[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

SYNTHESIS OF SUBSTITUTED QUINOLYLAMINES. DERIVATIVES OF 4-AMINO-7-CHLOROQUINOLINE

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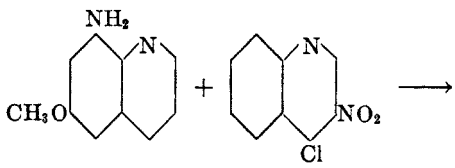
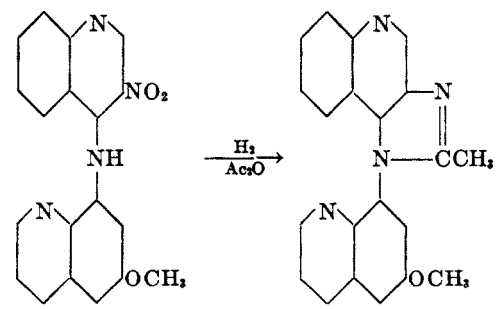
The high antimalarial activity of 4-(5′-diethylamino-2′-pentylamino)-7-chloroquinoline (SN 7618, chloroquine) has suggested the use of 4,7-dichloroquinoline in the synthesis of other antimalarials. It was the purpose of this investigation to prepare derivatives of 4-amino-7-chloroquinoline containing other side-chains, particularly side-chains of the type previously found active on the 4-amino-6-methoxyquinoline nucleus and reported from these laboratories (1). These side-chains were formed from 1,3-bis(dialkylamino)-2-propylamines obtained by reduction of the Mannich condensation products from nitromethane, formaldehyde, and secondary amines. The new compounds prepared are shown in Table I. The side-chain for compound 5 was one of a series of complex amines recently described by one of us (2). Compound 6 was prepared from an amine whose preparation from nitromethane, formaldehyde, and isopropylamine was recently described by Senkus (3).

Certain new derivatives of 8-amino-6-methoxyquinoline (I) have also been obtained and submitted for testing as antimalarials. The first of these (III) resulted from the condensation of I with 4-chloro-3-nitroquinoline (II). It gave an imidazole (IV) upon reduction in the presence of acetic anhydride.



I II



III IV

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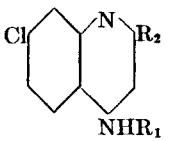
TABLE I

N-SUBSTITUTED 4-AMINO-7-CHLOROQUINOLINES

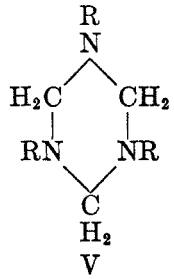


SUBSTITUENTS		YIELD, %	Q.E.[a]	M.P., °C.	FORMULA	ANALYSES	
R_1	R_2					Calc'd	Found
1. 1,3-Bis(dimethylamino)-2-propyl-	H	58		126	$C_{16}H_{23}ClN_3$	C, 62.61	62.50, 62.53
trihydrochloride			4.0	263–264		H, 7.56	7.52, 7.64
2. 1,3-Bis(dipropylamino)-2-propyl-	H	45		150			
triphosphate			0.8		$C_{24}H_{48}ClN_4O_{12}P_3$	N, 7.86	7.62, 7.79
3. 1,3-Bis(dibutylamino)-2-propyl-	H	40					
triphosphate			i	161	$C_{28}H_{56}ClN_4O_{12}P_3$	N, 7.28	7.29, 7.47
4. 1,3-Bis(diisobutylamino)-2-propyl-	H						
trihydrochloride		31.7	i	158–160	$C_{28}H_{50}Cl_4N_4$	N, 9.58	9.83, 9.88
5. 4-Aza-5,5-dimethyl-6-hydroxyhexyl-	H	42.9		149	$C_{16}H_{22}Cl_3N_3O$	C, 62.40	62.29, 62.42
dihydrochloride			0.64	258–259		H, 7.21	7.15, 7.19
6. 1,3-Diisopropyl-5-hexahydropyrimidyl-	H						
trihydrochloride dihydrate		63.4	1.2	245–250[b]	$C_{19}H_{34}Cl_4N_4O_2$	N, 11.38	11.37, 11.51
7. 1,3-Bis(methylisobutylamino)-2-propyl-	H	61	1.6	86–88[c]			
trihydrochloride				205	$C_{22}H_{35}N_4Cl \cdot 3HCl$	N, 11.19	11.05
8. 1,3-Bis(dimethylamino)-2-propyl-	CH_3	52		108–110	$C_{17}H_{25}ClN_4 \cdot H_2O$	N, 16.55	16.80
trihydrochloride methylate			i	253–255	$C_{17}H_{25}ClN_4 \cdot 3HCl \cdot CH_3OH$	N, 12.15	12.41
9. 1,3-Bis(dimethylamino)-2-propyl	*p*-ClC_6H_4	63		156–157	$C_{22}H_{26}Cl_2N_4$	N, 13.42	13.28
trihydrochloride isopropylate			i	250–252	$C_{22}H_{26}Cl_2N_4 \cdot 3HCl \cdot C_3H_7OH$	N, 9.56	9.53

