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

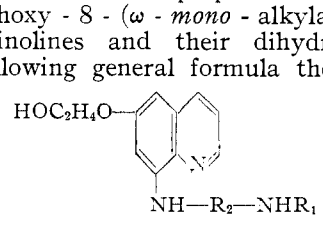
[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

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.

TABLE I

MELTING POINTS AND ANALYSES[a] OF SOME 6-β-HYDROXYETHOXY-8-(ω-MONO-R_1-AMINO-R_2-AMINO)-QUINOLINES

			Bases								Dihydrochlorides				
					Analyses, %							Analyses, %			
			M. p.,		Carbon		Hydrogen		Nitrogen		M. p.,	Nitrogen		Chlorine	
R_1	R_2	SN[b]	°C.	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	°C.	Calcd.	Found	Calcd.	Found
Ethyl	Ethyl	14,933[c]	70–72	$C_{15}H_{21}N_3O_2$	65.43	65.18	7.7	7.5	15.26	14.81	216–218	12.07	11.55	20.36	19.81
Isopropyl	Ethyl	14,999[c]	79–81	$C_{16}H_{23}N_3O_2$	66.39	66.34	8.0	8.1	14.53	14.73	245–247	11.60	12.14	19.57	19.49
Ethyl	Propyl	14,842[c]	87–88	$C_{16}H_{23}N_3O_2$	66.39	66.27	8.0	8.0	14.53	14.62	188–190	11.60	11.48	19.57	18.78
Isopropyl	Propyl	14,993[c]	88–90	$C_{17}H_{25}N_3O_2$	67.28	67.28	8.3	8.2	13.86	13.55	216–218	11.17	11.45	18.84	18.90
Ethyl	Hexyl	15,252[d]	66–68	$C_{19}H_{29}N_3O_2$	68.83	68.34	8.8	8.7	12.69	12.66	194–195	10.39	10.52	17.54	17.40
Isopropyl	Hexyl	15,281[d]	101–103	$C_{20}H_{31}N_3O_2$	69.53	69.45	9.1	9.0	12.16	11.97	140–142[e]	10.04	9.56	16.95	17.00

[a] Some of these microanalyses were performed by G. L. Stragand of the University of Pittsburgh. [b] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. [c] From the alkylaminoalkyl chloride hydrochloride. [d] From the alkylaminoalkyl bromide hydrobromide. [e] Sintered at 125–127°.

investigated were as follows: R_1 = ethyl and isopropyl; R_2 = ethyl, propyl and hexyl. Contrary to expectations, these compounds appear to have lower antimalarial potencies than had the two drugs previously reported.[1] A detailed account concerning the pharmacological assays of these compounds will be found in a forthcoming monograph, "A Survey of Antimalarial Drugs, 1941–1945," edited by F. Y. Wiselogle, under the auspices of the National Research Council.

Since 6-hydroxy-8-nitroquinoline is best obtained by dealkylation of a corresponding 6-alkyl ether, it was considered expedient to start with the readily available, inexpensive 3-nitro-4-aminoanisole (in preference to the corresponding phenetole derivative) from which pure 6-methoxy-8-nitroquinoline was prepared[3] in 80% yield. A study of the rate of demethylation of the 6-methoxy derivative with 65% sulfuric acid indicated that the maximum yield (77%) of pure 6-hydroxy-8-nitroquinoline is obtained after refluxing for seventy-two hours, whereas Magidson and Strukov[4] reported a 97% yield from the 6-ethoxy derivative after heating for sixty hours. More rapid and complete demethylation was accomplished with hot hydrobromic acid (48%), the phenolic base being obtained in 91% yield after refluxing for some four hours.

Hydroxyethylation and reduction to 6-hydroxyethoxy-8-aminoquinoline were conducted essentially as previously described[1]. The latter was condensed with the appropriate monoalkylaminoalkyl halide hydrohalide and the product isolated as crystalline, free base. The melting points and analyses of the bases and their crystalline dihydrochlorides are presented in Table I, from which it may be seen that, when R_1 is increased from ethyl to isopropyl, the melting point is raised.

Experimental

6-Methoxy-8-nitroquinoline was prepared by the Skraup reaction as modified by Strukov,[3] with the following improvements. Glycerol (U. S. P., 438 g.) was treated with 200 g. of 3-nitro-4-aminoanisole (du Pont), 142.5 g. of arsenic pentoxide, and 113 cc. of concentrated sulfuric acid. After the removal of 91 cc. of water at 100° (20 mm.), and dropwise addition of a further 85 cc. of concentrated sulfuric acid during two hours under reflux, the mixture was kept overnight at room temperature and then treated as usual[3]; yield of crude product, 92%. This was finely powdered and extracted with ten volumes of boiling ethylene dichloride under reflux, giving tan-colored crystals, m. p. 161–162° (80% yield).

