[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of Certain 8-(5-Alkylamino-1-methylpentylamino)- Derivatives of Quinoline[1]

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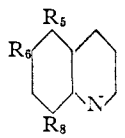
The marked effectiveness of Pamaquine (I) in permanently curing a high percentage of cases of relapsing malaria[2] and the still higher efficacy of Pentaquine (II) coupled with the lower toxicity of Pentaquine as compared to Pamaquine suggests that if the branching methyl group of the side chain of Pamaquine be combined with the five carbon straight side chain of Pentaquine, still more favorable drugs might result. In the present communication we wish to present the synthesis of certain representative derivatives of 8-aminoquinoline in which such a 5-alkylamino-1-methylpentylamino side chain is present.



I. $R_5 = H$; $R_6 = OCH_3$; $R_8 = NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$

II. $R_5 = H$; $R_6 = OCH_3$; $R_8 = NH(CH_2)_5NHCH(CH_3)_2$

III. $R_5 = H$; $R_6 = OCH_3$; $R_8 = NHCH(CH_3)(CH_2)_4N(C_2H_5)_2$

IV. $R_5 = H$; $R_6 = OCH_3$; $R_8 = NHCH(CH_3)(CH_2)_3NHCH(CH_3)_2$

V. $R_5 = H$; $R_6 = OCH_3$; $R_8 = NHCH(CH_3)(CH_2)_4NHCH(CH_3)_2$ (or $NHCH_2CH_2CH_3$)

VI. $R_5 = OCH_3$; $R_6 = OCH_3$; $R_8 = NHCH(CH_3)(CH_2)_4NHCH(CH_3)_2$ (or $NHCH_2CH_2CH_3$)

6-Methoxy-8-(5-diethylamino-1-methylpentylamino)-quinoline (III), for which we propose the trivial name "homo-pamaquine" has been described by Magidson and Bobyshev[3] without further characterization or analysis as an oil boiling at 205–208° (1.5 mm.). It has also been mentioned by Krichevskii, Sternberg and Hal'perin[4] and in the patent literature.[5] In all of the references no detail of the synthesis of the drug or of the intermediate side chain, 1-diethylamino-5-bromohexane (homonoval bromide) is given. Likewise the analytical data presented leave much to be desired. Of perhaps greater concern is the fact that the aminobromide was prepared from the carbinol, 1-diethylaminohexanol-5, in at least one case,[3] by the action of hydrobromic acid, a method now known to lead to mixtures of isomers and hence to highly inhomogeneous final drugs.[6]

Accordingly, this side chain has been prepared by the following series of reactions, a sequence which has led to uniformly pure products in other instances.[6]

$$CH_3COCH_2COOC_2H_5 + Cl(CH_2)_3N(C_2H_5)_2 \xrightarrow{Na} CH_3COCH[(CH_2)_3N(C_2H_5)_2]COOC_2H_5 \longrightarrow$$

$$CH_3CO(CH_2)_4N(C_2H_5)_2 \xrightarrow{Al(O\text{-}i\text{-}Pr)_3} CH_3CHOH(CH_2)_4N(C_2H_5)_2 \xrightarrow{SOBr_2} CH_3CHBr(CH_2)_4N(C_2H_5)_2 \cdot HBr$$

In order to take advantage of the favorable effect of a terminal *i*-propylamino group on antimalarial properties as exemplified by Pentaquine (II) and its branched chain isomer (IV), 1-isopropylamino-5-bromohexane has been prepared and coupled with 6-methoxy-8-aminoquinoline. However, due to the ease with which 1-monoalkylaminohexanone-5 derivatives cyclize with the formation of N-alkyltetrahydropicolines[7,8,9] a modification of the above synthesis for the homonoval side chain was required. This modification is based on that used successfully in these Laboratories for alkylaminoalkyl bromides of similar types.[6] In a similar manner 1-*n*-propylamino-5-bromohexane has been prepared.

$$CH_3CO(CH_2)_4Br \xrightarrow{Al(O\text{-}i\text{-}Pr)_3} CH_3CHOH(CH_2)_4Br \xrightarrow{NH_2CH(CH_3)_2} CH_3CHOH(CH_2)_4NHCH(CH_3)_2 \xrightarrow{SOBr_2} CH_3CHBr(CH_2)_4NHCH(CH_3)_2 \cdot HBr$$

Each of the amino bromides has been coupled with 6-methoxy-8-aminoquinoline or 5,6-dimethoxy-8-aminoquinoline by standard methods to yield the drugs III, V and VI. Pertinent data on the drugs are given in Tables I and II.

