(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.

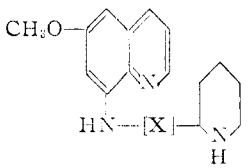
PITTSBURGH 13, PA. RECEIVED MAY 3, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

The Synthesis of Some Substituted 8-Aminoquinolines[1]

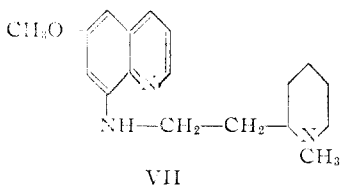
BY T. R. NORTON,[2] R. A. SEIBERT, A. A. BENSON AND F. W. BERGSTROM[3]

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

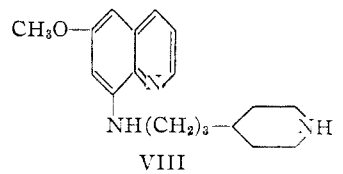


I, X = $CH_2{\cdot}CH_2$
II, X = $CH(CH_3)CH_2$
III, X = $(CH_2)_3$
IV, X = $(CH_2)_4$
V, X = $(CH_2)_6$
VI, X = $(CH_2)_7$

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.

hours. The predominant side reaction in this step was the cyclization of the side chain to form azabicyclic compounds. This was most pronounced with the 3-(2-piperidyl)-propyl and 4-(2-piperidyl)-butyl side chains in which cases five- and six-membered rings are formed.

Two pamaquine analogs were prepared with an 8-amino-5,6-dimethoxyquinoline nucleus. These compounds, 5,6-dimethoxy-8-[2-(2-piperidyl)-ethylamino]-quinoline and 5,6-dimethoxy-8-[3-(2-piperidyl)-propylamino]-quinoline were obtained in lower yield and were found to be more susceptible to air-oxidation than the monomethoxy analogs.

Acknowledgment.—We are indebted to Dr. J. B. Koepfli of the California Institute of Technology for his helpful suggestions during the course of this investigation and preparation of the manuscript.

Experimental[4]

2-Piperidylmethyl Chloride Hydrochloride.[5]—A solution of 19.6 g. of 2-piperidylcarbinol[6] in 100 ml. of chloroform was saturated with hydrogen chloride without cooling. The solution was then placed in an ice-bath and 25 ml. of pure thionyl chloride added with mechanical stirring. Heating under reflux caused considerable darkening but was continued for two hours. After the addition of 10 ml. of water to decompose excess thionyl chloride, the chloroform solution was extracted four times with 200-ml. portions of 6 *N* hydrochloric acid. Two treatments with Norit gave a light yellow solution which was evaporated to dryness on the water-bath at reduced pressure. The residue was taken up in 50 ml. of absolute alcohol. Addition of dry ether caused the separation of large colorless prisms of 2-piperidylmethyl chloride hydrochloride (16.4 g.) of m. p. 171–173°. Recrystallization of a sample from acetone–ethanol for analysis raised the melting point to 177–178°.

Anal. Calcd. for $C_6H_{12}NCl\cdot HCl$: equiv. wt., 170.1. Found:[7] equiv. wt., 170.0, 168.7.

2-(2-Piperidyl)-1-chloroethane Hydrochloride.[8]—1-(2-Pyridyl)-2-ethanol, prepared from 2-picolyllithium by the method of Finkelstein and Elderfield,[9] was catalytically hydrogenated in ethanol solution over Raney nickel catalyst at 150° and 130 atmospheres pressure to give a 66% yield of 2-(2-piperidyl)-1-ethanol,[10,11] b. p. 90–95° (2 mm.). Treatment of 21.6 g. of 2-(2-piperidyl)-1-ethanol with thionyl chloride in the manner described above gave 26.1 g. (85%) of colorless crystals, m. p. 148–150°, of 2-(2-piperidyl)-1-chloroethane hydrochloride.

Anal. Calcd. for $C_7H_{14}NCl\cdot HCl$: equiv. wt., 184.1. Found:[7] equiv. wt., 184.0.

