tion of 5-alkylamino-2-pentanone oximes. These and other diamines have been condensed with 4,7-dichloroquinoline to give derivatives of 7-chloroquinoline with aminoalkylamino or monoalkylaminoalkylamino substituents in the 4-position.

CAMBRIDGE, MASS. RECEIVED APRIL 5, 1946

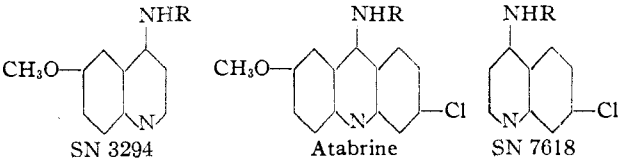
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Preparation of Some 4-Aminoquinolines[1]

BY BYRON RIEGEL, GERALD R. LAPPIN, CHARLES J. ALBISETTI, JR., BERNARD H. ADELSON, R. M. DODSON, LEONARD G. GINGER AND ROBERT H. BAKER

Because of the reported antimalarial activity[2] of 4-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline (SN 3294) and 4-(3-diethylamino-1-methylpropylamino)-6-methoxyquinoline (SN 5063) it seemed to be desirable to reinvestigate these compounds. Their synthesis by the method described by Magidson and Rubtsov[3] was duplicated and they were both found to compare favorably with atabrine as a suppressive drug.

The Russian workers prepared the nucleus for these two compounds by treating the N-oxide hydrochloride of 6-methoxyquinoline[4] with phosphorus oxychloride. This gave a mixture of 2- and 4-chloro-6-methoxyquinoline. These two isomers were separated by taking advantage of their difference in basicity. The 4-chloro-6-methoxyquinoline was then coupled with the side chains, 2-amino-5-diethylaminopentane (Noval diamine) and 2-amino-4-diethylaminobutane. To increase the water solubility of the free bases of SN 3294 and 5063, salts were made with 4,4'-methylenebis-(3-hydroxy-2-naphthoic acid) and with phosphoric acid. Because of their antimalarial activity an extensive investigation in this and other laboratories was made of substituted 4-aminoquinolines including SN 7618.



SN 3294 Atabrine SN 7618

R = —CH(CH$_3$)CH$_2$CH$_2$CH$_2$N(C$_2$H$_5$)$_2$

The synthetic work reported in this paper was directed toward further variations in both the side chains and nuclei of related quinolines. The nucleus of SN 3294 has been varied by substituting the dimethylamino group for the methoxyl group. Modifications of SN 7618 have been made by changing the side chain to dioctyl- and dihexylaminopropyl, adding a benzylmercapto group at the 6-position, as well as by replacing the 7-chloro by 3-bromo. Two 4-aminoquinolines which have neither a methoxyl nor a chlorine but which have sulfur in the 8-position have been included in the study. Some of the 4-haloquinolines required for the preparation of these compounds have been described elsewhere.[5]

3,4-Dihaloquinolines are difficult to prepare in quantity. The Meisenheimer reaction, applied to 3-chloroquinoline, fails to produce the desired compound, and the cyclization of aniline derivatives which place functional groups in positions 3 and 4 involves an impractical series of reactions to the desired compound. Attempts to chlorinate the readily available 4-quinolinol led to an unidentified trichloroquinolinol, but it was possible to monobrominate in good yield. Since bromo and chloro groups are of near equivalence in their influence on antimalarial activity, the 3-bromo compound was satisfactory and no detailed study of the preparation of the chloro compound was made. Conversion of the 3-bromo-4-quinolinol into 3-bromo-4-chloroquinoline was carried out in the usual manner by means of phosphorus oxychloride, but this compound proved to be extraordinarily unreactive toward amines in the coupling reaction and it was necesssary to prepare a more reactive 4-halo compound. This was accomplished by refluxing the quinolinol with phosphorus tribromide to produce 3,4-dibromoquinoline from which the drug was finally obtained.

The drugs containing sulfur in the 8-position were prepared from 4-chloro-8-quinolinesulfonic acid which resulted from direct sulfonation of the chloroquinoline. Catalytic removal of the halogen followed by conversion into the known 8-quinolinesulfonyl chloride established the structure of this intermediate. The chloroquinoline sulfonic acid was converted into its acid chloride which, when heated with Noval diamine, gave a unique compound, SN 13,643, which contains the

(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 Northwestern University.

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.