For analysis it was purified by dissolving in chloroform and extracting with 8 *N* sodium hydroxide solution. The chloroform solution was washed, dried, and evaporated to dryness, yielding very pale yellow crystals which were recrystallized from three volumes of boiling ethylene dichloride; m. p. 162–163°. *Anal.* Calcd. for $C_{10}H_8N_2O_3$: C, 58.80; H, 4.0; N, 13.73. Found: C, 58.65; H, 4.2; N, 13.90. I. G. Farbenindustrie[5] gave m. p. 154°; Magidson and Strukov,[4] m. p., 157–159°; Misani and Bogert,[6] m. p. 162–164°.

6-Hydroxy-8-nitroquinoline. (a) **Using 65% Sulfuric Acid.**—Demethylation was conducted by a modification of the method applied by Magidson and Strukov[4] to the 6-ethoxy derivative. Dry, recrystallized 6-methoxy-8-nitroquinoline (190 g.) was placed in a 2-necked, 1-liter flask (ground glass joints, thermometer), 760 cc. of cooled 65% sulfuric acid was added and the solution boiled (inner temp., 140–145°) under reflux for the stated period of time. The mixture was then cooled to 60° only (to avoid crystallization), poured onto 2 liters of ice-water, the product isolated as usual[4] (*p*H 7.6–8.0), and then freed from unhydrolyzed 6-methoxy derivative by extraction with 5 volumes of boiling ethylene dichloride under reflux. The yields of crude product (m. p. 226°) were as follows: 15% (7 hours); 48% (24 hours); 83% (48 hours); 86% (72 hours); 82% (96 hours). It was now freed from some acetone-insoluble impurity (found: S, 1.9%) by extraction with 30 volumes of boiling acetone under reflux. The suspension was filtered while hot and the filtrate evaporated to dryness under diminished pressure, giving material which was re-extracted with 5 volumes of ethylene dichloride to remove final traces of 6-methoxy derivative. The yields were then: 75% (48 hours); 77% (72 hours); 69% (96 hours).

For analysis it was purified by dissolving 10 g. in 40 cc. of water plus 10 cc. of 8 *N* sodium hydroxide, filtering, and adding 3 *N* hydrochloric acid dropwise to *p*H 7.6 to 8.0. The yellow solid was then filtered off, washed with water, and dried; wt., 9.8 g.; m. p. 232–233°. Magidson and Strukov[4] gave m. p., 230° (dec.); I. G. Farbenindustrie,[5] m. p. 239–240° (dec.). *Anal.* Calcd. for $C_9H_6N_2O_3$: C, 56.82; H, 3.2; N, 14.74. Found: C, 56.80; H, 3.5; N, 14.80.

(b) **Using 48% Hydrobromic Acid.**—This method was suggested in a German Patent[5] but no details are available. 6-Methoxy-8-nitroquinoline (50 g.) was dissolved in 250 cc. of hydrobromic acid (48%) in a 500-cc. flask fitted with a condenser set for distillation and a thermometer. The temperature was gradually raised until all the methyl bromide had been removed and the distillation temperature was that of the constant-boiling acid. The condenser was then changed to total reflux and heating was continued during four hours. The suspension of yellow crystals was cooled, filtered through a fritted glass funnel, and the filtrate concentrated to about one-third its volume (thereby

(3) Strukov, *Org. Chem. Ind.* (U. S. S. R.), **4**, 523 (1937).

(4) Magidson and Strukov, *Arch. Pharm.*, **271**, 359 (1933).

(5) I. G. Farbenindustrie, German Patent 451,730 (*Chem. Zentr.*, **99**, I, 414 (1928)).

(6) Misani and Bogert, *J. Org. Chem.*, **10**, 347 (1945).

recovering much acid, and a small second crop of product from the residue).

Sufficient sodium hydroxide solution was added to an aqueous suspension of the hydrobromide just to dissolve the liberated phenolic base, the solution filtered, and the filtrate rendered neutral with 5 *N* hydrochloric acid (to *p*H 7.6–8.0). After washing with water and drying, the precipitated 6-hydroxy-8-nitroquinoline weighed 45 g., and had m. p. 225–227° (dec.). To ensure complete removal of any 6-methoxy derivative, the product was extracted with 5 volumes of boiling ethylene dichloride under reflux for one hour. The tan powder weighed 42.3 g. (91%) and had m. p., 226–228° (dec.).