6-Methoxy-8-[2-(2-piperidyl)-ethylamino]-quinoline Dihydrochloride (I) (SN 10,309).[12]—An intimately ground mixture of 25 g. of 8-amino-6-methoxyquinoline (Winthrop Chem. Co.) and 26.1 g. of 2-(2-piperidyl)-1-chloroethane hydrochloride was heated *in vacuo* at 130° for nineteen hours. The resultant orange mass was dissolved in hot water, cooled, and made alkaline. The ether extract of this mixture was dried and distilled. The 26.5 g. (65%) of yellow oil, b. p. 180–190° (0.01 mm.) was converted to the hydrochloride by addition of excess methanolic hydrochloric acid to an ethanol solution of the base followed by addition of dry ether to induce crystallization. The yield of dihydrochloride was 27.5 g., m. p. 239–240°. Several recrystallizations from methanol raised the melting point to 242.5–243°.

Anal. Calcd. for $C_{17}H_{23}ON_3\cdot 2HCl\cdot H_2O$: C, 54.26; H, 7.23; equiv. wt., 188.1. Found:[13] C, 54.47; H, 7.25; equiv. wt., 186.5.[7]

5,6-Dimethoxy-8-[2-(2-piperidyl)-ethylamino]-quinoline Dihydrochloride (SN 13,141).—An intimately ground mixture of 8.5 g. of 1-(2-piperidyl)-2-chloroethane hydrochloride and 7.0 g. of 8-amino-5,6-dimethoxyquinoline[14] was heated at 125–130° for twenty hours *in vacuo*. The resultant red melt was taken up in water and made alkaline with excess potassium hydroxide solution. The product was extracted twice with ether and the aqueous phase removed to leave a considerable amount of black tar. Most of the tar was found to be soluble in ether when shaken with both ether and anhydrous potassium carbonate. The combined ether solutions were evaporated and the residual oil was distilled to give the following fractions: 1.0 g. of yellow oil, b. p. 70–80° (30 mm.); 0.8 g. of viscous yellow oil, b. p. 140–150° (0.1 mm.); 6.3 g. of light red oil, b. p. 190–210° (0.1 mm.). The last fraction is a 40% yield of the desired product which was converted to the dihydriodide by addition of the theoretical amount of 70% hydriodic acid to an ethanol solution of the free base. The salt separated upon careful addition of dry ether as hygroscopic red crystals, m. p. 164–165.5° (dec. begins at 151°).

Anal. Calcd. for $C_{18}H_{25}O_2N_3\cdot 2HI$: C, 37.83; H, 4.76. Found: C, 37.54; H, 4.96.

2-(1-Methyl-2-piperidyl)-1-chloroethane Hydrochloride.—A solution of 80 g. of 2-(2-pyridyl)-ethanol and 95 g. of methyl iodide was warmed to 40° for three hours and finally at 80° for two hours. The viscous methiodide was converted to the methochloride by addition of 200 ml. of water and equimolar silver chloride. The solution was shaken for twelve hours, filtered, and evaporated to dryness. The residue was taken up in 100 ml. of absolute ethanol and hydrogenated at 60° in nine hours with Adams catalyst and 3 atmospheres pressure. Upon removal of the catalyst and evaporation of the solvent, a portion of the residue was treated with alkali to obtain the free base, 2-(1-methyl-2-piperidyl)-ethanol,[15] b. p. 80° (2 mm.). The crude hydrochloride was treated with thionyl chloride for two hours in the previously described manner. The white crystalline residue, m. p. 105–110°, weighed 73 g. (55% yield based on 2-(1-methyl-2-pyridyl)-ethanol). A portion was recrystallized from acetone to give a pure product, m. p. 132–133°. Another run with pure 2-(1-methyl-2-piperidyl)-ethanol gave an 80% yield.

Anal. Calcd. for $C_8H_{16}NCl$: equiv. wt., 198.1. Found:[7] equiv. wt., 199.5, 200.2.

6-Methoxy-8-[2-(1-methyl-2-piperidyl)-ethylamino]-quinoline (VII) (SN 13,144).—An intimately ground mixture of 21.4 g. of 2-(1-methyl-2-piperidyl)-chloroethane hydrochloride and 19 g. of 8-amino-6-methoxyquinoline was heated *in vacuo* for fourteen hours at 130°. Isolation of the product as described above gave 5.5 g. of 8-amino-6-methoxyquinoline, b. p. 130–150° (0.1 mm.) and 24.2 g. (75% yield) of yellow viscous oil, b. p. 180–190° (0.1 mm.). The latter was converted to 25 g. of orange crystalline di-

(4) All melting points are corrected.