Experimental[10,11]

1-Diethylaminohexanone-5.—To 23 g. of sodium sand in 800 ml. of dry xylene was added dropwise 130 g. of ethyl acetoacetate. After all the sodium had reacted the mix-

(1) The work described in this paper was done in part under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Columbia University and in part under a grant from the United States Public Health Service to Columbia University.

(2) "Antimalarial Drugs 1941–1945," Edwards Brothers, Ann Arbor, Michigan, 1946.

(3) Magidson and Bobyshev, *J. Gen. Chem., U. S. S. R.*, **8**, 899 (1938).

(4) Krichevskii, Sternberg and Hal'perin, *J. Microbiol. Epidemiol. Immunobiol.* (*U. S. S. R.*), **14**, 642 (1935); *C. A.*, **30**, 4218 (1936).

(5) Schönhöfer and Henecka, U. S. Patent 2,042,023, May 26, 1936; Schönhöfer and Andersag, U. S. Patent 1,938,047, December 5, 1933.

(6) Elderfield, *et al.*, THIS JOURNAL, **68**, 1516, 1579 (1946).

(7) Lipp, *Ann.*, **289**, 209 (1896).

(8) Ladenburg, *ibid.*, **304**, 55 (1899).

(9) Lipp and Windmann, *ibid.*, **409** (1915).

(10) All melting points are corrected.

(11) Microanalyses by Miss Lois May of these Laboratories.

TABLE I

PHYSICAL CONSTANTS OF THE DRUGS

No.	R_4	R_6	R_8	Yield, %	B. p. of base, °C.	Mm.	M. p. of salt, °C.
CN 1005	H	OCH_3	$NHCH(CH_3)(CH_2)_4N(C_2H_5)_2$	28	191–194	0.5	126–127
CN 1001	H	OCH_3	$NHCH(CH_3)(CH_2)_4NHCH(CH_3)_2$	37	178–185	.25	156–161
CN 1028	H	OCH_3	$NHCH(CH_3)(CH_2)_4NHCH_2CH_2CH_3$	37	202–209	.4	169–172
CN 1027	OCH_3	OCH_3	$NHCH(CH_3)(CH_2)_4NHCH(CH_3)_2$	9	212–219	.4	111–114
CN 1033	OCH_3	OCH_3	$NHCH(CH_3)(CH_2)_4NHCH_2CH_2CH_3$	20	195–199	.4	159–161

ture was cooled and 150 g. of 3-diethylaminopropyl chloride was added. After stirring for two hours at room temperature and heating at 110° for fourteen hours, the cooled solution was filtered from sodium chloride and the solvent was removed *in vacuo*. The keto-ester was hydrolyzed and decarboxylated by refluxing it with 520 ml. of water and 160 ml. of hydrochloric acid (sp. gr. 1.19) for three hours. The cooled solution was neutralized with potassium carbonate and thoroughly extracted with ether. After drying over anhydrous potassium carbonate, 104 g. (60%) of the amino ketone boiling at 95–101° (12 mm.) was obtained. A small sample redistilled from barium oxide boiled at 95–98° (11 mm.), $n^{25}D$ 1.4380. Magidson and Bobyshev[3] report the boiling point as 95–101° (10 mm.).

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.1; H, 12.4. Found: C, 70.1; H, 12.5.

