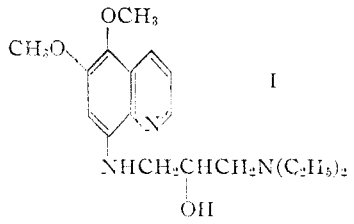


I

diethylamino-2-hydroxypropylamino)-6-methoxyquinoline was prepared.

Experimental

8-(3-Diethylamino-2-hydroxy-propylamino)-5,6-dimethoxyquinoline.[5]—To molten 5,6-dimethoxy-8-aminoquinoline (20.4 g.) was added dropwise over a period of three hours, 1-diethylamino-2,3-epoxypropane (14.0 g.). The temperature was maintained at 175–180° and the mixture was stirred continuously. Heating and stirring was continued for one-half hour after the addition of the oxide was completed. The warm reaction mixture was then dissolved in 1 *N* hydrochloric acid (200 ml.). A solution of sodium citrate (40 g. of citric acid in 200 ml. of 1 *N* sodium hydroxide), was added and the tarry material which separated was removed by filtration and extraction with ether. Sodium hydroxide (300 ml., 1 *N*) was then added and some 5,6-dimethoxy-8-aminoquinoline (2.5 g.) was recovered. The further addition of 1 *N* sodium hydroxide (300 ml.) yielded a black tarry material (20 g.). Purification of this material by crystallization was exceedingly difficult and therefore it was subjected to distillation under low pressures (*ca.* 10^{-4} mm.). During this distillation most of the remaining 5,6-dimethoxy-8-aminoquinoline sublimed into the neck of the distillation apparatus. The distillate solidified on standing overnight, but a considerable residue remained in the distillation apparatus. Repeated crystallization of the distillate gave a yellow crystalline product melting at 88–90°.

Anal. Calcd. for $C_{18}H_{27}O_3N_3$: C, 64.85; H, 8.16. Found: C, 64.87; H, 8.57.

8-(3-Di-*n*-butylamino-2-hydroxy-propylamino)-5,6-dimethoxyquinoline.—This substance was prepared in essentially the same way as the above-described diethylamino compound.

5,6-Dimethoxy-8-aminoquinoline (17.5 g., 0.087 mole) and 1-di-*n*-butylamino-2,3-epoxypropane (16.0 g., b. p. 105–110 at 22 mm.) were heated together at 180°. The reaction mixture was worked up as in the previous case using a citrate buffer to separate the major portion of unreacted 5,6-dimethoxy-8-aminoquinoline. Addition of 1 *N* sodium hydroxide, followed by ether extraction and evaporation of solvent, gave a dark residue which was distilled under low pressure (*ca.* 10^{-4} mm.). There was obtained a dark viscous liquid (22.7 g.). The distillate could not be obtained in crystalline form. Redistillation gave a liquid product (18.5 g.) of the expected composition.

Anal. Calcd. for $C_{22}H_{35}O_3N_3$: C, 67.83; H, 9.06. Found: C, 68.08; H, 9.01.

Further distillation failed to give a crystallizable product.

8-(3-Diethylamino-2-hydroxy-propylamino)-6-methoxyquinoline.—This compound was prepared from 6-methoxy-8-aminoquinoline (17.4 g.) and 1-diethylamino-2,3-epoxypropane (14.0 g.). The procedure followed that already described for the 5,6-dimethoxy homolog. On distillation a yield of 12.3 g. was obtained. Further purification by redistillation and extraction from a phosphate buffer followed by a third distillation gave a liquid product which showed the following composition.

Anal. Calcd. for $C_{17}H_{25}O_2N_3$: C, 67.16; H, 8.29. Found: C, 67.18; H, 8.58.

Summary

The preparation of 8-(3-diethylamino-2-hydroxypropylamino) - 5,6 - dimethoxyquinoline and two homologs is described.

MINNEAPOLIS, MINN. RECEIVED APRIL 5, 1946

(5) We are indebted to Robert Elderfield of Columbia University for 5,6-dimethoxy-8-aminoquinoline used in this preparation.

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY No. 1038]

The Synthesis of Potential Antimalarials. Some 2-Substituted 8-(3-Diethylaminopropylamino)-quinolines[1]

BY KURT MISLOW AND J. B. KOEPFLI

This investigation was part of a general program to develop a drug with the desirable antimalarial properties of pamaquine but without its high toxicity.