(5) A preliminary condensation of 2-piperidylmethyl chloride hydrochloride with 8-amino-6-methoxyquinoline gave a mixture of the desired product and starting material separation of which was impossible due to the proximity of their boiling points.

(6) The 2-piperidylcarbinol used in this synthesis was kindly supplied by C. S. Pease and B. E. Christensen of Oregon State College.

(7) Equivalent weight by potentiometric silver nitrate titration.

(8) Löffler, *Ber.*, **37**, 1879 (1904).

(9) Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939).

(10) Ladenburg, *Ber.*, **22**, 2583 (1899).

(11) Marvel and Shelton, THIS JOURNAL, **51**, 915 (1929).

(12) 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.

(13) Microanalyses are by Dr. E. W. D. Huffman, Denver, Colorado, unless otherwise indicated.

(14) Kindly provided by Dr. R. C. Elderfield of Columbia University.

(15) Ladenburg, *Ber.*, **24**, 1619 (1891).

hydrochloride. A sample, recrystallized from absolute ethanol and washed with dry acetone, had m. p. 218–219°.

Anal. Calcd. for $C_{18}H_{25}ON_3 \cdot 2HCl$: C, 58.07; H, 7.33. Found: C, 58.09; H, 7.34.

1-(2-Piperidyl)-2-chloropropane Hydrochloride.[16]—Treatment of 49 g. of 1-(2-piperidyl)-2-propanol,[17,18,19] b. p. 83° (2 mm.), m. p. 48–55°, with thionyl chloride in the described manner gave 52.6 g. (78%) of the desired product, m. p. 168–170°, after crystallization from 2-propanol.

Anal. Calcd. for $C_8H_{16}NCl \cdot HCl$: equiv. wt., 198. Found:[7] equiv. wt., 201, 200.

6-Methoxy-8-[2-(2-piperidyl)-1-methyl-1-ethylamino]-quinoline Dihydriodide (II) (SN 13,140).—A mixture of 47.5 g. (0.24 mole) of 1-(2-piperidyl)-2-chloropropane hydrochloride and 46 g. (0.26 mole) of 8-amino-6-methoxyquinoline was heated *in vacuo* for twenty hours at 130°. The products, isolated as previously described, gave the following fractions upon distillation: 4.6 g., b. p. 86–87° (18 mm.); 32.5 g. of unreacted 8-amino-6-methoxyquinoline, b. p. 128–168° (0.1 mm.); 19.5 g. (27% yield) of yellow viscous oil, b. p. 190–203° (0.1 mm.). The product was converted to 34.5 g. of dihydriodide, orange solid, m. p. 189–191°.

Anal. Calcd. for $C_{18}H_{25}ON_3 \cdot 2HI$: C, 38.93; H, 4.91. Found: C, 38.94; H, 5.09.

3-(2-Piperidyl)-1-chloropropane Hydrochloride.—Hydrogenation of 3-(2-pyridyl)-1-propanol[17] in acetic acid solution at 80–90° using Adams catalyst gave quantitative yields of 3-(2-piperidyl)-1-propanol,[20] b. p. 102–103° (3 mm.), hydrochloride, m. p. 129–131°. Treatment of 61 g. of 3-(2-piperidyl)-1-propanol with 70 ml. of thionyl chloride in the described manner gave 82 g. (86%) of colorless needles, m. p. 157–159°; (acetyl derivative, b. p. 135–137° (2 mm.)).

Anal. Calcd. for $C_8H_{16}NCl \cdot HCl$: C, 48.53; H, 8.65. Found:[21] C, 48.26; H, 8.88.

Benzoyl derivative, b. p. 140–142° (0.018 mm.).

Anal. Calcd. for $C_{15}H_{20}ONCl$: C, 67.80; H, 7.57. Found: C, 67.90; H, 7.53.

