriodide, colorless needles from ethanol, m. p. 124–125° (dec.).

Anal. Calcd. for $C_{24}H_{38}O_2N_3I_2$: C, 44.39; H, 5.12; N, 6.47. Found: C, 44.46; H, 5.41; N, 6.65.

6-Methoxy-8-(3-diethylaminopropylamino)-carbostyril (IXb), (SN 12250).—The dihydriodide of VIIIc could not be reduced; the catalysts used were palladium black, palladium on charcoal, palladium oxide and Raney nickel. A solution of the free base in absolute ethanol over palladium oxide took up hydrogen very slowly. The following procedure was found to give the best results.

To a solution of 11.5 g. of VIIIc (free base) in 200 ml. of absolute ethanol was added 8 ml. of glacial acetic acid and 1.2 g. of palladium oxide. The suspension was shaken under hydrogen at one atmosphere and room temperature and the theoretical volume of hydrogen was absorbed after eighty minutes. The solution was filtered and a solution of 15.5 ml. of hydriodic acid (sp. gr. 1.7) in 310 ml. of ethanol was added to the filtrate. On cooling at 5° for twenty-four hours, the hydriodide of IXb crystallized out. Recrystallization from ethanol gave 11.5 g. (91%) of faintly yellow crystals, m. p. 234–235° (dec.).

Anal. Calcd. for $C_{17}H_{26}O_2N_3I$: C, 47.33; H, 6.07; N, 9.74. Found: C, 47.19; H, 5.99; N, 9.91.

Summary

Four compounds related to pamaquine have been synthesized in order to determine the effect of a 2-substituent in the quinoline ring on the antimalarial activity and toxicity of this type of drug.

PASADENA, CALIFORNIA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Studies in the Quinoline Series. III. The Preparation of Some 8-(ω-Alkylaminoalkylamino)-quinolines[1]

BY KENNETH N. CAMPBELL, ARMIGER H. SOMMERS,[2] JAMES F. KERWIN[3] AND BARBARA K. CAMPBELL

As part of the extensive antimalarial investigation carried out in this country during the war, a detailed study was made of compounds related to plasmochin. One phase of this study was concerned with replacing the terminal dialkylamino group of plasmochin by various secondary amino groups. In this connection we have synthesized several 8-(ω-alkylaminoalkylamino)-6-methoxyquinolines, namely, the 3′-ethylaminopropylamino-, 6′-ethylaminohexylamino and the four 6′-butylaminohexylamino compounds.

Baldwin and Robinson[4] attempted to prepare some compounds of this type by alkylation of the 8-aminoalkylaminoquinolines, but were unable to purify the products. Later Crum and Robinson[5] prepared some 8-γ-alkylaminopropylaminoquinolines by treating the 8-γ-chloropropylaminoquinoline with the requisite primary amines.

We have found it simpler to synthesize the desired alkylaminoalkyl halides and to couple these with 8-amino-6-methoxyquinoline. Comparatively few alkylaminoalkyl halides are described in the literature; we have found that they can be prepared by the methods used to make the more common dialkylamino analogs. Two general methods were used in the present work, starting from the α,ω-glycol

$$HOC_nH_{2n}OH \longrightarrow BrC_nH_{2n}Br \longrightarrow R'OC_nH_{2n}Br \longrightarrow R'OC_nH_{2n}NHR \longrightarrow BrC_nH_{2n}NHR\cdot HBr \quad (A)$$

$$HOC_nH_{2n}OH \longrightarrow ClC_nH_{2n}OH \longrightarrow RNHC_nH_{2n}OH \longrightarrow RNHC_nH_{2n}Br\cdot HBr \quad (B)$$

Method (B) was found to be superior to method (A), especially in the hexyl series.

The coupling reaction between 8-amino-6-methoxyquinoline and the alkylaminoalkyl bromide hydrobromides proceeded best in absolute alcohol, using two equivalents of the nucleus. Most of the excess nucleus could be recovered, and the products were obtained in 50–60% yields. When the coupling reaction was carried out in aqueous alcohol with sodium acetate as a buffer, much poorer yields were obtained.