The possibility suggested itself of reducing the toxicity of pamaquine by preparing an analog with a carbostyril or 2-alkoxyquinoline nucleus, because an *in vitro* degradation product of quinine[2] which was less toxic although less active than quinine itself, was found to possess a carbostyril structure.[3] The preparation of certain 2-hydroxy-4-methyl-8-(dialkylaminoalkyl)-quinolines as potential antimalarials had been previously reported[4]; however, the compounds had a 4-methyl substituent not present in the pamaquine nucleus.

In the present investigation, it had originally been intended that the side chain of pamaquine (4-diethylamino-1-methylbutyl) would be attached to the 8-aminoquinoline nucleus. Since, however, recent evidence[5] indicates that the use of this side chain may be accompanied by the formation of isomers, it is the preparation of the 8-(3-diethylaminopropylamino)-quinolines VIIIa, VIIIb, IXa and IXb which is described here.

The final compounds were prepared as indicated in the accompanying general scheme. 2-Methoxy-8-aminoquinoline (VIIa) was obtained by reduction of the known 2-methoxy-8-nitroquinoline

(1) This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

(2) Kelsey, Geiling, Oldham and Dearborn, *J. Pharmacol.*, **80**, 391 (1944).

(3) Mead and Koepfli, *J. Biol. Chem.*, **154**, 507 (1944).

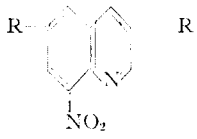
(4) Johnson and Hamilton, THIS JOURNAL, **63**, 2867 (1911).

(5) R. C. Elderfield, private communication.

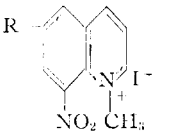
(VIa), whereas 2,6-dimethoxy-8-aminoquinoline (VIIb) was obtained from 6-methoxy-8-nitroquinoline (Ib) through the intermediate compounds IIb, IIIb, IVb, Vb and VIb.

Considerable difficulty was encountered in finding a workable synthesis of 6-methoxy-8-(3-diethylaminopropylamino)-carbostyril (IXb). In the first attempt 6-methoxy-8-nitrocarbostyril (Vb) was reduced to the corresponding amino compound, which could not be induced to condense with 1-diethylamino-3-chloropropane. The second attempt was based on the assumption that the 2-methoxy group in VIIIb was more labile than the 6-methoxy group and therefore could be preferentially hydrolyzed. However, this assumption proved to be fallacious, and all attempts at hydrolysis resulted in the formation of the 8-(3-diethylaminopropylamino)-2,6-quinolinediol (IXa); this method was adopted for the preparation of this compound.

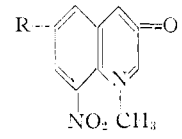
The synthesis of IXb was finally accomplished by making use of the well known hydrogenolysis of benzyloxy compounds to the corresponding alcohols by means of palladium catalysts,[6] a method apparently not hitherto applied to pyridine or quinoline benzyloxy derivatives. Thus Vb was benzylated to give VIc; the formulation of VIc as a 2-benzyloxy rather than a 1-benzyl-2-quinolone derivative was indicated by a comparison of absorption spectra. VIc was then reduced to yield the amine VIIc which on condensation with 1-diethylamino-3-chloropropane gave 2-benzyloxy-6-methoxy-8-(3-diethylaminopropylamino)-quinoline (VIIIc) in good yield. Numerous unsuccessful attempts were made to reduce catalytically the benzyloxy base VIIIc as the dihydroiodide salt; however, when a solution of the



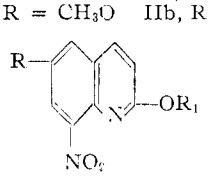
Ia, R = H
Ib, R = CH_3O



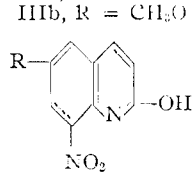
IIa, R = H
IIb, R = CH_3O



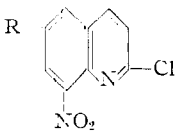
IIIa, R = H
IIIb, R = CH_3O



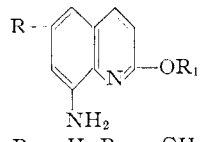
VIa, R = H, R_1 = CH_3
VIb, R = CH_3O, R_1 = CH_3
VIc, R = CH_3O, R_1 = $C_6H_5CH_2$



Va, R = H
Vb, R = CH_3O

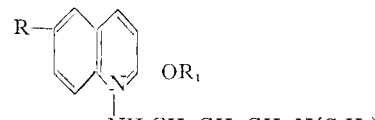


IVa, R = H
IVb, R = CH_3O

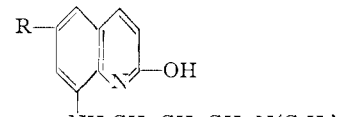


VIIa, R = H, R_1 = CH_3
VIIb, R = CH_3O, R_1 = CH_3
VIIc, R = CH_3O, R_1 = $C_6H_5CH_2$

(6) Richtmyer, THIS JOURNAL, **56**, 1633 (1934); Baltzly and Buck, *ibid.*, **65**, 1984 (1943).