1-Diethylaminohexanol-5.—A mixture of 250 ml. of anhydrous isopropanol and 60 g. of solid aluminum isopropoxide was heated until a clear solution resulted. To this was added 45.5 g. of 1-diethylaminohexanone-5 and the solution was distilled very slowly through a short column, isopropanol being added to keep the volume constant. When the distillate no longer gave a positive test for acetone with 2,4-dinitrophenylhydrazine (one to one and a half hours) the cooled solution was poured into an excess of sodium hydroxide solution and extracted with ether. The combined ether extracts were washed with saturated salt solution. After drying and removal of the solvent, fractional distillation under nitrogen yielded 40 g. (88%) of the aminocarbinol boiling at 105–110° (10 mm.), $n^{25}D$ 1.4490. Magidson and Bobyshev,[3] who prepared it by catalytic reduction of the ketone, report the boiling point 110–112° (10 mm.).

Anal. Calcd. for $C_{10}H_{23}NO$: C, 69.3; H, 13.4. Found: C, 69.2; H, 13.4.

1-Diethylamino-5-bromohexane Hydrobromide.—To a stirred solution of 62 g. of the above alcohol in 200 ml. of benzene below 10° was added dropwise 75 g. of thionyl bromide. After removal of the solvent *in vacuo* the crystalline residue (82 g.) was recrystallized from ethyl acetate (5 ml. per g.) using carbon (Norit). The hydrobromide formed colorless prisms which melted at 102–103°.

Anal. Calcd. for $C_{10}H_{22}BrN\cdot HBr$: C, 37.9; H, 7.3. Found: C, 38.2; H, 7.0.

1-Bromohexanol-5.—To a boiling solution of 118 g. of aluminum isopropoxide in 360 ml. of anhydrous isopropanol was added 104 g. of 1-bromohexanone-5, prepared according to Lipp[7] from sodio ethylacetoacetate and trimethylene bromide. The mixture was distilled through a short column at the rate of 2–3 drops per second for forty-five minutes during which isopropanol was added at such a rate as to keep the volume constant. The solution was concentrated as far as possible at 15 mm. on the steam-bath in fifteen minutes and the residue was poured with stirring into 240 g. of ice and 180 ml. of hydrochloric acid (sp. gr. 1.19) during which the temperature was kept below 50° by addition of ice. After extracting the solution with four 250-ml. portions of ether, the combined ether extracts were washed with four 120-ml. portions of saturated magnesium sulfate solution. The last washing was neutral to litmus. After drying and removal of the solvent, the product was fractionally distilled yielding 67 g. (64%) of 1-bromohexanol-5 boiling at 88–90° (4 mm.), $n^{25}D$ 1.4808.

TABLE II

ANALYSES AND ANTIMALARIAL ACTIVITY OF THE DRUGS

No.	Percentage composition of the oxalates Calcd. C	Calcd. H	Found C	Found H	Homogeneity, %	Activity × quinine	Test
SN 971	Pamaquine				....	40–50	G-5
SN 971	Pamaquine				....	64	D-1
CN 1005	63.0	7.9	62.7	7.8	91	64	D-1
CN 1001	62.2	7.7	62.0	7.8	94 ± 3	128	D-1
CN 1028	62.2	7.7	62.5	7.6	96 ± 1	100	G-5
CN 1027	60.7	7.6	60.4	7.6	93 ± 3	125[a]	G-5
CN 1033	60.7	7.6	60.5	7.4	98 ± 2	50[b]	G-5

[a] CN 1027 gave Q 400 against *P. lophurae* in the chick (Richardson). [b] CN 1033 gave Q 100 against *P. lophurae* in the chick (Richardson).

Anal. Calcd. for $C_6H_{13}BrO$: C, 39.8; H, 7.2. Found: C, 39.2; H, 6.9.

1-Isopropylaminohexanol-5.—To a stirred solution of 73 g. of isopropylamine in 100 ml. of absolute alcohol in a flask equipped with a reflux condenser, inside thermometer and dropping funnel, was added dropwise over a period of three hours 75 g. of 1-bromohexanol-5 while the temperature was maintained at 50° by a water-bath. After standing overnight at room temperature, the alcohol and excess isopropylamine were removed under reduced pressure and 200 g. of 50% sodium hydroxide solution was added to the residue. The cooled mixture was extracted exhaustively with ether and the extracts were dried over potassium hydroxide. The product was fractionally distilled yielding 45.5 g. (69%) of a solid which boiled at 112–113° (11 mm.). Recrystallization from petroleum ether gave colorless platelets melting at 52–53°.