6-Methoxy-8-[3-(2-piperidyl)-propylamino]-quinoline (III) (SN 11,888).—An intimately ground mixture of 40 g. (0.20 mole) of 1-(2-piperidyl)-3-chloropropane hydrochloride and 35 g. (0.20 mole) of 8-amino-6-methoxyquinoline was heated at 130° for twenty hours and worked up as described above. The following fractions were obtained upon distillation: 14 g. of piperolidine,[22] b. p. 55–60° (20 mm.) (b. p. 158° (760 mm.), chloroaurate, m. p. 192–197°, mercurichloride, m. p. 241–242°); 24 g. of 8-amino-6-methoxyquinoline, b. p. 130° (0.015 mm.); 14 g. of 6-methoxy-8-[3-(2-piperidyl)-propylamino]-quinoline, b. p. 187° (0.025 mm.). The desired base formed a sesquihydrate, m. p. 70–73°, in moist ether and was recrystallized as such from this solvent.

Anal. Calcd. for $2C_{18}H_{25}ON_3 \cdot 3H_2O$: H_2O, 8.30. Found: H_2O, 8.48.

The water was removed by drying over phosphorus pentoxide to give the anhydrous base.

Anal. Calcd. for $C_{18}H_{25}ON_3$: C, 72.20; H, 8.41; N, 14.03. Found: C, 72.23; H, 8.46; N, 14.00.

The dihydrochloride trihydrate, m. p. 207–208.5°, was recrystallized from absolute ethanol. Drying over phosphorus pentoxide gave the anhydrous salt and exposure to the air gave a stable monohydrate.

Anal. Calcd. for $C_{18}H_{25}ON_3 \cdot 2HCl \cdot H_2O$: C, 55.40; H, 7.49; N, 10.76; Cl, 18.15. Found: C, 55.74; H, 7.45; N, 11.21; Cl, 17.89.

5,6-Dimethoxy-8-[3-(2-piperidyl)-propylamino]-quinoline (SN 12,483).—A solution of 60 g. (0.294 mole) of 8-amino-5,6-dimethoxyquinoline[14] and 60 g. (0.303 mole) of 3-(2-piperidyl)-1-chloropropane hydrochloride in 180 ml. of absolute ethanol was refluxed by means of an oil-bath kept at 110–120° for forty-eight hours. To the cooled solution were added ice, excess 25% potassium hydroxide, and potassium carbonate. The aqueous solution was extracted with ether and the ether solution was dried and distilled at reduced pressure on the steam-bath to remove most of the solvents. When the residue was 110 ml. in volume it was poured into a beaker and cooled in an ice-bath to deposit 20 g. (33%) of gold-green colored cyrstals of unreacted 8-amino-5,6-dimethoxyquinoline. The filtrate was distilled to give the following fractions: (1) 18 g. of piperolidine, b. p. 50–55° (16 mm.); (2) 4.3 g. of impure 8-amino-5,6-dimethoxyquinoline, b. p. 145–190° (0.2 mm.) (crystallized upon cooling); (3) 15.0 g. of 5,6-dimethoxy-8-[3-(2-piperidyl)-propylamino]-quinoline, b. p. 215–230° (0.2 mm.).

Fraction (3) (19% yield) was converted to a red crystalline dihydriodide with hydriodic acid as described above. The product was recrystallized from absolute ethanol; a little ether was added to induce crystallization. The yield, m. p. 167–171° (dec.), was 19.0 g. (69%).

Anal. Calcd. for $C_{19}H_{27}O_2N_3 \cdot 2HI \cdot H_2O$: equiv. wt., 301.7. Found:[7] equiv. wt., 302, 304.

A sample was dried at 61° (1 mm.) over phosphorus pentoxide for two hours. *Anal.* Calcd. for $C_{19}H_{27}O_2N_3 \cdot 2HI$: C, 38.99; H, 5.00; N, 7.18. Found: C, 38.71; H, 5.00; N, 7.43.

Attempts to condense the 8-amino-5,6-dimethoxyquinoline with 3-(2-piperidyl)-1-chloropropane hydrochloride without solvent failed; excellent yields of piperolidine were obtained.