VIIIa, R = H, R_1 = CH_3
VIIIb, R = CH_3O, R_1 = CH_3
VIIIc, R = CH_3O, R_1 = $C_6H_5CH_2$



IXa, R = OH
IXb, R = CH_3O

base in ethanolic acetic acid was employed, complete reduction to IXb took place.

Experimental[7]

2-Methoxy-8-nitroquinoline (VIa).—8-Nitroquinoline (Ia), obtained by the Knüppel modification of the Skraup synthesis[8] was converted to the N-methyl iodide derivative IIa[9] which was in turn oxidized with 30% hydrogen peroxide (compare Ing[10]) to 1-methyl-8-nitro-2-quinolone (IIIa).[11] The quinolone IIIa with phosphorus pentachloride gave 2-chloro-8-nitroquinoline (IVa)[11] which was hydrolyzed in 20% hydrochloric acid to 8-nitrocarbostyril (Va).[11,12] Methylation of Va with dimethyl sulfate[9,13] gave the 2-methoxy-8-nitroquinoline (VIa) in 16% over-all yield.

2-Methoxy-8-aminoquinoline (VIIa).—Twenty-five grams of 2-methoxy-8-nitroquinoline (VIa) was suspended in 500 ml. of absolute ethanol and reduced with hydrogen at one atmosphere and room temperature for thirty minutes in the presence of platinum oxide. The solution was filtered, the solvent removed and the amine distilled at 125–129° (0.2 mm.). The amine crystallized to give 19 g. (90%) of colorless needles, which after recrystallization from ethanol melted at 75–76°.

Anal. Calcd. for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.89; H, 5.79; N, 16.06.

2-Methoxy-8-(3-diethylaminopropylamino)-quinoline (VIIIa), (SN 13058).[14]—The modified[15] procedure of Magidson, *et al.*,[16] was followed in this condensation. A solution of 7.0 g. of 2-methoxy-8-aminoquinoline, 16.4 g. of sodium acetate and 7.4 g. of 1-diethylamino-3-chloropropane hydrochloride[17] in 150 ml. of 66% ethanol was refluxed for five days with an additional 7.4 g. of 1-diethylamino-3-chloropropane hydrochloride added each day. The solu-

(7) All melting points are corrected. The microanalyses were performed by Dr. Gertrude Oppenheimer and Mr. G. A. Swinehart.

(8) Knüppel, *Ber.*, **29**, 705 (1896); Bradley and Robinson, *J. Chem. Soc.*, 1260 (1932).

(9) Decker, *Ber.*, **38**, 1149 (1905).

(10) Ing, *J. Chem. Soc.*, 2202 (1931).

(11) Decker and Stavropoulos, *J. prakt. Chem.*, **68**, 100 (1903).

(12) Fischer and Guthmann, *J. prakt. Chem.*, **93**, 383 (1916).

(13) Decker and Pollitz, *ibid.*, **64**, 92 (1901).

(14) The Survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey numbers have been assigned will be tabulated in a forthcoming monograph.

(15) Elderfield and Head, THIS JOURNAL, **68**, 1524 (1946).

(16) Magidson and Strukov, *Arch. Pharm.*, **271**, 569 (1933); Magidson, Strukov, Bobuishev and Torf, *J. Appl. chem.* (U. S. S. R.), **9**, 321 (1936).

(17) Prepared by brominating trimethylene chlorohydrin to trimethylene chlorobromide [Cloke, Anderson, Lachmann and Smith, THIS JOURNAL, **53**, 2794 (1931)], treating the latter with diethylamine and converting the resulting 1-diethylamino-3-chloropropane [Narxter, *Helv. Chim. Acta*, **24**, 2142 (1941)] to the hydrochloride [Hass and Huffman, THIS JOURNAL, **63**, 1234 (1941)].

tion was diluted with 300 ml. of water, made basic, saturated with potassium carbonate and extracted with ether. The ether extract was dried, the solvent removed and the residue distilled *in vacuo* under nitrogen. Nine grams (78%) of the desired base came over as the highest boiling fraction, b. p. 190–192° (0.15 mm.). It is a light yellow, viscous oil, unstable in air.