The alkylaminoalkylaminoquinolines were purified by high-vacuum distillation, and were obtained as yellow oils which darkened on exposure to light and air. They were converted to the hydrochlorides for testing. These salts were best prepared by titrating a solution of the base in anhydrous *n*-propanol with standardized propanolic hydrogen chloride. In all cases there was a sharp color change from pale yellow to red when one equivalent of hydrogen chloride had been added. The hydrochlorides prepared in *n*-propanol were much less hygroscopic than those prepared in ethanol or ether. Homogeneity tests carried out

(1) The work described in this paper 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 Notre Dame.

(2) Present address: Department of Chemistry, Columbia University.

(3) Present address: Smith, Kline and French Laboratories, Philadelphia, Pa.

(4) Baldwin and Robinson, *J. Chem. Soc.*, 2959 (1929).

(5) Crum and Robinson, *ibid.*, 561 (1943).

elsewhere by the method of Craig[6] showed that the samples submitted for testing did not have more than 3–5% inhomogeneity.

Two derivatives of 8-(6′-diethylaminohexylamino)-6-methoxyquinoline were also prepared in the course of this work. In one of these there was a phenoxy group in the 5-position, in the other, a methyl group in the 4-position. Attempts to prepare the intermediate 6-methoxy-8-nitrolepidine needed for this second compound led to some interesting observations. *m*-Nitroacetoacetanisidide would not undergo ring closure to the carbostyril,[7] and efforts to run a Doebner–Miller reaction under mild conditions[8] on *o*-nitro-*p*-methoxyaniline likewise led to no ring closure. The lepidine was finally obtained in fair yield by treating *o*-nitro-*p*-methoxyaniline with 1,3,3-trimethoxybutane under conditions approximating those used in the Skraup reaction. Apparently the nitro group in the nitromethoxyaniline has a strong deactivating influence on the open meta position.

The desired diethylaminohexylaminoquinolines were prepared from the nuclei and diethylaminohexyl bromide hydrobromide in absolute alcohol, by the general procedure of Rohrmann and Shonle,[9] or in 50% alcohol with sodium acetate as a buffer.

Experimental[10]

3-Bromopropylethylamine Hydrobromide.—3-Phenoxypropylethylamine (b. p. 110° (3 mm.), $n^{20}D$ 1.5092, d^{20}_4 0.9711) was prepared in 80% yield from 3-phenoxypropyl bromide by the method of Cowan and Marvel[11] and was converted to the amino bromide hydrobromide as described by them.

1-Phenoxy-6-ethylaminohexane.—1-Phenoxy-6-bromohexane, b. p. 153–156° (3 mm.), was prepared in 45% yield from hexamethylene bromide.[12] 1-Phenoxy-6-bromohexane (51.4 g., 0.2 mole) was added slowly, with shaking, to a cold solution of 36 g. (0.8 mole) of ethylamine in 110 ml. of absolute alcohol, and the mixture was allowed to stand in a closed bottle, with occasional shaking, for twenty-four hours. The alcohol was removed by evaporation and the residue was thoroughly washed with dry ether. The yield of product of m. p. 90–100° was 90%. The free base liberated from this salt had b. p. 147–148° (3 mm.), $n^{20}D$ 1.5010.

Anal. Calcd. for $C_{14}H_{23}NO$: N, 6.33. Found: N, 6.51.

The hydrochloride melted at 133–135°.

Anal. Calcd. for $C_{14}H_{24}NOCl$: Cl, 13.8. Found: Cl, 14.4.

1-Bromo-6-ethylaminohexane Hydrobromide.—This was prepared by the general procedure of Cowan and Marvel.[11] The crude material was evaporated to dryness under reduced pressure three times from aqueous solution and three times from alcoholic solution, and was then thoroughly washed with ether. The product melted at 150–155°.