6-Hydroxyethoxy-8-nitroquinoline was prepared as described by Morgan and Cretcher.[1] It is important that the three reactants be thoroughly mixed before heating and that the mixture should be gently heated until molten. The molten mass was then heated at 95°, with stirring, for two and a half hours; yield, 95 to 98%; m. p. 161–163°. It was purified by extraction with 22 volumes of boiling absolute methanol, giving crystals with a silvery sheen (m. p. 163–164°) which were then recrystallized from 25 volumes of boiling ethylene dichloride; yield, 86% of the theoretical; m. p., 163–164.5°.

6-Hydroxyethoxy-8-aminoquinoline was prepared by catalytic reduction of the nitro derivative as previously described,[1] except that a suspension of 15 g. of the nitro compound in 100 cc. of absolute methanol was employed, and water was removed from the reduction product by dissolving in absolute ethanol and reëvaporating to dryness.

General Method[7] for Preparation of 6-β-Hydroxyethoxy-8-(ω-monoalkylaminoalkylamino)-quinolines.—A mixture of 20 g. of distilled, crystalline 6-hydroxyethoxy-8-aminoquinoline, 1 equivalent of the monoalkylaminoalkyl halide hydrohalide,[8] and 2 equivalents of powdered, fused, anhydrous sodium acetate was dissolved in 50 cc. of 50% aqueous ethyl alcohol and boiled under reflux during seventy-two hours. The reaction mixture was then cooled, filtered,[9] the crystals of sodium chloride washed with absolute ethanol, and the filtrate evaporated to dryness under diminished pressure, giving a brown gum having an odor of acetic acid and ethyl acetate. This was dissolved by shaking with 100 cc. of water plus 100 cc. of chloroform, and the aqueous layer re-extracted with three 100-cc. portions of chloroform.

Except in the case of the two monoalkylamino*hexyl* derivatives, the chloroform extracts contained a preponderance of unreacted 6-hydroxyethoxy-8-aminoquinoline and the chloroform-extracted aqueous layer contained the alkylated product plus free "sidechain derivative." The united *chloroform extracts* were shaken with aqueous potassium carbonate until neutral, dried with anhydrous sodium sulfate, and evaporated to dryness, giving a brown gum or a crystalline mass. This was dissolved in 7 volumes of boiling chloroform, cooled, and kept overnight in the refrigerator, yielding a first crop of recovered 6-hydroxyethoxy-8-aminoquinoline. A second crop was isolated by adding to the mother liquor an equal volume of hexane.

The *aqueous layer* was cooled and a solution of potassium carbonate (60 g. in 90 cc. of water, cooled to +5°) added with shaking. The precipitated base was extracted with four 100-cc. portions of chloroform and the united chloroform extracts dried with anhydrous sodium sulfate and evaporated to dryness, yielding a brown, fairly mobile sirup of crude product.

6-β-Hydroxyethoxy-8-(2′-monoethylaminoethylamino)-quinoline.—The crude material (11.8 g.) was dissolved in seven volumes of chloroform at room temperature, 10 volumes of hexane were cautiously added, some dark gum (1.1 g.) filtered off, and the filtrate evaporated to dryness under diminished pressure. The resulting brown sirup was then extracted with two 200-cc. portions of dry ether, and the extracts evaporated to give an orange, viscous oil (7.9 g.). This was extracted with ten volumes of hexane and the undissolved material treated with a small volume of ether and kept overnight in the refrigerator, giving buff-colored crystals (4.3 g.); m. p. 62–69°. After lixiviating with ether, and drying, it weighed 3.3 g. and had m. p. 67.5–70°. It was recrystallized by dissolving in a mixture of 15 volumes of ether plus 5 volumes of chloroform, cooling, filtering from a trace of gummy substance, seeding, and then slowly adding 75 cc. of pentane. A second crop was obtained by combining the ether filtrate and washings, evaporating to dryness, and treating the residue as for the recrystallization of crop 1.