3-(4-Pyridyl)-1-methoxypropane.—To a solution of 0.80 mole of 4-picolylpotassium[23] in 1 l. of liquid ammonia was added 75 g. (0.80 mole) of 2-chloroethyl methyl ether.[24] The residue obtained by the usual procedure was distilled at 17 mm. to give the following fractions: (1) 8.5 g. of fore-run, b. p. 80–118°; (2) 59.2 g. of product, b. p. 121–130°; (3) 9.0 g., b. p. 130–161°; 11.0 g. (probably dialkylated picoline), b. p. 161–164°.

Fraction (2) represents a 49.5% yield. A small sample was converted to the picrate in 95% ethanol and recrystallized from ethanol, m. p. 89–90°.

Anal. Calcd. for $C_{15}H_{16}O_8N_4$: C, 47.36; H, 4.24. Found: C, 47.37; H, 4.26.

3-(4-Piperidyl)-1-methoxypropane.—A solution of 56.2 g. of 3-(4-pyridyl)-1-methoxypropane in 100 ml. of glacial acetic acid was hydrogenated at 2–3 atmospheres pressuer with Adams catalyst in eighteen hours at 25°. Isolation of the product as described above gave 51.5 g. (87.5%) of 3-(4-piperidyl)-1-methoxypropane, b. p. 112° (17 mm.).

Anal. Calcd. for $C_9H_{19}ON$: equiv. wt., 157. Found:[7] equiv. wt., 158.

3-(4-Piperidyl)-1-bromopropane Hydrobromide.—A solution of 48.8 g. of 3-(4-piperidyl)-1-methoxypropane in 300 ml. of 48% hydrobromic acid was refluxed for three hours. The excess of hydrobromic acid was then removed by distillation at 20 mm. The crystalline residue was dissolved in hot absolute ethanol and dry ether was added. A voluminous precipitate of fine platelets deposited. The precipitate was removed by filtration and washed with dry ether. The dry product, m. p. 101–110°, weighed 80.5 g. (90%). A small sample recrystallized several times from absolute ethanol and ether melted at 125–127°.

Anal. Calcd. for $C_8H_{16}NBr \cdot HBr$: equiv. wt., 287. Found:[7] equiv. wt., 287.5, 289.

6-Methoxy-8-[3-(4-piperidyl)-propylamino]-quinoline (VIII) (SN 13,143).—A ground mixture of 75 g. (0.26 mole) of 3-(4-piperidyl)-1-bromopropane hydrobromide and 45.5

(16) Löffler and Tschunke, *Ber.*, **42**, 938 (1909).
(17) *Organic Syntheses*, **23**, 83 (1943).
(18) Hess, Uibrig and Eichel, *Ber.*, **50**, 344 (1917).
(19) Meisenheimer and Mahler, *Ann.*, **462**, 301 (1928).
(20) Löffler and Flügel, *Ber.*, **42**, 3420 (1909).
(21) Microanalysis by Bruce F. Day and Jack W. Ralls, University of California at Los Angeles.
(22) Löffler and Kaim, *Ber.*, **42**, 94 (1909).
(23) Bergstrom, Norton and Seibert, *J. Org. Chem.*, **10**, 452 (1945).
(24) Bennett and Heathcoat, *J. Chem. Soc.*, 268 (1929).

g. (0.26 mole) of 8-amino-6-methoxyquinoline was heated at 130° for sixteen hours. Isolation of the product in the previously described manner gave 16.7 g. of desired product, b. p. 178–225° (0.40 mm.). Addition of dry hydrogen chloride to an absolute ethanolic solution of the base gave a total of 16 g. (16.5%) of 6-methoxy-8-[3-(4-piperidyl)-propylamino]-quinoline dihydrochloride, m. p. 224–225°.

Anal. Calcd. for $C_{18}H_{25}ON_3 \cdot 2HCl$: C, 58.07; H, 7.31. Found: C, 58.06; H, 7.40.