Anal. Calcd. for $C_8H_{19}NBr_2$: N, 4.84; Br, 55.3. Found: N, 4.91; Br, 55.0.

Hexamethylene Chlorohydrin.—A modification of the method of Bennett and Turner[13] was used which gave better results. A mixture of 105 g. (0.89 mole) of hexamethylene glycol, 785 ml. of concentrated hydrochloric acid, 130 ml. of water and 55 ml. of toluene was placed in the main flask of a liquid–liquid extractor[14] and 350 ml. of toluene was placed in the other flask, which was heated in an oil-bath at 140–155°. The main flask was placed in an oil-bath which was heated to 92° in the course of two hours, and kept at 92–96° for six hours. The toluene extract was concentrated under reduced pressure, and the residue was distilled through a 12-plate Fenske–Whitmore column. There was obtained 25.6 g. (18.5%) of hexamethylene chloride, b. p. 79° (8 mm.), $n^{20}D$ 1.4565 and 56 g. (46%) of hexamethylene chlorohydrin, b. p. 89–89.5° (4 mm.), $n^{20}D$ 1.4552–1.4544. By refractionation of the intermediate cuts and residue the total yield of chlorohydrin was raised to 50–55%.

***s*-Butylamine.**—The following procedure was found more convenient than the sodium–alcohol reduction described by Marvel and Noyes.[15] A mixture of 9 g. of Raney nickel, 26.1 g. of methyl ethyl ketoxime[15] and 25 ml. of absolute alcohol was shaken with hydrogen at 50–60° and 60 lb. pressure. Hydrogen absorption was complete and quantitative in three hours. The solutions from several runs were combined, acidified with hydrochloric acid and evaporated to dryness. The amine was liberated, dried over potassium hydroxide and distilled through a Fenske–Whitmore column. From 163 g. of oxime there was obtained 75 g. (54%) of *s*-butylamine, b. p. 63° (745 mm.), $n^{20}D$ 1.3939.

***t*-Butylamine.**—This was prepared by the procedure of Campbell, Sommers and Campbell.[16]

***i*-Butylamine.**—A mixture of 0.4 mole of isobutyraldoxime, 1 ml. of concentrated ammonium hydroxide, 50 ml. of absolute alcohol and 12 g. of Raney nickel was shaken with hydrogen at 50° and an initial pressure of 60 lb./sq. in. Absorption of hydrogen was complete in five hours. The solutions from several runs were combined and worked up as described above. The yield of amine of b. p. 66–68° (745 mm.), $n^{20}D$ 1.3969, was 52%.

6-Butylamino-1-hexanols.—These were prepared by heating 0.25 mole of hexamethylene chlorohydrin and 1 mole of the butylamine in an autoclave at 150–160° for twenty hours. Part of the excess amine was recovered by distillation, the residue was poured into water, made basic with potassium hydroxide and the product taken up in ether. The aminohexanols were purified by distillation

TABLE I

6-BUTYLAMINO-1-HEXANOLS

Compound	Yield, %	B. p., °C.	Press., mm.	$n^{20}D$	d^{20}_4	MR_D obs.	MR_D calcd.
n-Butyl	70	119–121	5	1.4568	0.8818	53.42	53.51
i-Butyl	76	117–119	6	1.4535	0.8735	53.59	53.51
s-Butyl	85	122–123	3	1.4562	0.8829	53.49	53.51
t-Butyl	63	117–118	4	Solid, m. p. 48–52°			

TABLE II

6-BUTYLAMINO-1-HEXANOL HYDROCHLORIDES

Compound	M. p., °C.	Analyses,[a] % Carbon	Hydrogen	Nitrogen	Chlorine
n-Butyl	114–116	57.6	11.6	6.72	17.3
i-Butyl	111–114	57.1	11.7	7.1	16.8
s-Butyl	81– 82.5	57.5	11.7	6.69	17.2
t-Butyl	134–135	57.4	11.6	6.71	17.1

[a] Calcd. for $C_{10}H_{24}NOCl$: C, 57.26; H, 11.53; N, 6.67; Cl, 16.9.

