and dried to give 4.2 g. (64%). A single crystallization brought the melting point up to 217–219°. This material contained a persistent impurity, presumably R-36, and only after seven crystallizations was the melting point raised to 232° dec., mixed melting point with the previous preparation (R-120) from trimethylene diamine and 8-(3-chloropropylamino)-6-methoxyquinoline was 232°. Similarly a mixed melting point with sample furnished by Dr. Carmack was 232° dec. A picrate prepared from the above material melted at 164–165° and its melting point was undepressed when mixed with the picrate from our R-120 preparation.

Summary

1. The synthesis of Crum and Robinson's R-120, 8-[3-(3′-aminopropylamino)-propylamino]-6-methoxyquinoline, has been repeated and the structure of the product confirmed.

2. It has been demonstrated that a purified preparation made approximately according to the method utilized by Baldwin and Robinson for the synthesis of R-63, has the same structure as R-120.

3. In addition it has been indicated that probably the major impurity in Baldwin and Robinson's R-63 preparation is the unreacted starting material, R-36.

4. An improved synthesis for the starting material, R-36, has been described.

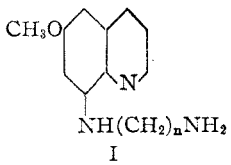
STATE COLLEGE, PA. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Aminoalkylamino Derivatives of 8-Aminoquinoline[1]

BY ROBERT C. ELDERFIELD, WALTER J. GENSLER, THOMAS H. BEMBRY, FREDERICK BRODY, LOUIS WIEDERHOLD III AND BERNICE NEWMAN

Derivatives of 6-methoxy-8-aminoquinoline of the type Formula I



I

have been described previously in the cases where n = 1–5.[2-7] The series does not appear to have been extended to longer side chains. As part of a program dealing with the systematic investigation of the 8-aminoquinolines as antimalarials, compounds of type I in the cases where n = 6, 8 and 10 have been prepared. Further, in order to take advantage of the reputed effectiveness of the 5,6-dimethoxy-8-aminoquinoline nucleus[8] 5,6-dimethoxy-8-(3′-aminopropylamino)-quinoline has been prepared.

The mode of synthesis used followed closely that used by previous workers and involved condensation of the appropriate 8-aminoquinoline with an ω-bromoalkylphthalimide followed by cleavage of the phthalimido group. In the course of the work, several new bromoalkylphthalimides were prepared.

(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 Columbia University.

(2) Baldwin, *J. Chem. Soc.*, 2959 (1929).

(3) Bramachari and Bhattacharjee, *J. Indian Chem. Soc.*, **8**, 571 (1931).

(4) Fourneau, *et al.*, *Ann. Inst. Pasteur*, **50**, 731 (1933).

(5) Robinson and Tomlinson, *J. Chem. Soc.*, 1524 (1934).

(6) Beer, *J. Gen. Chem.* (U. S. S. R.), **9**, 2158 (1936).

(7) Magidson and Bobyshev, *ibid.*, **8**, 899 (1938).

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

Experimental[9,10]

8-Bromooctylphthalimide.—This was prepared according to the method of Muller and Kraus[11] by heating 4 moles of 1,8-dibromoöctane with 1 mole of potassium phthalimide at 140–145° for six hours. The substance formed white needles from alcohol and melted at 54–55°.

Anal. Calcd. for $C_{16}H_{20}BrO_2N$: C, 56.8; H, 5.9. Found: C, 57.0; H, 6.0.

10-Bromodecylphthalimide.—This was prepared exactly as was the octyl compound. It crystallized as needles from alcohol and melted at 62–63°.

Anal. Calcd. for $C_{18}H_{24}BrNO_2$: C, 59.0; H, 6.6. Found: C, 59.1; H, 6.7.

6-Methoxy-8-(ω-phthalimidoalkylamino)-quinolines.—These were prepared by a modification of the method of Ing and Manske[12] of which the preparation of 6-methoxy-8-(6′-phthalimidohexylamino)-quinoline is representative. A solution of 85 g. of 6-bromohexylphthalimide and 73 g. of 6-methoxy-8-aminoquinoline in 150 ml. of isopropyl alcohol was heated in an open round-bottom flask in an oil-bath at an initial temperature of 80°. The temperature was raised to 125° over thirty minutes and then held at 125–130° for an additional hour and a half. During the course of the heating, the isopropyl alcohol evaporated and the residual solid was broken up occasionally with a stout stirring rod. To the warm melt 500 ml. of benzene was added and the mixture was digested on the steam-bath for ten minutes. Insoluble 6-methoxy-8-aminoquinoline hydrobromide was filtered off, and the filtrate was concentrated. On cooling, 6-methoxy-8-(6′-phthalimidohexylamino)-quinoline crystallized. After recrystallization from acetone, it melted at 126–127°. The yield was 60 g. or 70% based on the 6-methoxy-8-aminoquinoline available for the reaction.

Anal. Calcd. for $C_{24}H_{25}N_3O_3$: C, 71.4; H, 6.3. Found: C, 71.5; H, 6.5.

6-Methoxy-8-(8′-phthalimidoöctylamino)-quinoline.—This was prepared as was the hexyl compound, except that the free base crystallized only after being rubbed up in acetone–alcohol. It melted at 88–89°. The yield was 72%.

(9) All melting points are corrected.

(10) Microanalyses by the Misses Lois May and Lathrope Baker.

(11) Muller and Kraus, *Monatsh.*, **61**, 219 (1932).

(12) Ing and Manske, *J. Chem. Soc.*, 2348 (1926).