The dihydriodide was obtained by dissolving the base in 38 ml. of ethanol and adding a solution of 8.5 ml. of hydriodic acid (sp. gr. 1.7) in 38 ml. of ethanol. The solution was diluted with ether until it was turbid, and cooled at 5° overnight. The salt, which had precipitated, was recrystallized from ethanol to give 9.6 g. (56%) of colorless needles, m. p. 140–142° (dec.). Unlike the dihydrochloride, it is not hygroscopic.

Anal. Calcd. for $C_{17}H_{27}ON_3I_2$: C, 37.58; H, 5.01; N, 7.74. Found: C, 37.84; H, 5.15; N, 7.57.

6-Methoxy-8-nitroquinoline Methiodide (IIb).—A mixture of 408 g. of 6-methoxy-8-nitroquinoline (Ib) (Winthrop technical) and 380 ml. of dimethyl sulfate was heated on the steam-bath for four hours. The oil was diluted with 500 ml. of water, and 600 g. of sodium iodide added to the solution, whereupon 662 g. (96%) of IIb crystallized out in red needles. A sample, recrystallized from butanol, melted at 149°.

Anal. Calcd. for $C_{11}H_{11}O_3N_2I$: C, 38.17; 3.20; N, 8.10. Found: C, 38.26; H, 3.06; N, 8.31.

6-Methoxy-1-methyl-8-nitro-2-quinolone (IIb).—To 242 g. of 6-methoxy-8-nitroquinoline methi (IIb) dissolved in 1150 ml. of 96% ethanol, 460 ml. *N* potassium hydroxide was added. When all of the base had been added, the solution set to a crystalline slurry. While keeping the suspension at 30–50°, 920 ml. of 30% hydrogen peroxide was added in small portions. When all of the peroxide had been added, the suspension was cooled and filtered, and the residue recrystallized from methanol to give 95 g. (58%) of yellow needles, m. p. 186–187°.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$: C, 56.40; H, 4.30; N, 11.96. Found: C, 56.76; H, 4.21; N, 12.21.

2-Chloro-6-methoxy-8-nitroquinoline (IVb).—A mixture of 189 g. of 6-methoxy-1-methyl-8-nitro-2-quinolone (IIIb) and 169 g. of phosphorus pentachloride was heated under reflux at 170–185° for five hours. The resulting cake was hydrolyzed by the addition of 1 liter of water, the suspension basified and filtered. The residue was recrystallized from methyl cellosolve to give 133 g. (77%) of colorless needles, m. p. 225–226°.

Anal. Calcd. for $C_{10}H_7O_3N_2Cl$: C, 50.32; H, 2.96; N, 11.74. Found: C, 50.30; H, 3.00; N, 11.74.

6-Methoxy-8-nitrocarbostyril (Vb).—A suspension of 125 g. of 2-chloro-6-methoxy-8-nitroquinoline (IVb) in 1200 ml. of 6 *N* hydrochloric acid was refluxed for twenty-four hours. A few milliliters of capryl alcohol had to be used as a foam-depressant. The solution was brought to *p*H 8 with concentrated ammonium hydroxide, filtered and the residue recrystallized from methyl cellosolve to give 96 g. (83%) of golden platelets, m. p. 210–211°.

Anal. Calcd. for $C_{10}H_8O_4N_2$: C, 54.54; H, 3.66; N, 12.73. Found: C, 54.33; H, 3.50; N, 12.87.

2,6-Dimethoxy-8-nitroquinoline (VIb).—To a solution of 95.4 g. of 6-methoxy-8-nitrocarbostyril (Vb) in 2 liters of hot 2.5 *N* sodium hydroxide was added 800 ml. of dimethyl sulfate in 100-ml. portions the solution being basified after each addition. On cooling, VIb crystallized out. Recrystallization from ethanol gave 76.8 g. (76%) of light yellow needles, m. p. 149–150°.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$: C, 56.40; H, 4.30; N, 11.96. Found: C, 56.29; H, 4.30; N, 12.03.