(6) Craig, *J. Biol. Chem.*, **155**, 519 (1944); **161**, 321 (1945).

(7) Private communication from Dr. M. Carmack, University of Pennsylvania.

(8) Campbell and Schaffner, THIS JOURNAL, **67**, 86 (1945).

(9) Rohrmann and Shonle, *ibid.*, **66**, 1640 (1944).

(10) Most of the analyses reported here were carried out at Northwestern University.

(11) Cowan and Marvel, THIS JOURNAL, **58**, 2277 (1936).

(12) Lehman, Thompson and Marvel, *ibid.*, **55**, 1977 (1933).

(13) Bennett and Turner, *J. Chem. Soc.*, 814 (1938).

(14) Morton, "Laboratory Technique of Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1938, p. 206.

(15) Marvel and Noyes, THIS JOURNAL, **42**, 2276 (1920).

(16) Campbell, Sommers and Campbell, *ibid.*, **68**, 140 (1946).

from a modified Claisen flask.[17] The properties of the butylaminohexanols and their hydrochlorides are given in Tables I and II.

6-Butylamino-1-bromohexane Hydrobromides.—Thirty grams of the amino alcohol was added with shaking to 520 ml. of 48% hydrobromic acid, and the solution was refluxed in an all-glass apparatus for six hours. The solution was concentrated to a thick sirup under reduced pressure at 60–90°; the sirup was taken up in water and again evaporated. It was then evaporated twice from 95% alcohol and twice from absolute alcohol. The white solid was thoroughly washed with ether and dried at 80° and 5 mm. The yields were excellent. The data are summarized in Table III.

TABLE III

6-BUTYLAMINO-1-BROMOHEXANE HYDROBROMIDES

Compound	Yield, %	M. p., °C.	Analyses[a] Nitrogen	Bromine
n-Butyl	98	207–213	4.8	49.7
i-Butyl	98	197–201	4.87	50.0
s-Butyl	95	136–139	4.6	50.1
t-Butyl	98	143–145	4.7	49.8

[a] Calcd. for $C_{10}H_{23}NBr_2$: N, 4.42; Br, 50.44.

6-Diethylaminohexyl Bromide Hydrobromide.—Diethylaminohexanol, prepared by Work's method[18] in 80% yield (b. p. 105–108° (5 mm.), $n^{20}D$ 1.4549, d^{20}_4 0.8776) was treated with 48% hydrobromic acid as described above. The product, obtained in 92% yield, melted at 60–63° after recrystallization from alcohol–ether mixture.

Anal. Calcd. for $C_{10}H_{23}NBr_2$: N, 4.42; Br, 50.44. Found: N, 4.36; Br, 50.0.

8-(3′-Ethylaminopropylamino)-6-methoxyquinoline, SN-3557.[19]—The general procedure of Rohrmann and Shonle[9] was used. A mixture of 32 g. (0.13 mole) of 3-ethylaminopropylbromide hydrobromide, 45 g. (0.26 mole) of redistilled 8-amino-6-methoxyquinoline and 125 ml. of absolute alcohol was refluxed in an oil-bath at 95–100° for forty-eight hours. There was obtained 20 g. of recovered nucleus and 20.4 g. (60%) of product, b. p. 170–175° (0.2 mm.). The product was converted to the dihydrochloride by titration with propanolic hydrogen chloride. The dihydrochloride was a powdery yellow solid, m. p. 202–204°, very soluble in water, less soluble in alcohol; the aqueous solution was acid to litmus but neutral to congo red.

Anal. Calcd. for $C_{15}H_{23}N_3OCl_2 \cdot 0.5H_2O$: C, 52.8; H, 7.1; Cl, 21.26. Found: C, 52.6; H, 6.9; Cl, 21.4.