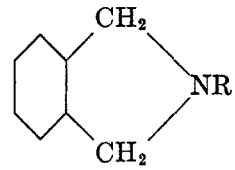
[a] The letters Q.E. are an abbreviation for quinine equivalent. [b] Sinters at 178–180°. [c] B.p. 185–188° at 0.5–1 mm.

Unsuccessful attempts were made to prepare diquinolylamines by condensations of I or its *p*-toluenesulfonate (sodium salt) with 2- or 8-chloro-5-nitroquinoline. Only tars or no reactions were obtained. On the other hand, I gave the expected 6-methoxy-8-(7′-chloro-4′-quinolyl)aminoquinoline with 4,7-dichloroquinoline.

With formaldehyde I gives mainly polymer, but a small amount of a pyridine-soluble compound analyzing correctly for V was also obtained. With formaldehyde and hydrogen sulfide a non-crystalline yellow powder was obtained. *o*-Xylylene chloride and I give the isoindoline (VI).



V



VI

VII

R = 6-methoxy-8-quinolyl-

Buu-Hoï (4) has described the preparation of colored compounds from the reaction of sulfanilamides with pyridine and cyanogen bromide. Although no yields, physical constants, or analyses were reported, structures were proposed, and the products were found to be effective against bacteria. With pyridine and cyanogen bromide I gave a purple crystalline solid which could not be recrystallized because of its insolubility in most solvents and its instability in acids. If its structure is analogous to those proposed by Buu-Hoï it may be represented by VII.

Pharmacological testing. None of the compounds showed antimalarial activity except those listed in Table I. It is interesting to note the activity of those compounds containing side chains derived from ditertiary monoprimary amines and the dependence of this activity on the presence of at least one methyl or methylene group attached to each tertiary nitrogen atom (*cf.* compounds 1, 6, and 7). This activity is largely lost if other alkyl groups replace the methyl or methylene groups (compounds 2, 3, and 4) or if a substituent is introduced at the 2-position on the quinoline nucleus (compounds 8 and 9). Efforts are now being made to prepare more active related antimalarials in which the tertiary nitrogens are separated from the primary nitrogens of the side chain amines by more than 3 carbon atoms.

Acknowledgment. We wish to express our gratitude to Eli Lilly and Company of Indianapolis and to the Purdue Research Foundation for financial support and to the former for pharmacological testing.

EXPERIMENTAL

All melting points and boiling points are corrected and all analyses were carried out by the Huffman Microanalytical Laboratories, Denver, Colorado unless otherwise indicated.

4-[1′,3′-Bis(dimethylamino)-2′-propylamino]-7-chloroquinoline. Twenty grams (0.085 mole) of 4,7-dichloroquinoline hydrochloride, 12.3 g. (0.085 mole) of 1,3-bis(dimethylamino)-2-propylamine, and 100.0 ml. of *n*-amyl alcohol were heated at reflux temperature for 24 hours. The solution was saturated with anhydrous hydrogen chloride, filtered, and the yellow precipitate dissolved in dilute hydrochloric acid. On addition of 10% sodium hydroxide a gray precipitate formed. Recrystallization from hexane gave 15.3 g. (58%) of white needles, m.p. 126°.

