[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

The Synthesis of 4-(4′-Amino-1′-methylbutylamino)-7-chloroquinoline and Some 4-(4′-Monoalkylamino-1′-methylbutylamino)-7-chloroquinolines[1]

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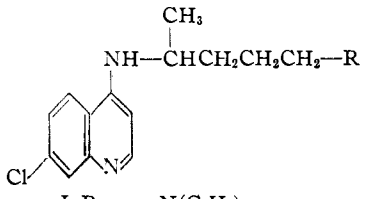
The high antimalarial activity and relatively low toxicity of 4-(4′-diethylamino-1′-methylbutylamino)-7-chloroquinoline (I, R = —$N(C_2H_5)_2$; also known as SN-7618) prompted the synthesis of related compounds. The present paper describes the synthesis of a group of compounds which differ from SN-7618 only in having the terminal tertiary amino group in the side chain replaced by a primary amino group or by various simple aliphatic secondary amino groups.

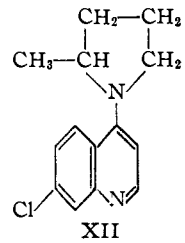


I R = —$N(C_2H_5)_2$
II R = —OH
III R = —Br
IV R = —Cl
V R = —NH_2
VI R = —$NHCH_3$
VII R = —NHC_2H_5
VIII R = —$NHCH(CH_3)_2$
IX R = —$NH(CH_2)_3CH_3$
X R = —$NHCH_2CH(CH_3)_2$
XI R = —$NHCH(CH_3)C_2H_5$

The drugs were prepared from an intermediate compound having the same carbon skeleton but with a hydroxyl group in the terminal position (II, R = —OH). The hydroxyl group in II was replaced with halogen, preferably bromine, and the resulting halide (III hydrobromide) was then converted into the final drugs by reaction with an excess of anhydrous ammonia or the appropriate primary amine.

The intermediate, II, with the terminal alcohol group in the side chain was prepared by the heating of two moles of 4-amino-1-pentanol with one mole of 4,7-dichloroquinoline. About half of the extra mole of 4-amino-1-pentanol could be recovered in pure condition. The synthesis of 4-amino-1-pentanol from acetobutyrolactone through the intermediate stages of acetopropyl alcohol and 1-hydroxy-4-pentanone oxime was worked out in detail; the procedure offers a considerable improvement in yield and quality over the directions of Glynn and Linnell[6] and of Marshall and Perkin.[7]

The conversion of the alcohol, II, to the hydrobromide of III, was accomplished by brief heating with 48% hydrobromic acid containing sulfuric acid. The insoluble liquid product was extracted with chloroform from the reaction mixture. A convenient and satisfactory simplification of the procedure was to use the crude liquid mixture of salts directly without purification in the next step, since the isolation of the pure crystalline hydrobromide of III is wasteful of material and, moreover, the crystalline free base, III, is unstable and readily undergoes ring closure to form the solid hydrobromide of the pyrrolidine derivative, XII.



XII

The intermediate bromo compound, III, was characterized as the crystalline monopicrate.

The liquid salt of III (probably a mixture of hydrobromide and sulfate salts) was allowed to react with an excess of anhydrous liquid ammonia or the appropriate primary aliphatic amine to produce the desired drugs. The side reaction involving cyclization to the pyrrolidine derivative, XII, occurred in every case. The main reaction to form the drug was favored, however, by use of a considerable excess of ammonia or amine without other solvent and by running the reaction at room rather than elevated temperatures. When higher temperatures were employed (autoclave) the conversion to drug was completed in a much shorter time, but the yields were lower than at room temperature. In the case of the preparation of the methylamino drug (VI), one run carried out at 125° with a large excess of methylamine gave some 4-methylamino-7-chloroquinoline. It therefore appears that under drastic reaction conditions the 4-amino side chain can be replaced by the methylamino group. Such a side

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(6) Glynn and Linnell, *Quart. J. Pharm. Pharmacol.*, **5**, 496 (1932).

(7) Marshall and Perkin, *J. Chem. Soc.*, **59**, 867 (1891).

reaction was not observed in any of the reactions at room temperature. The synthesis of the ethylamino drug (VII) is described in detail in the Experimental and is typical of the best conditions for the other members of the series also.

The chloro compound, IV, was prepared as a stable, crystalline free base by the action of thionyl chloride upon II, and was successfully converted into the ethylamino drug, VII, but the over-all yield of IV from II was rather low and the purification time-consuming, so that the alternative procedure involving the bromide hydrobromide proved to be the most convenient.