6-β-Hydroxyethoxy-8-(2′-monoisopropylaminoethylamino)-quinoline.—The crude product (12.7 g.) was dissolved in seven volumes of chloroform, 15 volumes of hexane were added, the solution filtered from some dark resinous matter, and the filtrate evaporated to dryness. The resulting red sirup (10.6 g.) was dissolved in 200 cc. of dry ether, filtered, and the filtrate evaporated to dryness. After extracting the residue with ten volumes of hexane, it was dissolved in ten volumes of dry ether and 25 cc. of pentane were added, precipitating a red, oily substance (A) on cooling. The supernatant liquid (B) was decanted and A was dissolved in 25 cc. of ether. On cooling in the refrigerator, this solution deposited a crop (2.1 g.) of crystals. Pentane (25 cc.), was added to B, and the solution seeded and cooled, giving a further crop (3.1 g.) of tan-colored crystals; total yield of crystalline base, 5.2 g.

6-β-Hydroxyethoxy-8-(3′-monoethylaminopropylamino)-quinoline.—This crude product (10.5 g.) crystallized spontaneously on standing overnight in the refrigerator. It was dissolved in seven volumes of chloroform at room temperature, ten volumes of hexane were cautiously added, a trace of dark brown flocculent impurity filtered off, and the filtrate evaporated to dryness under diminished pressure. The brown sirup was extracted with two 200-cc. portions of dry ether and the extracts decanted through a fluted filter (wt. of insol., 0.9 g.). The product then crystallized spontaneously; after keeping overnight in the refrigerator, it was filtered off, washed with dry ether (3 × 25 cc.) and dried, giving 4.2 g. of very pale yellow crystals.

6-β-Hydroxyethoxy-8-(3′-monoisopropylaminopropylamino)-quinoline.—The crude product (11.5 g.) was dissolved in seven volumes of chloroform, fifteen volumes of hexane were added, a trace of flocculent impurity filtered off, and the filtrate evaporated to dryness. The brown sirup was dissolved in 100 cc. of dry ether, filtered, and kept in the refrigerator. The crystalline product was filtered off, washed with dry ether and dried; wt., 4.8 to 5 g.; m. p., 88–90°. The product (5 g.) was recrystallized by dissolving in 4 volumes of cold chloroform and adding 8 volumes of dry ether to give rosets of colorless, feathery needles (4 g.).

6-β-Hydroxyethoxy-8-(6′-monoethylaminohexylamino)-quinoline.—The *aqueous layer* (when neutralized, extracted with chloroform, and the chloroform layer evaporated to dryness) gave only 4.5 g. of dark brown, very mobile sirup from which no product could be isolated. The *chloroform extracts* were rendered neutral and evaporated to dryness, yielding 27 g. of a dark brown gum. By a series of fractional precipitations and crystallizations from chloroform (7 volumes) and hexane (*e. g.*, 7 + 7 + 7 volumes) this was separated into three main fractions (together with intermediate fractions): the least soluble, *viz.*, recovered 6-hydroxyethoxy-8-aminoquinoline (8.4 g.); *product* (10.5 g.); and hexane-soluble, free "side-chain derivative."

Five grams of product was recrystallized by dissolving in 50 cc. of dry ether, adding 50 cc. of hexane and keeping in the refrigerator, to give almost colorless crystals (4 g.).

6-β-Hydroxyethoxy-8-(6′-monoisopropylaminohexylamino)-quinoline.—The aqueous layer was similar to that obtained in the previous experiment. The *chloroform extracts* were neutralized and evaporated to dryness, yielding 28.2 g. of a dark brown gum which was dissolved in 4 volumes of chloroform and treated with 12 volumes of hexane to precipitate a gum (A). The supernatant liquor was evaporated to dryness (8.6 g.), lixiviated with hexane

(7) Suggested, in part, by Dr. Robert C. Elderfield.

(8) Kindly presented by Dr. Robert C. Elderfield of Columbia University.

(9) When bromide hydrobromides were employed, there was, of course, no crystallization of sodium bromide.

(10 volumes) and the undissolved residue kept in the refrigerator, where it crystallized after several days. This *product* was washed with ten volumes of dry ether to give 5.4 g. of pure material.

By a series of fractional precipitations from chloroform and hexane as in the previous experiment, fraction A was further separated into two main fractions (together with intermediate fractions). The less soluble was unchanged 6-hydroxyethoxy-8-aminoquinoline and the more soluble contained the product. On evaporating the chloroform-hexane filtrate to dryness, there was obtained 4.8 g. of an orange-colored viscous gum. To a solution of this gum in dry ether (10 volumes) plus several cc. of chloroform was added hexane (10 cc.), which precipitated a light red oil. The oil was crystallized by seeding, followed by the portionwise addition of hexane (10 volumes) to give a second crop weighing 3.8 g.; total yield of product, 9.2 g. The product (5 g.) was recrystallized from ten volumes of hot benzene to give 4.3 g. of buff-colored crystals.