Anal. Calc'd for $C_{16}H_{23}ClN_3$: C, 62.61; H, 7.56.
Found: C, 62.50, 62.63; H, 7.52, 7.64.

The *trihydrochloride* was best obtained from the free base in ethanol with anhydrous hydrogen chloride. It recrystallized from ethanol and was a white solid, m.p. 263–264°.

4-(4′-Aza-5′,5′-dimethyl-6′-hydroxyhexylamino)-7-chloroquinoline. A mixture of 27.2 hexg. (0.14 mole) of 4,7-dichloroquinoline and 20.0 g. (0.14 mole) of 6-amino-3-aza-2,2-dimethylanol was heated, with stirring, at 145–150° for a period of 24 hours. The temperature tended to rise above this point due to heat evolution; therefore, the flask was cooled periodically. At room temperature the contents of the flask became solid. The product was pulverized, dissolved in hot 5% acetic acid, and made alkaline with 4 *N* potassium hydroxide. The free base was recrystallized from isopropyl ether to give 18.0 g. (42.9%) of white product, m.p. 149°.

Anal. Calc'd for $C_{16}H_{22}ClN_3O$: C, 62.40; H, 7.21.
Found: C, 62.29, 62.42; H, 7.15, 7.19.

The *dihydrochloride* was obtained by saturating an ethanolic solution of the free base with anhydrous hydrogen chloride and diluting with isopropyl ether. Recrystallization from ethanol-isopropyl ether gave a crystalline dihydrochloride, m.p. 258–259°.

The 4-[1′,3′-bis(dipropylamino)-, (dibutylamino)-, and (diisobutylamino)-2′-propylamino][3] (3), and 4-(1′,3′-diisopropyl-5′-hexahydropyrimidyl)- derivatives of 7-chloroquinoline were prepared by procedures similar to those above, but the first two were characterized as the triphosphates, which were recrystallized from methanol-water-isopropanol.

6-Methoxy-8-(7′-chloro-4′-quinolyl)aminoquinoline dihydrochloride hydrate. Thirteen grams (0.055 mole) of 4,7-dichloroquinoline hydrochloride and 9.65 g. (0.055 mole) of 8-amino-6-methoxyquinoline in 40 ml. of *n*-butanol were heated at reflux temperature for 48 hours. On cooling, a dark yellow solid formed, which turned orange upon contact with air. It was dissolved in hot pyridine and diluted with water. The yellow crystalline product, after recrystallization from ethanol, weighed 10.0 g. (53.8%); m.p. 203–205°. Anhydrous hydrogen chloride was added to a chloroform solution of the free base and after removal of the chloroform the residue was recrystallized from moist methanol-isopropyl ether. The *dihydrochloride* obtained showed a transition point at 150° and melted at 276°. A sample dried at 100° over phosphorus pentoxide showed no change before melting at 276°. This indicated that the original product was a hydrate.

Anal. Calc'd for $C_{19}H_{16}Cl_3N_3O$: N, 10.28. Found: N, 10.20, 10.15.

6-Methoxy-8-(3′-nitro-4′-quinolyl)aminoquinoline (III). A mixture of 4.2 g. (0.024 mole) of 8-amino-6-methoxyquinoline and 5.0 g. (0.024 mole) of 4-chloro-3-nitroquinoline (5) in 40 ml. of ethanol was stirred at room temperature for five hours. The orange solid was filtered, dissolved in hot pyridine, and diluted with water. Orange needles formed upon cooling. Recrystallization from ethanol gave 7.25 g. (87.5%) of the diquinolylamine, m.p. 230–232°.

Anal. Calc'd for $C_{19}H_{14}N_4O_3$: C, 65.88; H, 4.08; N, 16.18.
Found: C, 65.88, 65.75; H, 4.03, 4.10; N, 16.21, 16.32.