The oxalate melted at 148–149° after recrystallization from alcohol–ethyl acetate mixture. Crum and Robinson[5] prepared this quinoline from ethylamine and 8-(3′-chloropropylamino)-6-methoxyquinoline; they reported the dihydrochloride monohydrate as melting at 206° and the dioxalate at 139°.

8-(6′-Ethylaminohexylamino)-6-methoxyquinoline, SN-12,451.—This was prepared as described above. The yield of material of b. p. 195–200° (0.15 mm.) was 49%.

Anal. Calcd. for $C_{18}H_{27}N_3O$: C, 71.7; H, 9.03; N, 13.94. Found: C, 71.5; H, 9.14; N, 13.85.

The dihydrochloride, prepared in propanol, melted at 185°.

Anal. Calcd. for $C_{18}H_{29}N_3OCl_2$: C, 57.8; H, 7.8; Cl, 18.94. Found: C, 57.2; H, 7.9; Cl, 19.1.

8-(6′-*n*-Butylaminohexylamino)-6-methoxyquinoline, SN-13,380.—The yield of compound of b. p. 190–200° (0.2 mm.) was 57%. The dihydrochloride, prepared in propanol, melted at 178–181°, and had about the same solubilities as the other dihydrochlorides reported.

Anal. Calcd. for $C_{20}H_{33}N_3OCl_2 \cdot H_2O$: C, 57.14; H, 8.39; N, 10.0; Cl, 16.9. Found: C, 57.2; H, 8.33; N, 10.6; Cl, 17.2.

8-(6′-Isobutylaminohexylamino)-6-methoxyquinoline, SN-13,379.—The free base, obtained in 62% yield, had b. p. 200–210° (0.05 mm.). The monohydrochloride precipitated from *n*-propanol. It melted at 147–150° and was much less soluble in water than the dihydrochlorides described above.

Anal. Calcd. for $C_{20}H_{32}N_3OCl$: C, 65.6; H, 8.82; N, 11.5; Cl, 9.7. Found: C, 65.2; H, 9.0; N, 11.6; Cl, 10.1.

8-(6′-*s*-Butylaminohexylamino)-6-methoxyquinoline, SN-13,378.—This quinoline, obtained in 62% yield, boiled at 190–200° (0.02 mm.).

Anal. Calcd. for $C_{20}H_{31}N_3O$: N, 12.75. Found: N, 12.9.

The dihydrochloride, prepared in propanol, melted at 102–105°, resolidified at 110° and remelted at 172–175°.

Anal. Calcd. for $C_{20}H_{33}N_3OCl_2 \cdot 0.5H_2O$: C, 58.4; H, 8.33; N, 10.2; Cl, 17.24. Found: C, 58.5; H, 8.30; N, 10.9; Cl, 17.4.

The monohydrochloride was obtained as a non-hygroscopic greenish-yellow powder melting at 145–146°.

Anal. Calcd. for $C_{20}H_{32}N_3OCl$. Cl, 9.7; Found: Cl, 10.0.

8-(6′-*t*-Butylaminohexylamino)-6-methoxyquinoline, SN-13,377.—In this case the reaction mixture was filtered while hot from the nucleus hydrobromide, as on cooling the salt of the product precipitated. The free base, obtained in 53% yield, had b. p. 190–195° (0.1 mm.). The dihydrochloride melted at 190–195°.

Anal. Calcd. for $C_{20}H_{33}N_3OCl_2$: C, 59.7; H, 8.3; Cl, 17.6. Found: C, 59.3; H, 8.6; Cl, 17.5.

The monohydrochloride melted at 160–163°.

8-(6′-Diethylaminohexylamino)-6-methoxy-5-phenoxyquinoline, SN-14,229.—A mixture of 30 g. (0.113 mole) of 8-amino-6-methoxy-5-phenoxyquinoline,[20] 18 g. (0.057 mole) of 6-diethylaminohexyl bromide hydrobromide and 75 ml. of absolute alcohol was refluxed for seventy-four hours. There was obtained 19.2 g. of recovered nucleus and 15.0 g. (62%) of product, b. p. 233–235° (0.05 mm.), m. p. 37–40°.