Anal. Calcd. for $C_9H_{21}NO$: C, 67.9; H, 13.3. Found: C, 68.1; H, 13.4.

1-*n*-Propylaminohexanol-5 was prepared exactly as was the above compound except that *n*-propylamine was used. The yield of material boiling at 106–108° (3 mm.) and melting at 50–51° was 56%.

Anal. Calcd. for $C_9H_{21}NO$: C, 67.9; H, 13.3. Found: C, 68.0; H, 13.5.

1-Isopropylamino-5-bromohexane Hydrobromide.—This was prepared with thionyl bromide in benzene as in the preceding case. The yield of material, m. p. 130–135°, which after one recrystallization from acetone–ether (charcoal), was suitable for further work, was 88%. Three more recrystallizations from acetone–ether gave colorless plates melting at 142–143.5°.

Anal. Calcd. for $C_9H_{20}BrN\cdot HBr$: C, 35.7; H, 7.0. Found: C, 35.7; H, 6.8.

1-*n*-Propylamino-5-bromohexane hydrobromide was formed similarly from **1-*n*-**propylaminohexanol-5 and thionyl bromide in 76% yield. Successive recrystallizations from acetone–ether gave a product melting unchanged each time at 188–189° but with a persistent impurity as indicated in the analyses.

Anal. Calcd. for $C_9H_{20}BrN\cdot HBr$: C, 35.7; H, 7.0. Found: C, 35.2; H, 6.5.

Condensation of the Amino Halides with 8-Aminoquinolines.—The above aminobromohexanes were con-

densed with 6-methoxy-8-aminoquinoline (Winthrop Chemical Company material further purified by one recrystallization from methanol) and with 5,6-dimethoxy-8-aminoquinoline,[12] according to Procedure B of Elderfield and co-workers.[13] Heating the reaction mixture after removal of the excess 8-aminoquinoline was dispensed with. The free bases, after two distillations under nitrogen, were converted to the oxalates.[13] In Table I are given the pertinent physical constants of the drugs. The numbers prefixed CN refer to numbers assigned to the drugs in this Laboratory. In Table II are given the elementary analyses of the oxalates and the homogeneity of the drug bases determined by the method of Craig,[14] using a chloroform citrate buffer system (*p*H 3.70) and a concentration of drug base of 0.5 mg. per ml.

The antimalarial activities also given in Table II are against *P. lophurae* in the duck.[15] The tests used, D-1 and G-5, are the standardized tests described elsewhere.[2] For comparison, data on Pamaquine are also included in Table II. Activities are expressed in terms of quinine as unity. Results of toxicity studies on the drugs will be reported elsewhere.

(12) Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946).

(13) Elderfield, *et al.*, *ibid.*, **68**, 1521 (1946).

(14) Craig, *et al*, *J. Biol. Chem.*, **161**, 321 (1945).

Summary

1. Syntheses of five derivatives of 8-aminoquinoline containing 5-alkylamino-1-methylpentylamino side chains have been described.

2. Antimalarial activities of the drugs against avian malaria are given.

(15) We are indebted to Drs. Arthur P. Richardson, of the Squibb Institute for Medical Research, and E. K. Marshall, Jr., of Johns Hopkins University, for permission to incorporate their screening test data in this paper.