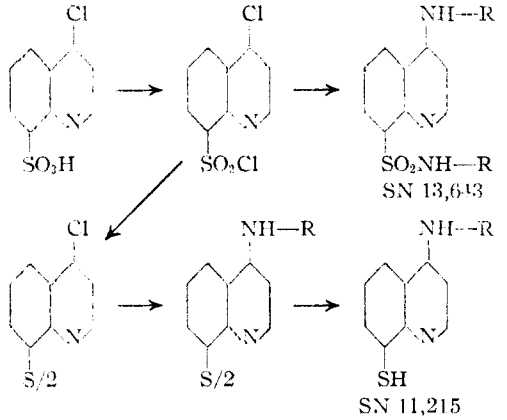
(2) E. P. Hal'perin, *Med. Parasitol. Parasitic Diseases (USSR)*, **9**, 44 (1940).

(3) O. Yu. Magidson and M. V. Rubtsov, *J. Gen. Chem. (USSR)*, **7**, 1896 (1937). The laborious repetition of this work on a large scale was carried out by Dr. Richard I. Jackson and Dr. Joseph C. Sandza.

(4) J. Meisenheimer, *Ber.*, **59**, 1848 (1926).

(5) B. Riegel, G. R. Lappin, B. H. Adelson, Richard I. Jackson, C. J. Albisetti, Jr., R. M. Dodson and Robert H. Baker, THIS JOURNAL, **68**, 1264 (1946).

sulfonamide group. Reduction of the acid chloride to the mercapto compound and oxidation to the disulfide followed by coupling with Noval diamine afforded the precursor of the other sulfur-containing drug, SN 11,215.



R = —CH(CH$_3$)CH$_2$CH$_2$CH$_2$N(C$_2$H$_5$)$_2$

Acknowledgment.—We are indebted to Prof. Kenneth C. Blanchard for suggesting this investigation of the 4-aminoquinolines.

Experimental[6]

3-Bromo-4-quinolinol.—To a solution of 4.8 g. (0.033 mole) of 4-quinolinol in 75 ml. of warm glacial acetic acid was added slowly with stirring 5.3 g. (0.033 mole) of bromine. The reaction mixture was allowed to stand for twelve hours on the steam-bath, cooled, and the 3-bromo-4-quinolinol hydrobromide was collected by filtration. This was dissolved in 75 ml. of dilute sodium hydroxide, the solution was filtered, and the product was precipitated by passing carbon dioxide into the alkaline filtrate. The yield of 3-bromo-4-quinolinol, m. p. 288–289° after recrystallization from ethanol,[7] was 7.0 g. (94.7%).

Anal. Calcd. for C$_9$H$_6$BrNO: N, 6.25. Found: N, 6.12.

3-Bromo-4-chloroquinoline.—A solution of 4.8 g. (0.023 mole) of 3-bromo-4-hydroxyquinoline in 40 ml. of phosphorus oxychloride was refluxed for two hours, and after cooling the solution was poured onto cracked ice. After hydrolysis of the oxychloride the suspension was made alkaline with sodium hydroxide solution to dissolve unchanged quinolinol and the insoluble dihalide was collected on the filter. The yield of crude product, m. p. 67–68°, was 4.9 g. (94.4%). Crystallization from 80% ethanol raised the melting point to 68–68.5°.

Anal. Calcd. for C$_9$H$_6$BrClNO: N, 5.78. Found: N, 5.74.

3,4-Dibromoquinoline.—A mixture of 10 g. (0.049 mole) of 3-bromo-4-quinolinol and 40 ml. of phosphorus tribromide was refluxed for five hours. After cooling the reaction mixture was hydrolyzed by pouring onto cracked ice and the resulting aqueous suspension made strongly alkaline with a solution of sodium hydroxide. The insoluble product was collected by filtration, washed with water, and dried. There was obtained 9.7 g. (76%) of 3,4-dibromoquinoline which after crystallization from ethanol melted at 78.5–79.5°.

Anal. Calcd. for C$_9$H$_5$Br$_2$N: N, 4.88. Found: N, 4.76.

3-Dihexylaminopropylamine.—β-Dihexylaminopropionitrile was prepared by the reaction of dihexylamine and acrylonitrile.[8] A solution of 289 g. (1.21 moles) of β-dihexylaminopropionitrile in 150 ml. of ethanol was saturated with ammonia at 0° and hydrogenated using Raney nickel catalyst at 115° and an initial hydrogen pressure of 3100 lb. Distillation of the product at reduced pressure gave 131 g. (45%) of 3-dihexylaminopropylamine, b. p. 142–144° at 5 mm., n^{25}D 1.4520.