Anal. Calcd. for $C_{26}H_{35}N_3O_2$: C, 74.1; H, 8.37; N, 9.97. Found: C, 73.7; H, 8.30; N, 9.8.

The monohydrochloride, prepared in propanol, was a light yellow powder, m. p. 127–129°, slightly soluble in water, more soluble in alcohol.

Anal. Calcd. for $C_{26}H_{36}N_3O_2Cl$: Cl, 7.74. Found: Cl, 7.68.

The dihydrochloride (dihydrate) was a red crystalline solid, m. p. 137–138°. It was very soluble in water but not hygroscopic.

Anal. Calcd. for $C_{26}H_{37}N_3O_2Cl_2 \cdot 2H_2O$: Cl, 13.36. Found: Cl, 13.53.

6-Methoxy-8-nitrolepidine.—A mixture of 170 g. of arsenic acid, 50 ml. of water, 168 g. (1.0 mole) of *m*-nitro-*p*-anisidine and 280 g. of concentrated sulfuric acid was placed in a 1-liter flask fitted with stirrer, dropping funnel and condenser set for downward distillation. The mixture was heated in an oil-bath at 110–115° while 148 g. (1.0 mole) of 1,3,3-trimethoxybutane was added dropwise in the course of two and a half hours. The mixture was stirred at 115–125° for an additional two hours while methanol distilled out. It was cooled, poured into ice water and filtered. The filtrate was made basic with ammonium hydroxide, and the reddish-brown precipitate recrystallized from 2 liters of benzene. The product melted at 160–165° and weighed 71 g. (33%). It was used without further purification. A sample, recrystallized twice from benzene, melted at 169.5–171.5°.

(17) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 18.

(18) Work, *J. Chem. Soc.*, 426 (1942).

(19) The numbers are those assigned by the Survey of Antimalarial Drugs to identify the drugs in their records. The antimalarial activities of these compounds will be tabulated in their forthcoming monograph.

(20) We wish to thank Dr. W. M. Lauer of the University of Minnesota for supplying this compound.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62. Found: C, 60.61; H, 4.93.

8-Amino-6-methoxylepidine.—A mixture of 33 g. of the nitro compound, 25 ml. of absolute alcohol, 75 ml. of ethyl acetate and 9 g. of Raney nickel was shaken with hydrogen at 50° and 60 lb. pressure. The theoretical amount of hydrogen was absorbed in eighty minutes. The product boiled at 164–170° (3 mm.), and weighed 20.5 g. (73%). It solidified to white crystals, m. p. 86.5–87.5° after recrystallization from ligroin.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43. Found: C, 70.32; H, 6.57.

8-(6′-Diethylaminohexylamino)-6-methoxylepidine, SN-14,011.—A mixture of 28.5 g. (0.15 mole) of 8-amino-6-methoxylepidine, 57 g. (0.18 mole) of diethylaminohexyl bromide hydrobromide, 25 g. (0.3 mole) of anhydrous sodium acetate and 90 ml. of 50% alcohol was refluxed for forty-eight hours. The solution was poured into 500 ml. of water, made alkaline with potassium hydroxide and extracted with ether. Distillation of the ether extract gave 15 g. of recovered nucleus and 19.1 g. (80% based on unrecovered nucleus) of product, b. p. 190–200° (0.05 mm.). This was dissolved in 50 ml. of *n*-propanol and titrated with propanolic hydrogen chloride. The yellow dihydrochloride so obtained weighed 21 g., and melted at 176–178°. Recrystallization from propanol raised the melting point to 179–180°.

Anal. Calcd. for $C_{21}H_{35}N_3OCl_2$: C, 60.57; H, 8.47; Cl, 17.11. Found: C, 60.43; H, 8.60; Cl, 17.5.