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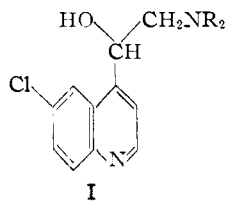
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Antimalarials. 6- and 7-Chloro-α-(dialkylaminomethyl)-4-quinolinemethanols[1]

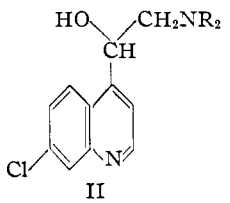
BY ROBERT E. LUTZ, JOHN F. CODINGTON[2a] AND NORMAN H. LEAKE[2b]

In an extension of the work on the quinoline 4-(β-*t*-amino alcohols)[3] three higher homologs of the 6-chloro-α-dialkylaminomethyl-4-quinolinemethanols (Ia,b,c) and the dioctylamino compound in the 7-chloroquinoline series (IIb) were synthesized for the purpose of antimalarial tests. This work was done in connection with the program of exploration of the activating effect of a chlorine atom at the various nuclear positions. The choice of homologs of relatively high molecular weight was made with the expectation of striking close to the highest antimalarial activity of which these particular series are capable.[4]



I

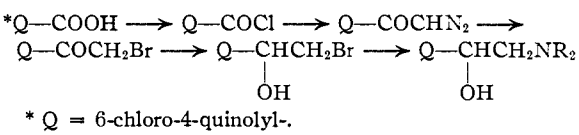
(a) R = hexyl
(b) R = octyl
(c) R = decyl
(d) NR_2 = morpholino



II

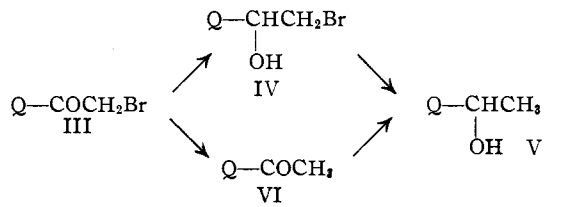
(a) R = hexyl
(b) R = octyl

The preparation of 6-chlorocinchoninic acid which was necessary in the making of the first of these series (I), followed the Halberkann[5] and Pfitzinger[5] procedures through 5-chloroisatin and 6-chloroquinoline-2,4-dicarboxylic acid; and the conversion of this to the amino alcohols was by way of the acid chloride through diazomethylation, hydrobromination, aluminum isopropoxide reduction and condensation with the appropriate amine, following the now well established procedures.[6]



* Q = 6-chloro-4-quinolyl-.

One point of particular interest in this synthesis was the ease of over-reduction of the bromoketone (III) to the secondary alcohol (V).



The elimination of the bromine in this reaction did not occur as the first step[7,8]; the bromohydrin (IV) is first formed in the reduction and can be isolated in good yield under identical reaction con-

(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 Virginia.

(2) Present location: (a) National Institute of Health, Bethesda, Md.; (b) Rohm and Haas Co., Phila., Pa.

(3) (a) King and Work, *J. Chem. Soc.*, 1307 (1940); (b) the lower members of the 6-chloro series were made by Campbell and Kerwin, THIS JOURNAL, **68**, 1837 (1946); for the α-(2-piperidyl)-methyl-4-quinolinemethanols see (c) Ainley and King, *Proc. Roy. Soc.* (*London*), **125B**, 60 (1938); (d) Buchman, Sargent, Myers and Seneker, THIS JOURNAL, **68**, 2692 (1946); and (e) Senear, Sargent, Mead and Koepfli, *ibid.*, **68**, 2695 (1946).

(4) *Cf.* (a) May and Mosettig, *J. Org. Chem.*, **11**, 1 (1946); Lutz, *et al.*, (b) THIS JOURNAL, **68**, 1813 (1946); (c) *J. Org. Chem.*, in press; (d) F. Y. Wiselogle, A Survey of "Antimalarial Drugs, 1941–1945." J. W. Edwards (1947).

(5) (a) Halberkann, *Ber.*, **54**, 3090 (1921); (b) *Cf.* Ref. 3e; (c) Pfitzinger, *J. prakt. Chem.*, **38**, 583 (1888).

(6) *Cf.* ref. 3 and 4; and especially see ref. 4b and references cited therein.

(7) *Cf.* Stevens, Allenby and DuBois, THIS JOURNAL, **62**, 1424 (1940).

(8) "Organic Reactions," Vol. II, Wiley and Sons, Inc., New York, N. Y., 1944, p. 193.