Anal. Calcd. for C$_{15}$H$_{34}$N$_2$: neut. equiv., 121. Found: neut. equiv., 121.

3-Dioctylaminopropylamine.—β-Dioctylaminopropionitrile was prepared by the reaction of dioctylamine and acrylonitrile.[9] A solution of 210 g. (0.72 mole) of this nitrile in 250 ml. of ethanol was saturated with ammonia at 0° and hydrogenated using Raney nickel catalyst at 125° and 2100 lb. initial pressure. Distillation under reduced pressure gave 110 g. (52%) of 3-dioctylaminopropylamine, b. p. 162–165° at 1 *mm.*, n^{25}D 1.4529.

Anal. Calcd. for C$_{19}$H$_{42}$N$_2$: neut. equiv., 149. Found: neut. equiv., 148.

3-Bromo-4-(4-diethylamino-1-methylbutylamino)-quinoline (SN 14,186).—A mixture of 22.4 g. (0.075 mole) of 3,4-dibromoquinoline, 28 g. (0.19 mole) of Noval diamine (2-amino-5-diethylaminopentane) and 16 g. of phenol was heated at 150° for three hours. The reaction product was poured into 250 ml. of 10% aqueous sodium hydroxide solution. The alkaline mixture was extracted several times with ether and the ethereal extract was washed with dilute sodium hydroxide and water. The product was extracted from the ether solution with several portions of sodium acetate-acetic acid buffer of *p*H 4.7. The buffer solution was then made strongly alkaline and the product extracted with ether. The ether solution was dried over anhydrous sodium sulfate and the ether was removed *in vacuo*. Distillation of the residue gave 18.4 g. (65%) of product, a yellow oil, b. p. 209–210° at 1 mm.

Anal. Calcd. for C$_{18}$H$_{26}$BrN$_3$: N, 11.53. Found: N, 11.22.

The structure of the 3-bromo-4-(4 diethylamino-1-methylbutylamino)-quinoline was established by heating with concd. sulfuric acid which caused dealkylation giving 3-bromo-4-aminoquinoline. This method of dealkylation will be described in a subsequent publication.

7-Chloro-4-(3-dihexylaminopropylamino)-quinoline (SN 11,619).—A mixture of 155 g. (0.65 mole) of 3-dihexylaminopropylamine, 115 g. (0.58 mole) of 4,7-dichloroquinoline, and 200 g. of phenol was heated with stirring for two hours at 130°, one hour at 140°, and one hour at 150°. (Note: If the mixture was heated initially to 140–150° the reaction was uncontrollably vigorous.) The reaction mixture was poured into 1000 ml. of 30% aqueous sodium hydroxide solution and stirred for thirty minutes. The non-aqueous layer was then separated and the sodium hydroxide solution extracted with five 100-ml. portions of ether. The combined non-aqueous layer and ether extracts was washed with water, then with 50 ml. of 10% acetic acid–10% sodium acetate solution, dried over anhydrous potassium carbonate, and the ether was removed *in vacuo*. The residual oil gave on distillation 128 g. (44%) of an oil, b. p. 220–225° at 0.5 mm. This oil crystallized on standing to give a yellow solid, m. p. 111–112° after three crystallizations from a benzene-heptane mixture.

Anal. Calcd. for C$_{24}$H$_{38}$ClN$_3$: N, 10.42. Found: N, 10.66.

Diphosphate Salt (SN 11,619–5).—The diphosphate salt of the above drug was prepared by dissolving 10 g. (0.20 mole) of crude distillate in 50 ml. of ethanol and 20 ml. of dioxane, heating on the steam-bath, and adding dropwise

(6) We wish to thank Margaret Ledyard, Winifred Brandt and Rita Pivan for the microanalyses reported in this paper.

(7) This compound was prepared by an alternate method by St. von Niementowski and E. Sucharda, *J. prakt. Chem.*, **24**, 225 (1916), who report a melting point of 282°.

(8) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel and W. Yanko, THIS JOURNAL, **66**, 725 (1944).

(9) J. H. Burckhalter, E. M. Jones, W. F. Holcomb and L. A. Sweet, *ibid.*, **65**, 2012 (1943).

a hot 10% solution of 85% phosphoric acid in dioxane until no further precipitate formed. The mixture was heated for thirty minutes and the product collected by filtration from the hot solution to give 13.7 g. (90%) of the diphosphate salt, m. p. 198–200° after crystallization from water.