4-(2-Pyridyl)-1-methoxybutane.—A solution of 0.30 mole of the potassium salt of 2-picoline in 500 ml. of liquid ammonia (prepared from 27.5 g. of 2-picoline and the potassium amide from 11.5 g. of potassium) was treated with 32 g. (0.3 mole) of 3-chloropropyl methyl ether.[25] Within five minutes the color of the potassium salt disappeared. When the ammonia had evaporated, the product was taken up in ether, washed with water, and dried. After removal of the solvent the product was distilled to give the following fractions: (1) 5.5 g., b. p. 48–120° (18 mm.), largely 2-picoline; (2) 34.0 g. of 4-(2-pyridyl)-1-methoxybutane, b. p. 122–125° (18 mm.); (3) 2.0 g. intermediate cut, b. p. 125–175° (18 mm.); (4) 1.3 g. of dialkylated picoline, b. p. 175° (18 mm.). The gold chloride salt of the desired product crystallized as yellow needles, m. p. 77–78°. The picrate, crystallized from ethanol, melted at 83–84°.

Anal. Calcd. for $C_{16}H_{18}O_8N_4$: C, 48.74; H, 4.60. Found: C, 48.72; H, 4.64.

4-(2-Piperidyl)-1-methoxybutane.—A solution of 34 g. of 4-(2-pyridyl)-1-methoxybutane in 100 ml. of glacial acetic acid was hydrogenated using 1.0 g. of Adams catalyst. The reduction was complete after shaking for ninety minutes at 70° and a pressure of 2–3 atmospheres. Isolation of the product in the usual manner gave 33 g. (94%) of 4-(2-piperidyl)-1-methoxybutane, b. p. 115–117° (18 mm.).

Anal. Calcd. for $C_{10}H_{21}ON$: equiv. wt., 171. Found: equiv. wt., 172.

4-(2-Piperidyl)-1-bromobutane Hydrobromide.—Hydrolysis of 60 g. of 4-(2-piperidyl)-1-methoxybutane in the manner described above for the trimethylene analog gave a dried product weighing 96 g. (91%), m. p. 106–111°. A small sample was recrystallized from absolute ethanol and ether, m. p. 108–110°.

Anal. Calcd. for $C_9H_{18}NBr \cdot HBr$: equiv. wt., 301. Found:[7] equiv. wt., 296, 297.

6-Methoxy-8-[4-(2-piperidyl)-butylamino]-quinoline (IV) (SN 13,129).—An intimately ground mixture of 38.6 g. (0.222 mole) of 8-amino-6-methoxyquinoline and 67 g. (0.222 mole) of 4-(2-piperidyl)-1-bromobutane hydrobromide was heated at 130–150° for sixteen hours. Isolation of the products in the described manner gave the following fractions upon distillation: (1) 7.5 g. of norlupinane (?), b. p. 68–80° (17 mm.); (2) 15.5 g. of impure 8-amino-6-methoxyquinoline, b. p. 100–185° (0.07 mm.); (3) 32.4 g. (46.6% yield based on unrecovered 8-amino-6-methoxyquinoline) of desired product, b. p. 190–205° (0.07 mm.).

An ether solution of the free base was treated with anhydrous hydrogen chloride to precipitate a yellow solid which gave 37 g. (81%) of crystals, m. p. 199–201° after being recrystallized from absolute ethanol and ether. A further recrystallization raised the melting point to 202–203°.

Anal. Calcd. for $C_{19}H_{27}ON_3 \cdot 2HCl$: C, 59.06; H, 7.57. Found: C, 59.04; H, 7.75.

A 5.0-g. sample of the free base (from another preparation) in ethanol gave, upon addition of 70% hydriodic acid, 6.0 g. of yellow-orange dihydriodide, m. p. 205–206°.

Anal. Calcd. for $C_{19}H_{27}ON_3 \cdot 2HI$: equiv. wt., 284. Found: equiv. wt., 285, 286.

6-(2-Pyridyl)-1-methoxyhexane.—1-Bromo-5-methoxypentane was prepared according to the method of Drake[26] in 56% yield, based upon the amount of pentamethylene dibromide[27] used less that recovered in the final distillation. A solution of 0.28 mole of 2-picolylpotassium (prepared from 10.8 g. of potassium and 25.8 g. of 2-picoline) in 500 ml. of liquid ammonia was treated with 50.0 g. (0.28 mole) of 1-bromo-5-methoxypentane in the usual manner. A 74% yield (39.3 g.) of product, b. p. 120–128° (5 mm.), was obtained.

Anal. Calcd. for $C_{12}H_{19}ON$: C, 74.53; H, 9.92. Found: C, 74.23; H, 10.24.