1-(6′-Methoxy-8′-quinolyl)-2-methylquinolino-[3,4-d]imidazole (IV). A mixture of 14.0 g. (0.04 mole) of the above diquinolylamine, 70.0 ml. of glacial acetic acid, 80.0 ml. of acetic

[3] The intermediate 1,3-bis(diisobutylamino)-2-nitropropane from which this amine was prepared was previously reported as a yellow oil (1). We found it to be a yellow solid, m.p 86.0–87.5°.

anhydride, and 100 mg. of platinum oxide catalyst was reduced under 60 pounds hydrogen pressure. During reduction the orange solid dissolved. After hydrogen uptake had ceased the mixture was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in hydrochloric acid, decolorized, and made alkaline with ammonia. The precipitate was recrystallized from ethanol to give 7.0 g. (51.2%) of white crystalline product, m.p. 253–254°.

Anal. Calc'd for $C_{21}H_{16}N_4O$: C, 74.1; H, 4.74; N, 16.40.
Found: C, 73.73, 73.79; H, 4.80, 4.84; N, 16.05, 16.10.

6-Methoxy-8-(p-toluenesulfonyl)aminoquinoline. Eleven grams (0.058 mole) of *p*-toluenesulfonyl chloride was added in portions to 10.0 g. (0.057 mole) of 8-amino-6-methoxyquinoline in 50 ml. of pryidine. After the initial reaction had subsided the mixture was allowed to stand for two hours at room temperature and then for ten minutes over a steam-cone. Pouring into water gave a gray precipitate. Recrystallization from ethanol gave 11.6 g. (61.5%) of a white crystalline product, m.p. 133–134°.

Anal.[a]: Calc'd for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91.
Found: C, 61.90, 62.05; H, 5.09, 5.21.

1,3,5-Tris(6'-methoxy-8'-quinolyl)hexahydro-sym-triazine (V). A mixture of 17.4 g. (0.1 mole) of 8-amino-6-methoxyquinoline, 4.05 g. (0.05 mole) of 37% formalin solution, and 40.0 ml. of acetone was refluxed for six hours, then cooled. The acetone was removed under reduced pressure and the resinous product was heated with pyridine. Only a small amount of the product was soluble, the remainder being polymer. Three recrystallizations from pyridine gave 1.0 g. (5%) of a yellow product, m.p. 203–205°.

Anal. Calc'd for $C_{33}H_{30}N_6O_3$: C, 70.95; H, 5.41.
Found: C, 71.32, 71.23; H, 5.79, 5.80.

Condensation of 8-amino-6-methoxyquinoline, formaldehyde, and hydrogen sulfide. A 20% aqueous-ethanolic formaldehyde solution (0.086 mole) saturated with hydrogen sulfide was added to an ethanolic solution of 10.0 g. (0.058 mole) of 8-amino-6-methoxyquinoline and the mixture was refluxed for 30 minutes. A yellow oil formed which solidified on cooling. The solvent was removed and the product was purified by repeated reprecipitation from a pyridine-water mixture. The yield of the yellow solid, m.p. 185-190° (with decomposition), was 7.0 g. (61.9%).

Anal. Calc'd for $C_{33}H_{30}N_6O_3 \cdot H_2S$: C, 66.86; H, 5.44; N, 14.19; S, 5.41.
Found: C, 66.88, 66.99; H, 5.27, 5.39; N, 14.01, 14.07; S, 5.33, 5.43.

2-(6'-Methoxy-8'-quinolyl)isoindoline (VI). A mixture of 5.0 g. (0.024 mole) of *o*-xylylene chloride, 8.25 g. (0.047 mole) of 8-amino-6-methoxyquinoline, 4.1 g. (0.05 mole) of anhydrous sodium acetate, and 15 ml. of 95% ethanol was stirred at room temperature for four days and then refluxed for 1½ hours. After cooling, the inorganic salt was filtered and the dark filtrate was evaporated to dryness. Decolorization with Norit and recrystallization from ethanol-water gave 1.0 g. (12.65%) of a white crystalline product, for m.p. 141–142°.