Anal. Calcd. for $C_{24}H_{38}ClN_3 \cdot 2H_3PO_4$: N, 7.00. Found: N, 7.65.

7-Chloro-4-(3-dioctylaminopropylamino)-quinoline (SN 11,620).—In a similar manner as described for the dihexylamino side chain, 4,7-dichloroquinoline and 3-dioctylaminopropylamine condensed to give 7-chloro-4-(3-dioctylaminopropylamino)-quinoline. The product was a dark yellow oil, b. p. 250–260° at 0.5 mm., which did not crystallize on standing. It was not analyzed but converted immediately to the phosphate salt.

Diphosphate Salt (SN 11,620-5).—By the method described above the diphosphate salt was obtained as a white crystalline solid, m. p. 208–210° after crystallization from water.

Anal. Calcd. for $C_{25}H_{48}ClN_3 \cdot 2H_3PO_4$: N, 6.40. Found: N, 6.48.

6-Benzylthio-7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (SN 12,945).—Using the same method as previously described, except that a reaction temperature of 170° was used, 6-benzylthio-4,7-dichloroquinoline was coupled with Noval diamine. A 54% yield of 6-benzylthio-7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline was obtained as a solid when the ether was removed. It was purified by crystallizing from a mixture of heptane and benzene, m. p. 107.5–108.5°.

Anal. Calcd. for $C_{25}H_{32}ClN_3S$: N, 9.55. Found: N, 9.50.

4-(4-Diethylamino-1-methylbutylamino)-6-dimethylaminoquinoline (SN 8,773).—Noval diamine and 4-chloro-6-dimethylaminoquinoline were heated together at 165° for eight hours. They coupled in an 80% yield to give 4-(4-diethylamino-1-methylbutylamino)-6-dimethylaminoquinoline as a white crystalline solid, m. p. 139–141°, when crystallized from heptane.

Anal. Calcd. for $C_{20}H_{32}N_4$: N, 17.05. Found: N, 16.61.

4-Chloro-8-quinolinesulfonic Acid.—To 300 ml. of 25% oleum there was added 60 g. (0.37 mole) of 4-chloroquinoline. The mixture was stirred at 100–110° for forty-eight hours. The acid solution was then poured slowly into twice its volume of cracked ice, and the insoluble 4-chloro-8-quinolinesulfonic acid was removed by filtration. After one crystallization from water there was obtained 70 g. (89.9%) of acid, m. p. over 300°.

Anal. Calcd. for $C_9H_6ClNO_3S$: N, 5.76. Found: N, 6.00.

Proof of Structure of 4-Chloro-8-quinolinesulfonic Acid.—To 100 ml. of 1 *N* aqueous sodium hydroxide solution there was added 2.43 g. (0.01 mole) of 4-chloro-8-quinolinesulfonic acid. To this solution there were added 1 g. of palladium-on-charcoal catalyst and 1 g. of calcium carbonate. The resultant suspension was shaken with hydrogen at 30 lb. pressure and room temperature in a Parr hydrogenation apparatus. The theoretical drop in pressure (0.8 lb.) seemed to occur in forty-five minutes. The solution was heated on the steam-bath, filtered, and acidified with concd. hydrochloric acid. The acidic solution was evaporated to dryness and the solid residue was treated with phosphorus pentachloride in the usual way.[10] From the reaction mixture there was obtained a small quantity of sulfonyl chloride, m. p. 118–121°. Crystallization did not raise the melting point (119–121°). The reported[10] melting point for 8-quinolinesulfonyl chloride is 124–126°.

4-Chloro-8-quinolinesulfonyl Chloride.—A dry mixture of 50 g. (0.21 mole) of 4-chloro-8-quinolinesulfonic acid with 60 g. of phosphorus pentachloride was placed in a 500-ml. round-bottom flask equipped for distillation. The flask was heated by means of an oil-bath. At 150–160° (pot temperature) a reaction began, and heating was continued for forty-five minutes. At the end of this time the disillation of phosphorus oxychloride had ceased. The residue which solidified on cooling was crushed and triturated with water. Filtration gave 64 g. (84%) of the solid sulfonyl chloride, m. p. 135–138°. The sulfonyl chloride was crystallized from benzene, m. p. 138–138.5°.

Anal. Calcd. for $C_9H_5Cl_2NO_2S$: N, 5.34. Found: N, 5.17.