Summary

1. Several 8 - (ω - alkylaminoalkylamino)-6-methoxyquinolines have been prepared.

2. The four isomeric 6-butylamino-1-hexanols and their corresponding bromides have been prepared.

3. The synthesis of 6-methoxy-8-nitrolepidine is described.

NOTRE DAME, INDIANA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Studies in the Quinoline Series. IV. The Preparation of Some 5-Amino-8-(ω-dialkylaminoalkylamino)-quinolines[1]

BY KENNETH N. CAMPBELL, JAMES F. KERWIN,[2] ARMIGER H. SOMMERS[3] AND BARBARA K. CAMPBELL

It has been reported by Schönhöfer[4] that the introduction of a methoxyl group in the 5-position in compounds of the plasmochin type enhances their antimalarial activity. In this connection it was of interest to test the antimalarial properties of plasmochin-like compounds containing other susceptible groups in the 5-position, and we undertook the preparation of several 5-amino-8-(ω-dialkylaminoalkylamino) - quinolines and of 5-hydroxy- and 5-acetoxyplasmochin.

A few 5-amino-8-alkylaminoquinolines have been reported in the literature.[5,6,7,8,9] These were prepared by selective alkylation of the 5,8-diamine[5,7] or by reduction of the corresponding 5-nitro compound.[6,8,9] The products were found to be very unstable in air, and in some cases no analytical data, physical constants or salts are reported. There appears to be no record in the literature of a 5-hydroxy-8-alkylaminoquinoline, but Moness and Christiansen[10] have reported the preparation of 8-hydroxy-5-(diethylaminoethylamino)-quinoline.

(1) The work reported here was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Notre Dame.

(2) Present address: Smith, Kline and French Laboratories, Philadelphia, Pa.

(3) Present address: Department of Chemistry, Columbia University.

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

(5) Frisch and Bogert, *J. Org. Chem.*, **9**, 338 (1944).

(6) Slater, *J. Chem. Soc.*, 2104 (1932).

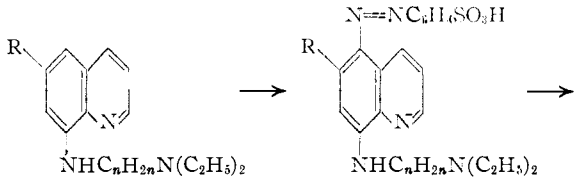
(7) Baldwin, *ibid.*, 2959 (1929).

(8) Fourneau, *et al.*, *Ann. Inst. Pasteur*, **44**, 719 (1930).

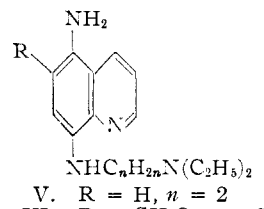
(9) Topchiev, *Compt. rend. acad. sci. U. R. S. S.*, **4**, 264 (1935); *C. A.*, **30**, 3821.

(10) Moness and Christiansen, *J. Am. Pharm. Assoc.*, **25**, 501 (1936).

Five 5 - amino - 8 - (ω - dialkylaminoalkylamino)-quinolines are described in this paper; namely, 5-aminoplasmochin, 5-amino-6-methoxy- and 5 - amino - 8 - (2′ - diethylaminoethylamino)-quinolines, and 5-amino-6-methoxy- and 5-amino - 8 - (6′ - diethylaminohexylamino)-quinolines. These were prepared easily and in good yields by a series of reactions



I. R = H, n = 2
II. R = CH_3O, n = 2
III. R = H, n = 6
IV. R = CH_3O, n = 6



V. R = H, n = 2
VI. R = CH_3O, n = 2
VII. R = H, n = 6
VIII. R = CH_3O, n = 6

As would be expected from their analogy to *p*-phenylenediamine, the 5-amino-8-(dialkylaminoalkylamino)-quinolines were found to be extremely unstable in air. They could be distilled, however, in an atmosphere of nitrogen. Considerable difficulty was encountered in preparing suitable salts for testing; in most cases the hydro-