6-(2-Piperidyl)-1-methoxyhexane.—A solution of 30 g. of 6-(2-pyridyl)-1-methoxyhexane in 50 ml. of glacial acetic acid was hydrogenated in two hours at 70° using 1.0 g. of Adams catalyst. The 30 g. (97%) of product boiled at 151–152° (17 mm.).

Anal. Calcd. for $C_{12}H_{22}ON$: equiv. wt., 199. Found: equiv. wt., 199.5 (by acid titration).

6-(2-Piperidyl)-1-bromohexane Hydrobromide.—Hydrolysis of 25.7 g. of 6-(2-piperidyl)-1-methoxyhexane in the described manner gave a yield of 36.5 g. (86%), m. p. 95–98°.

Anal. Calcd. for $C_{11}H_{22}NBr \cdot HBr$: equiv. wt., 329. Found:[7] equiv. wt., 312.

6-Methoxy-8-[6-(2-piperidyl)-hexylamino]-quinoline (V) (SN 13,142).—A mixture of 20 g. of 8-amino-6-methoxyquinoline and 36.5 g. of 6-(2-piperidyl)-1-bromohexane hydrobromide was heated eighteen hours at 130° and worked up in the usual way. A yield of 24.5 g. (65%) of lemon-colored viscous oil, b. p. 215–225° (0.04 mm.), was obtained. This oil gave 23.5 g. of dihydrochloride, m. p. 147–149°, upon treatment with excess ethanolic hydrogen chloride.

Anal. Calcd. for $C_{21}H_{31}ON_3 \cdot 2HCl$: C, 60.88; H, 8.03. Found: C, 60.79; H, 8.19.

7-(2-Pyridyl)-1-methoxyheptane.—A solution of 0.35 mole of 2-picolylpotassium (prepared from 13.7 g. of potassium and 33 g. of 2-picoline) in 500 ml. of liquid ammonia was treated with 68.3 g. of 1-bromo-6-methoxyhexane[26] in the usual manner. A 68% yield (49.3 g.) of 7-(2-pyridyl)-1-methoxyheptane, b. p. 122–123° (2 mm.) was obtained.

Anal. Calcd. for $C_{13}H_{21}ON$: C, 75.32; H, 10.21. Found: C, 75.19; H, 10.32.

A 12.7-g. yield of by-product, b. p. 180–185° (2 mm.) (picrate, m. p. 194–195°) was obtained.

7-(2-Piperidyl)-1-methoxyheptane.—Using 0.4 g. of Adams catalyst 48.3 g. of the corresponding pyridyl compound was readily hydrogenated in 100 ml. of glacial acetic acid at 60°. A yield of 46.8 g. (94%) of 7-(2-piperidyl)-1-methoxyheptane, b. p. 123–124° (2 mm.), was obtained.

Anal. Calcd. for $C_{13}H_{27}ON$: equiv. wt., 213.3. Found: equiv. wt., 216 (by acid titration).

1-Bromo-7-(2-piperidyl)-heptane.—A solution of 300 ml. of 48% hydrobromic acid and 46.8 g. of 1-methoxy-7-(2-piperidyl)-heptane was refluxed for fifteen hours and evaporated to dryness on a steam-bath at reduced pressure. The crude crystalline residue, 74.8 g., was used directly in the following condensation. A portion was recrystallized from acetone to give colorless crystals with a constant melting point of 110–111.5°.

Anal. Calcd. for $C_{12}H_{24}NBr \cdot HBr$: equiv. wt., 343.2. Found:[7] equiv. wt., 341.0.

6-Methoxy-8-[7-(2-piperidyl)-heptylamino]-quinoline (VI) (SN 13,407).—An intimately ground mixture of 36.5 g. of 8-amino-6-methoxyquinoline and 74.8 g. of 1-bromo-7-(2-piperidyl)-heptane hydrobromide (crude) was heated *in vacuo* for fifteen hours at 130°. Isolation of the product in the described manner gave, upon distillation, 10 g. of yellow oil, b. p. 90° (5 mm.), unreacted 8-amino-6-methoxyquinoline, b. p. 120–140° (0.1 mm.), and 26.5 g. of the desired product, b. p. 220–225° (0.1 mm.). The product was converted to the dihydrochloride salt by addition of a small excess of ethanolic hydrochloric acid to an absolute ethanolic solution of the free base. Addition of an equi-

(25) Paul, *Ann. chim.*, [10] **18**, 303 (1932).