Anal.[a]: Calc'd for $C_{18}H_{16}N_2O$: C, 78.2; H, 5.8; N, 10.1.
Found: C, 78.6, 78.7; H, 5.7, 5.8; N, 10.1, 10.2.

Condensation of 8-amino-6-methoxyquinoline with cyanogen bromide and pyridine (VII). A solution of 3.25 g. (0.05 mole) of potassium cyanide and 2.60 ml. of bromine in 80.0 ml. of water was added to a warm (60°) mixture of 17.4 g. (0.10 mole) of 8-amino-6-methoxyquinoline, 3.95 g. (0.05 mole) of pyridine, 660.0 ml. of water, and 40.0 ml. of ethanol. On standing a purple crystalline solid formed which could not be recrystallized because of its insolubility. It was purified by washing with water, ethanol, and ether respectively, and finally by continuous extraction with benzene. The purple residue, 8.0 g. (39%), decomposed at 134–135°.

Anal. Calc'd for $C_{25}H_{22}N_4O_2$: N, 13.65. Found: N, 16.68, 16.80.

4,7-Dichloroquinaldine. 4-Hydroxy-7-chloroquinaldine (6), 50 g., was refluxed with phosphorus oxychloride, 150 ml., for two hours. The cooled mixture was poured on ice, neutra-

[a] Analyses by Dr. H. Galbraith, Purdue University.

lized with a saturated potassium carbonate solution, and the solid precipitate extracted with chloroform. The chloroform was dried and the product crystallized by evaporation of the solvent. This procedure removed a major portion of the contaminating red color that seemed to go along with the desired product. The pink crystals were recrystallized from methanol (Norit) to yield long white needles, m.p. 101–102°.

Anal. Calc'd for $C_{10}H_7Cl_2N$: N, 6.62. Found: N, 6.66.

4-[1',3'-Bis(dimethylamino)-2'-propylamino]-7-chloroquinaldine. 4,7-Dichloroquinaldine, 25.5 g., 1,3-bis(dimethylamino)-2-propylamine, 28 g., potassium iodide, 0.2 g., and hydrogen chloride, 3.8 g., were held at 165° for eight hours. The mixture was cooled and shaken with a mixture of 75 ml. of ether and 200 ml. of 2 *N* hydrochloric acid until solution had been effected. The aqueous phase was separated, neutralized with dilute sodium hydroxide, and the solid precipitate, 18.2 g. (52%) taken up in methanol (Norit) and the methanol concentrated to about 50 ml. Crystallization of the free base monohydrate, m.p. 108–110°, was effected by the addition of hot water to incipient precipitation and then allowing to stand. The free base was taken up in methanol and added to a saturated ethanol-hydrogen chloride solution. The resultant hydrochloride had m.p. 253–255° (from ethanol-methanol).

7-Chloro-4-hydroxy-2-p-chlorophenylquinoline. Distilled *m*-chloroaniline, 12.7 g., ethyl *p*-chlorobenzoylacetate, 21.4 g., glacial acetic acid, 6.0 ml., and one drop of concentrated hydrochloric acid were refluxed at 55–65° in the presence of petroleum ether, 130 ml., and the water formed was removed by azeotropic distillation. After 24 hours, the solvent was removed under a vacuum and the residue added to 2 l. of Finol stirred at 250–255°. The addition was effected over a period of 20 minutes, distilling out the water as rapidly as formed. It was noted that a period of heating longer than 30 minutes resulted in a darker product. The Finol mixture was cooled and about 200 ml. of petroleum ether was added. The mixture was filtered and the residue was removed and washed several times with hot isopropanol, which resulted in a product essentially pure for the chlorination step; yield, 17 g. (58%).