Bis-(4-chloro-8-quinolyl) Disulfide.—A solution of 64 g. (0.25 mole) of 4-chloro-8-quinolinesulfonyl chloride in 500 ml. of cold concd. hydrochloric acid was added with stirring to a cold solution of 226 g. of stannous chloride dihydrate in 600 ml. of concd. hydrochloric acid. The reaction mixture was cooled in an ice–salt-bath during the addition of the sulfonyl chloride solution, and the final mixture was allowed to stand overnight at room temperature. The mixture was filtered and there was obtained, after air drying, 107 g. of the tin salt, m. p. 175–180°. To a well-stirred solution of 20 g. of iodine and 120 g. of sodium hydroxide in 1 liter of water contained in a 2-liter Erlenmeyer flask cooled by an ice–salt-bath, there was added portion-wise 20 g. of 4-chloro-8-quinolinethiol tin salt. The temperature was maintained at 0–10° during the addition and for one hour afterwards. The resulting yellow precipitate was filtered and dissolved in 6 *N* hydrochloric acid. Nuchar C was added to the solution and the resulting suspension was heated on the steam-bath for a half hour. The solution was filtered free of carbon and the disulfide was precipitated by neutralization of the acid solution with concd. ammonium hydroxide. The disulfide was crystallized from ethanol to give 6 g. (31% based on the sulfonyl chloride) of material melting at 240–248° dec.

Anal. Calcd. for $C_{18}H_{10}Cl_2N_2S_2$: N, 7.19. Found: N, 7.33.

Bis-[4-(4-diethylamino-1-methylbutylamino)-8-quinolyl] Disulfide.—To a mixture of 40 g. (excess) Noval diamine with 40 g. of phenol there was added 25 g. (0.065 mole) of bis-(4-chloro-8-quinolyl) disulfide. The temperature immediately rose to 60° and the solution was heated at 160–170° for seven hours. The cool reaction mixture was poured into 100 ml. of 10% aqueous sodium hydroxide, and the reaction flask was rinsed with a second 100-ml. portion of 10% aqueous sodium hydroxide. The combined sodium hydroxide solutions were extracted with ether. The ether solution was washed once with 5% aqueous sodium hydroxide and twice with water. The ether solution was then extracted with 50-ml. portions of 50% acetic acid solutions until the acid extracts were colorless. The combined acid extracts were heated with Nuchar C, the carbon was removed by filtration and the solution was made basic with concd. ammonium hydroxide. The disulfide separated as a fine dispersion, and it was extracted with ether. The ether solution was dried over magnesium sulfate, it was filtered free of drying agent, and the ether was removed by distillation. There remained 26 g. (63%) of a light yellow oil.

Anal. Calcd. for $C_{36}H_{52}N_6S_2$: N, 13.28. Found: N, 13.26.

4-(4-Diethylamino-1-methylbutylamino)-8-quinolinethiol (SN 11,215).—This was prepared by the reduction of the disulfide described above using sodium sulfide. The quinolinethiol, which is also an oil, could not be readily isolated in the pure state because of its ease of oxidation to the disulfide. After reduction, the solution was acidified to a *p*H of 5, the hydrogen sulfide was expelled and the aqueous mixture submitted for the malarial tests.

N-(4-Diethylamino-1-methylbutyl)-4-(4-diethylamino-1-methylbutylamino)-8-quinolinesulfonamide Trihydrochloride (SN 13,643-4).—To 95 g. (excess) of Noval diamine contained in a 500-ml. round-bottomed flask equipped with a reflux condenser there was added 39 g. (0.15 mole) of 4-chloro-8-quinolinesulfonyl chloride. An exothermic reaction immediately ensued. The reaction flask was heated two and one half hours at 150–160°. After cooling, the contents of the flask was suspended in

(10) A. Edinger, *Ber.* **41**, 937 (1908).

ether, and the ether was washed with five 100-ml. portions of 10% aqueous sodium hydroxide and with five 100 ml. portions of water, and dried over magnesium sulfate. The ether solution was then filtered and saturated with dry hydrogen chloride gas. The mixture of the hydrochloride of the desired base with the hydrochloride of N-(4-diethylamino-1-methylbutyl)-4-chloro-8-quinolinesulfonamide settled as an orange gum. The ether was removed by decanting and the gum was washed with anhydrous ether. It was then dissolved in absolute ethanol, the ethanolic solution was heated with Nuchar C and filtered, and absolute ether was added to the warm ethanolic solution until the first appearance of cloudiness. The ethanol–ether solution was then maintained at −5° for two weeks. There resulted from this, 7.3 g. (8%) of light, hygroscopic crystals, m. p. 155–156°.