(26) Private communication, N. L. Drake, University of Maryland.

(27) "Organic Syntheses" Coll. Vol. I, 428 (1941).

molar amount of water, followed by a little dry ether gave an orange, hygroscopic powder, m. p. 105–106°.

Anal. Calcd. for $C_{22}H_{33}ON_3 \cdot 2HCl \cdot H_2O$: C, 59.21; H, 8.35. Found: C, 59.97; H, 8.39.

Summary

The syntheses of ten pamaquine analogs having piperidylalkylamino side chains are described. From lithium and potassium salts of 2-picoline, piperidylalkyl halides having two to seven carbon atoms in the bridge between the halogen atom and the 2-piperidyl group were prepared as hydrohalides for condensation with 8-aminoquinolines. 3-(4-Piperidyl)-propyl chloride was prepared similarly from 4-picoline.

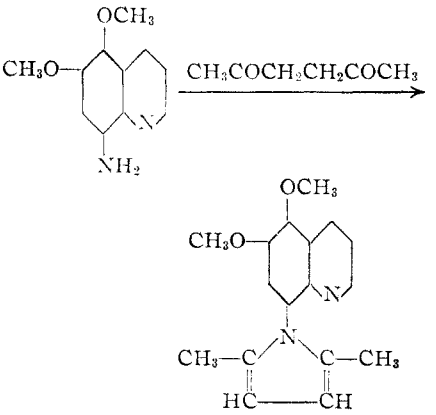
STANFORD UNIVERSITY, CALIF. RECEIVED MAY, 13 1946

NOTE

5,6-Dimethoxy-8-(2,5-dimethyl-1-pyrryl)-quinoline[1]

BY HENRY GILMAN AND LEO TOLMAN

The activity of some 2,5-dimethyl-1-pyrryl derivatives in avian malaria[2] suggested an examination of 5,6-dimethoxy-8-(2,5-dimethyl-1-pyrryl)-quinoline which was prepared in accordance with the reaction shown.



Experimental

5,6-Dimethoxy-8-aminoquinoline was obtained in 96% yield by reduction of 5,6-dimethoxy-8-nitroquinoline with stannous chloride and concd. hydrochloric acid.[3]

A mixture of 14.5 g. (0.075 mole) of 5,6-dimethoxy-8-aminoquinoline, 12 g. (0.1 mole) of acetonylacetone, 3 drops of concd. hydrochloric acid, and 15 cc. of absolute ethanol was heated in an oil-bath at 120–130° for four and one-half hours. The mixture refluxed gently during the heating period. After cooling, the product was poured into a mixture of ether and water. Several ether extracts were combined and washed with water. After drying the ether solution over sodium sulfate, the ether was removed by distillation from a steam-bath. The residue was distilled to give 7 g. (33%) of a viscous liquid boiling at 188–192° (0.7 mm.).

Anal. Calcd. for $C_{17}H_{18}O_2N_2$: N, 9.93. Found: N, 10.20.

The **picrate of 5,6-dimethoxy-8-(2,5-dimethyl-1-pyrryl)-quinoline** melted, after recrystallization from ethanol, at 189–191°.

Anal. Calcd. for $C_{23}H_{21}O_9N_5$: N, 13.70. Found: N, 13.80.

The **picrate of 5,6-dimethoxy-8-aminoquinoline** melted, after recrystallization from ethanol, at 186–187°.

Anal. Calcd. for $C_{17}H_{15}O_9N_5$: N, 16.16. Found: N, 16.01. A mixed melting point determination of the picrates showed a depression.

CHEMICAL LABORATORY
IOWA STATE COLLEGE
AMES, IOWA

RECEIVED APRIL 5, 1946

(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 Iowa State College.

(2) Gilman, Stuckwisch and Nobis, THIS JOURNAL, **68**, 326 (1946).

(3) Elderfield, *et al.*, *ibid.*, **68**, 1584 (1946).