2,6-Dimethoxy-8-aminoquinoline (VIIb).—A suspension of 77 g. of 2,6-dimethoxy-8-nitroquinoline (VIb) in 1 liter of absolute ethanol was reduced by shaking with hydrogen at one atmosphere and room temperature for one hour in the presence of platinum oxide. The solution was filtered from the catalyst, concentrated to 100 ml., diluted to 1 liter with water and filtered. The residue was recrystallized from ethanol to give 48 g. (72%) of silvery crystals, m. p. 135–136°.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.71; H, 5.93; N, 13.72. Found: C, 64.62; H, 5.88; N, 13.95.

2,6-Dimethoxy-8-(3-diethylaminopropylamino)-quinoline (VIIIb), (SN 12251).—This compound was prepared in the same manner as VIIIa, by condensing VIIb with 1-diethylamino-3-chloropropane hydrochloride.[18] The desired base came over as a yellow, viscous oil, b. p. 216–218° (0.15 mm.). The yield was 86%. VIIIb was analyzed as the dihydriodide, colorless needles from ethanol, m. p. 139–140° (dec.).

Anal. Calcd. for $C_{18}H_{29}O_2N_3I_2$: C, 37.70; N, 5.10; N, 7.33. Found: C, 37.91; H, 4.98; N, 7.28.

8-(3-Diethylaminopropylamino)-2,6-quinolinediol (IXa), (SN 14184).—A solution of 36.5 g. of 2,6-dimethoxy-8-(3-diethylaminopropylamino)-quinoline (VIIIb) in 182 ml. of 6 *N* hydrochloric acid was refluxed four hours. It was cooled, neutralized with ammonium hydroxide, and the green gum which precipitated was collected by centrifugation and recrystallized from methyl cellosolve to give 8.5 g. (26%) of yellow crystals, m. p. 208–210° (dec.).

Anal. Calcd. for $C_{16}H_{23}O_2N_3$: C, 66.40; H, 8.01; N, 14.52. Found: C, 66.14; H, 8.24; N, 14.60.

6-Methoxy-8-aminocarbostyril.—A suspension of 67.5 g. of 6-methoxy-8-nitrocarbostyril (Vb) in 500 ml. of absolute ethanol was reduced by shaking with hydrogen at one atmosphere and room temperature for four hours, in the presence of platinum oxide. The suspension was diluted with 400 ml. of water and filtered. The residue was dissolved in 1 l. of hot 6 *N* hydrochloric acid, the suspension filtered hot and the filtrate brought to *p*H 8 with concentrated ammonium hydroxide to give 53.0 g. (91%) of the carbostyril. The compound is only very slightly soluble in most organic solvents, and could be recrystallized only with difficulty from butanol or methyl cellosolve to give brown crystals, melting above 300°.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.04; H, 5.30; N, 14.73. Found: C, 63.06; H, 5.72; N, 14.73.

Due to the extreme insolubility of 6-methoxy-8-aminocarbostyril, no suitable solvent was found in which condensation with 1-diethylamino-3-chloropropane could be carried out. Attempts to effect condensation by fusion were unsuccessful.

2-Benzyloxy-6-methoxy-8-nitroquinoline (VIc).—To a solution of 83.7 g. of 6-methoxy-8-nitrocarbostyril (Vb) in 1670 ml. of 2.5 *N* sodium hydroxide was added 480 ml. of benzyl chloride. The mixture was stirred vigorously on the steam-bath for eight hours and then allowed to stand overnight. Two layers had formed. The aqueous layer was siphoned off, and the other layer, which had set to a semisolid, was boiled with 1.5 liters of ethanol. The ethanolic solution was chilled, filtered and the residue recrystallized from ethanol to give 80 g. (68%) of faintly yellow crystals, m. p. 139–140°.

Anal. Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.89; H, 4.73; N, 8.88.

A comparison of the absorption spectrum maxima and minima of IIIb, VIb, and VIc (Table I) indicates that VIc is 2-benzyloxy-6-methoxy-8-nitroquinoline, rather than 1-benzyl-6-methoxy-8-nitro-2-quinolone.

TABLE I

Compound	Maximum		Minimum	
	(mμ)	E_{mcbld}	(mμ)	E_{mcbld}
IIIb	373	4860	307	1430
VIb	349	5530	297	1310
VIc	351	4110	297	1000

2-Benzyloxy-6-methoxy-8-aminoquinoline (VIIc).—Sixty-one grams of 2-benzyloxy-6-methoxy-8-nitroquinoline (VIc) and 225 g. of iron powder (Iron by Hydrogen

(18) The base was kindly supplied by Dr. R. C. Elderfield, Columbia University.

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]

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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

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

(5) Crum and Robinson, *ibid.*, 361 (1943).