TABLE I

AMINOALKYL DERIVATIVES OF 8-AMINOQUINOLINE

	SN	R₈	Other R's	Yield, %	M. p. of di-HCl, °C.	Analyses, % Calculated C	Calculated H	Found C	Found H
1	11,645	$NH(CH_2)_3NH_2$	$R_5 = R_6 = OCH_3$	93	207.5–208	50.3	6.3	50.4	6.6
2	12,352	$NH(CH_2)_6NH_2$	$R_6 = OCH_3$	72	189 –190	55.5	7.2	55.5	7.4
3	12,354	$NH(CH_2)_6NH_2$	$R_5 = R_6 = OCH_3$	70	204 –205	54.2	7.2	54.0	7.4
4	5,692	$NH(CH_2)_{10}NH_2$	$R_6 = OCH_3$	64	171 –172	59.7	8.2	59.7	8.5

Anal. Calcd. for $C_{26}H_{29}N_3O_3$: C, 72.3; H, 6.8. Found: C, 72.1; H, 6.8.

6-Methoxy-8-(10′-phthalimidodecylamino)-quinoline.—This was prepared as in the above cases and purified by conversion of the oily free base to the hydrochloride, which melted at 157–158° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{28}H_{34}ClN_3O_3$: C, 67.7; H, 6.9. Found: C, 67.4; H, 6.9.

The free base, regenerated from the hydrochloride, melted at 69–70° after crystallization from alcohol.

5,6-Dimethoxy-(3′-phthalimidopropylamino)-quinoline.—A modification of the method of Magidson and Bobyshev[7] was used. A mixture of 44.5 g. of 3-phthalimidopropylchloride, prepared from trimethylene chlorobromide according to the method given in "Organic Syntheses"[13] for the preparation of bromoethylphthalimide, 37 g. of sodium iodide and 49 g. of 5,6-dimethoxy-8-aminoquinoline[8] was refluxed in 200 ml. of absolute alcohol for sixteen hours. The mixture was carefully diluted and on standing overnight a brown, crystalline mass contaminated with tar separated. This was filtered off and taken up in 1500 ml. of hot alcohol. The filtered alcohol solution deposited 41 g. of tan needles on cooling. Three recrystallizations from alcohol (600 ml.) (charcoal) gave 23 g. of 5,6-dimethoxy-8-(3′-phthalimidopropylamino)-quinoline melting at 125–125.5°. This was used directly for hydrolysis.

5,6-Dimethoxy-8-(6′-phthalimidohexylamino)-quinoline.—This was prepared by the method used for the corresponding 6-methoxy derivative, the reactants being heated at 110–115° for one and one-half hours. It formed greenish yellow needles from alcohol and melted at 89–90°.

Anal. Calcd. for $C_{25}H_{27}N_3O_4$: C, 69.3; H, 6.5. Found: C, 69.5; H, 6.5.

8-(ω-Aminoalkylamino)-quinolines.—The phthalimido group in the above substances was cleaved by the hydrazine method of Ing and Manske.[12] With the exception of 6-methoxy-8-(8′-aminoöctylamino)-quinoline (SN-13,082),[14] the drugs were isolated as the dihydrochlorides by cautiously passing dry hydrogen chloride into the dry ether solutions of the bases. The hydrochloride of 6-methoxy-8-(8′-aminoöctylamino)-quinoline could not be readily purified. Accordingly the base was isolated as the oxalate which melted at 105–108° and was analyzed by the method previously described.[15]

Anal. Base content of the oxalate found: 71.9%. Oxalic acid content found: 25.5%. Calcd. for salt of base content, 71.9%: C, 59.0; H, 7.1. Calcd. for salt of oxalic content, 25.5%: C, 60.2; H, 7.3. Found: C, 58.9; H, 7.3.

The properties and analyses of the other compounds are summarized in Table I.

Summary

1. Five new 8-(ω-aminoalkylamino)-quinoline derivatives and two new ω-bromoalkylphthalimides have been described.

(13) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 2nd ed., p. 119.

(14) The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. The activities of these drugs will be tabulated in a forthcoming monograph.

(15) Elderfield, *et al.*, THIS JOURNAL, **68**, 1524 (1946).

NEW YORK 27, N. Y. RECEIVED APRIL 5, 1946

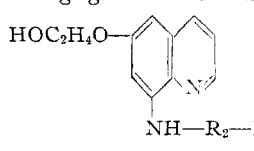
[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Studies in the Quinoline Series. V. Some 6-β-Hydroxyethoxy-8-(ω-monoalkylaminoalkylamino)-quinolines

BY MARCUS S. MORGAN AND R. STUART TIPSON

As reported in a previous publication[1] from this Laboratory, an investigation was undertaken with the object of synthesizing a less toxic analog of pamaquine, the approach employed consisting in the substitution of a β-hydroxyethoxy group in place of the methoxy group at position 6 of the quinoline nucleus. The two 6-β-hydroxyethoxy-8-(ω-diethylaminoalkylamino)-quinolines then described were found to be considerably less toxic than pamaquine to mice, but also less active against avian malarial infections. Consequently, the Survey of Antimalarial Drugs[2] suggested that an 8-ω-*mono*alkylaminoalkyl derivative might exhibit enhanced antimalarial activity and that the synthesis of a series of such drugs be undertaken. This suggestion was based on results obtained by other investigators (in the 6-*methoxy* series) indicating that a terminal secondary amine group on the side-chain (at the 8-position) considerably augmented plasmodicidal activity in avian malarias.

We now describe the preparation of six 6-β-hydroxyethoxy - 8 - (ω - *mono* - alkylaminoalkylamino)-quinolines and their dihydrochlorides. In the following general formula the variables



(1) Morgan and Cretcher, THIS JOURNAL, **68**, 781 (1946).

(2) Private communication from Dr. F. Y. Wiselogle.