4,7-Dichloro-2-p-chlorophenylquinoline. 7-Chloro-4-hydroxy-2-*p*-chlorophenylquinoline, 50 g., was refluxed with phosphorus oxychloride, 150 ml., for two hours. The black solution was cooled, poured on ice, neutralized with potassium carbonate, and the solid precipitate removed and washed with a small amount of hot methanol to remove a blue color. If the washing was omitted the product became darker blue when exposed to the air. The blue impurity, when crystallized by concentration of the methanol washings had m.p. 119–120°. It was not identified. The remaining undissolved 4,7-dichloro compound had m.p. 158–159° which was raised to 162–163° by recrystallization from chloroform. The yield was 48 g.

Anal. Calc'd for $C_{15}H_8Cl_3N$: N, 22.04. Found: N, 22.01.

4-[1',3'-Bis(dimethylamino)-2'-propylamino]-7-chloro-2-p-chlorophenylquinoline. Thirty grams of the 4-chloro compound was added to 100 ml. of hexanol containing 25 g. of 1,3-bis(dimethylamino)-2-propylamine and the mixture refluxed for 44 hours. The hexanol was removed under a vacuum and the residue shaken with a mixture of water and ether. The solid at the interface of the two liquids (32 g.) was separated by filtration, air-dried, and crystallized from benzene, m.p. 156–157°. A mixed melting point with the starting material was 135°. From isopropanol the *trihydrochloride* had m.p. 250–252°. It was found to contain one mole-equivalent of isopropanol. Ethanol was also found to be a satisfactory solvent for recrystallization.

1,3-Bis(methylisobutylamino)-2-propylamine. Fresh aqueous formaldehyde, 79.5 g., was slowly added to methylisobutylamine, 78 g., at 0° (stirring). After 10 minutes, distilled nitromethane, 28.7 g., was slowly added to the cold solution at 0°. The solution was stirred for ten hours at ice temperature, allowed to warm to room temperature, stirred for two hours, and the organic layer taken up in ether. The ether layer was washed thoroughly with 20% potassium hydroxide and water, the ether removed under a vacuum, and the product held under a high vacuum at room temperature for five hours. The oil, 110 g., (71%) was hydrogenated batchwise, at 60 pounds pressure, using freshly prepared Raney nickel and two volumes of ethanol as solvent. Cooling was effected with a jacketed condenser through which air could be blown. Absorption was controlled at the rate of one pound of hydrogen

per minute. The alcoholic solution, after filtration, was dried and the desired amine was obtained by distillation; yield 63 g., (63.3%), b.p. 85–88° (1 mm.), n_D^{25} 1.4422.

Anal. Calc'd for $C_{13}H_{31}N_3$: N, 18.32. Found: N, 18.45, 18.56.

4-[1',3'-Bis(methylisobutylamino)-2'-propylamino]-7-chloroquinoline. 4,7-Dichloroquinoline, 20 g., 1,3-bis(methylisobutylamino)-2-propylamine, 25 g., hexanol, 50 ml., hydrogen chloride, 4 g., and potassium iodide, 0.5 g., were held at reflux for 24 hours. The mixture was cooled, shaken with 250 ml. of ether, and extracted with dilute hydrochloric acid. The acidic solution was made basic with sodium hydroxide and extracted with ether. The ether solution, after drying, was distilled, yielding 24 g. (61%) of product, b.p. 175–195° (0.5–1 mm.). A yellow oil was obtained on redistillation, b.p. 185–188° (0.5–1 mm.) which solidified on cooling to a solid, m.p. 86–88°. An attempt was made to crystallize the phosphate (obtained by precipitation of the free base) from propanol with 85% phosphoric acid, but only an oil was obtained. The phosphate oil was reconverted to the free base and taken up in methanol containing slightly more than three equivalents of hydrogen chloride and the methanol removed under vacuum. A faintly-yellowish crystalline residue was obtained, m.p. 205° (45 seconds).

SUMMARY

1. A number of N-substituted 4-amino-7-chloroquinolines have been prepared and submitted for testing as antimalarials.

2. Some miscellaneous derivatives of 8-amino-6-methoxyquinoline have also been synthesized and characterized.

3. Active antimalarials have been found in the series of 4-alkylamino-7-chloroquinolines in which the alkyl group contains the skeletal structure $-C[CN(CH_3)R]_2$ where R is methyl or larger.

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