Dihydrochlorides.—The pure base (2 g.) was dissolved in 40 cc. of absolute ethanol and the solution treated with an excess (3 to 4 g.) of dry hydrogen chloride. (The first four compounds listed in Table I readily formed yellow crystalline precipitates, whereas the last two only deposited orange crystals after standing in the refrigerator for a day or two.) The dihydrochloride was filtered off on a Büchner funnel with the aid of a rubber dam and dried in a vacuum desiccator over phosphorus pentoxide and soda lime.

Acknowledgment.—The authors express their gratitude to Miss A. Farley Walton for extensive technical assistance in the preparation of relatively large amounts of 6-hydroxyethoxy-8-aminoquinoline and its intermediates, and to Dr. Leonard H. Cretcher for his interest and encouragement.

Summary

A fairly detailed study of the demethylation of 6-methoxy-8-nitroquinoline has been made.

Six new monoalkylaminoalkyl derivatives of 6-β-hydroxyethoxy - 8 - aminoquinoline, together with their dihydrochlorides, have been prepared in crystalline form.

Their antimalarial activities have been ascertained, and compared with that of pamaquine.

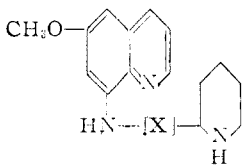
PITTSBURGH 13, PA. RECEIVED MAY 3, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

The Synthesis of Some Substituted 8-Aminoquinolines[1]

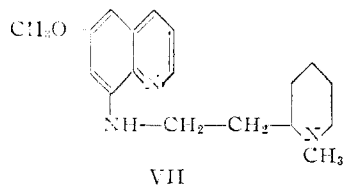
BY T. R. NORTON,[2] R. A. SEIBERT, A. A. BENSON AND F. W. BERGSTROM[3]

The antimalarial activities of the Ainley–King type piperidylquinolinemethanols suggested the combination of the 2-piperidyl group with the 8-amino-6-methoxyquinoline nucleus of pamaquine. A series of such analogs has been prepared in which the dialkylaminoalkylamino side chain of

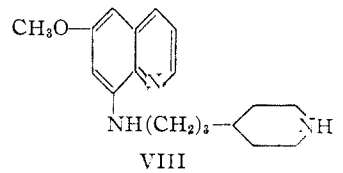


I, X = $CH_2{\cdot}CH_2$
II, X = $CH(CH_3)CH_2$
III, X = $(CH_2)_3$
IV, X = $(CH_2)_4$
V, X = $(CH_2)_6$
VI, X = $(CH_2)_7$

pamaquine has been replaced by piperidylalkylamino groups in order to investigate the effects of varying length and branching of the alkylene bridge (I to VI), methylation of the piperidine nitrogen (VII), and the use of a 4-piperidyl group (VIII).



VII



VIII

Addition of formaldehyde, acetaldehyde and ethylene oxide to ether solutions of 2-picolyllithium gave 2 - (2 - pyridyl) - ethanol - 1, 2-(2-pyridyl)-propanol-1 and 3-(2-pyridyl)-propanol-1, respectively. Catalytic hydrogenation of these alcohols and the N-methochloride of 2-(2-pyridyl)-ethanol-1 gave the corresponding piperidylalkanols which were converted to the piperidylalkyl chloride hydrochlorides by treatment with thionyl chloride. Addition of 2-chloroethyl methyl ether to the potassium salt of 4-picoline in liquid ammonia gave 3-(4-pyridyl)-1-methoxypropane. Similar reactions of 2-picolylpotassium with 3-methoxy-1-chloropropane, 5-methoxy-1-bromopentane and 6-methoxy-1-bromohexane gave 4 - (2 - pyridyl) - 1 - methoxybutane, 6-(2-pyridyl)-1-methoxyhexane and 7-(2 - pyridyl) - 1 - methoxyheptane, respectively. After hydrogenation of the pyridine nuclei the ethers were cleaved with hydrobromic acid to give good yields of the corresponding piperidylalkyl bromide hydrobromides.

Condensation of the piperidylalkyl halide hydrohalides with 8-amino-6-methoxyquinoline was carried out by heating the dry reactants in an inert atmosphere at 125–130° for twelve to twenty

(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 Stanford University.

(2) Present address: Great Western Division of Dow Chemical Company, Pittsburg, California.

(3) The untimely death of Professor Bergstrom occurred during the preparation of this manuscript.