Anal. Calcd. for $C_{27}H_{47}N_5O_2S\cdot 3HCl$: Cl, 17.3; N, 11.35. Found: Cl, 17.0; N, 11.59.

Summary

1. The repetition of some Russian work on 4-aminoquinolines, SN 3294 and 5063, confirmed their antimalarial activity.

2. The following modifications of SN 3294 and 7618 were made: 4-(4-Diethylamino-1-methylbutylamino)-6-dimethylaminoquinoline, 3-bromo-4-(4-diethylamino-1-methylbutylamino)-quinoline, 7-chloro-4-(3-dihexylaminopropylamino)-quinoline, 7-chloro-4-(3-dioctylaminopropylamino)-quinoline, 6-benzylthio-7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline, 4-(4-diethylamino-1-methylbutylamino)-8-quinolinethiol, N-(4-diethylamino-1-methylbutyl)-4-(4-diethylamino-1-methylbutyl-amino)-8-quinolinesulfonamide.

3. The preparation of some 4-haloquinolines required as intermediates for the above compounds is described.

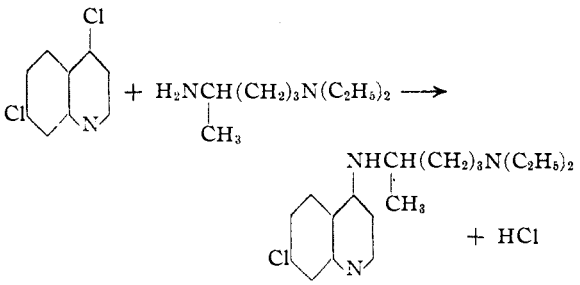
EVANSTON, ILLINOIS RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Synthesis of Antimalarials. V.[1] The Synthesis of Certain 4-Aminoquinoline Derivatives[2]

BY DAVID S. BRESLOW,[3] MELVIN S. BLOOM, JOSEPH C. SHIVERS, JOE T. ADAMS,[4] MARTIN J. WEISS, ROBERT S. YOST AND CHARLES R. HAUSER

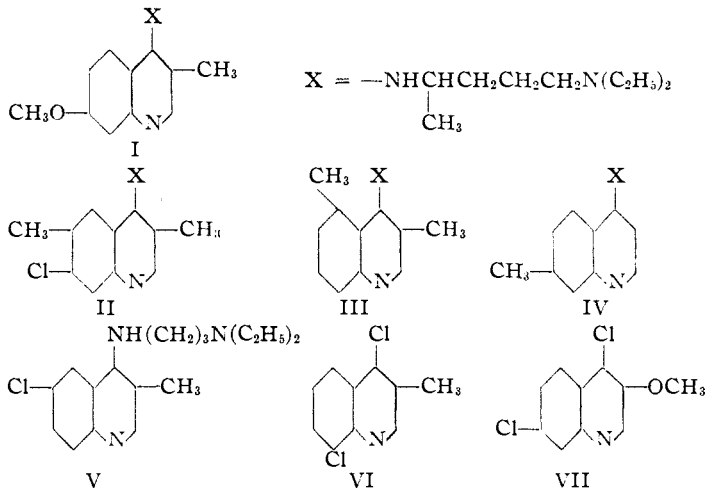
Certain 4-aminoquinolines having appropriate side chains are known to be active antimalarials. These compounds are obtained by coupling a 4-chloroquinoline with a primary amine. This may be illustrated with 4,7-dichloroquinoline and 1-diethylamino-4-aminopentane, the product of which may be considered the standard in this series.



In the present investigation several new 4-chloroquinolines have been synthesized and, in most cases, coupled with 1-diethylamino-4-aminopentane. Also, certain di- and triamines have been prepared and coupled with 4,7-dichloroquinoline. The couplings were effected by heating one mole of the 4-chloroquinoline with two moles of the di- or triamine; in certain cases, the reaction was effected in the presence of a small amount of phenol. The products were usually converted to their phosphate salts. The data on the couplings are summarized in Table II.

Variations in the Nucleus.—Compounds I through V have been synthesized and submitted for testing. Also, nuclei VI and VII have been prepared.

The nuclei for compounds I, II, III, V and VI,



(1) Paper IV of this series, THIS JOURNAL, **68**, 100 (1946).

(2) 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 Duke University.

(3) Present address: Hercules Experiment Station, Wilmington, Delaware.

(4) Present address: Carbide and Carbon Chemicals Corp., Charleston, West Virginia.