The crude drugs were isolated as highly viscous, yellow liquid bases containing varying proportions of the pyrrolidine derivative, XII. The viscosity even at high temperatures prevented a clean separation of the by-product by distillation under reduced pressure, and it was therefore necessary to utilize other means of purification. Advantage was taken of the fact that in both the drugs and the pyrrolidine by-product the pK_A of the quinoline nucleus is in the range 7.2–7.7 and the 4-amino group is nearly neutral in character, while the terminal aliphatic amino groups in the drugs are strongly basic, with pK_A values in the neighborhood of 9.8. At an apparent pH of 8–8.2 in alcohol-water solution, the pyrrolidine compound is extractable with ether, while the drugs remain in solution as the mono-acid salts; the drug bases are recoverable upon addition of an excess of strong alkali.

It was advantageous also to form the crystalline oxalate salts following the preliminary separation described above, and to digest the difficultly soluble solids with hot absolute alcohol to dissolve out a small amount of impurity, including some colored material. The oxalates are not as a rule too well defined in composition; consequently, the free bases were recovered from the oxalates and distilled at low pressure. The pale yellow distillates slowly crystallized spontaneously and were in most cases submitted for tests without further treatment.

The properties of the drug bases submitted for tests of antimalarial activity are shown in Table I. The properties of several salts which were submitted for testing are given in Table II. The results of the tests will be reported elsewhere.

One of the drugs of this series (VII, R = $-NHC_2H_5$) was prepared by an alternative method involving the presynthesis of the diamino side chain and its subsequent condensation with 4,7-dichloroquinoline. The product of this series of reactions was identical with the base obtained in the manner described above. This independent synthesis serves as a confirmation of the correctness of the assigned structures. It was considered desirable to develop a method for the presynthesis of the side chains as a more convenient means of preparing large quantities of individual drugs than methods involving intermediates of the type of II or III. Procedures using the halide intermediates are especially suited, on the other hand, for the rapid preparation of a variety of different homologs with a minimum of separate steps.

The side chain was prepared in the form of a mono-N-acetyl derivative, 1-(N-acetyl)-ethylamino-4-aminopentane, in order that the condensation with 4,7-dichloroquinoline would not give the undesired isomeric compound having the ethylamino grouping attached to the quinoline nucleus. Acetopropyl chloride was allowed to react with aqueous ethylamine solution, then without isolation of the intermediate condensation product (probably 1-ethyl-2-methyl-Δ^2-pyrroline[8,9]); treatment of the mixture with hydroxylamine gave 1-ethylamino-4-pentanone oxime. The oxime was isolated as a crystalline solid, then acetylated on the amine group and hydrogenated over Raney nickel to 1-(N-acetyl)-ethylamino-4-aminopentane. The side chain was condensed with 4,7-dichloroquinoline in the usual way and the N-acetyl group removed from the condensation product with hot concentrated hydrochloric acid, yielding VII.

The catalytic hydrogenation of 1-ethylamino-4-pentanone oxime was studied. The product appeared to consist of a mixture of 1-ethylamino-4-aminopentane and 1-ethyl-2-methyl-pyrrolidine, which could be separated by fractional distillation. No attempt was made to condense 1-ethylamino-4-aminopentane directly with 4,7-dichloroquinoline. It has been reported from another laboratory[10] that diamines of this type condense preferentially on the primary amino group and that drugs of the type of VI-XI can be conveniently prepared by such a procedure.

Experimental

1-Hydroxy-4-pentanone Oxime.—A solution of 1072 g. of acetobutyrolactone[11] in three liters of 5% hydrochloric acid was stirred and heated under reflux in a 5-liter round-bottomed flask for three hours; the temperature was raised cautiously to avoid excessive frothing. The solution was then cooled and treated with 700 g. of hydroxylamine hydrochloride and 870 g. of sodium carbonate monohydrate. Solid potassium hydroxide (400 g.) was added with stirring and cooling to maintain the temperature below 60°. After the mixture had stood at room temperature for twenty hours the pH was adjusted to 7–8 with concentrated hydrochloric acid and the crude 1-hydroxy-4-pentanone oxime was extracted with ether for twenty-four hours in a liquid-liquid extraction apparatus. The oxime recovered from the ether was distilled as a colorless, viscous liquid, b. p. 122–124° (0.6 mm.); yield, 72–74% from acetobutyrolactone. The oxime crystallized spontaneously upon standing, and was pure enough for hydrogenation. A sample recrystallized from ethyl acetate formed colorless crystals, m. p. 61.5–62°. Glynn and Linnell[6] and Marshall and Perkin[7] reported that the oxime was liquid and could not be distilled because of dehydration to a cyclic compound. No decomposition was noted under the conditions described above.

(8) Fischer and Orth, "Die Chemie des Pyrrols," Akademische Verlagsgesellschaft, Leipzig, 1934, Vol. I, p. 319 ff.

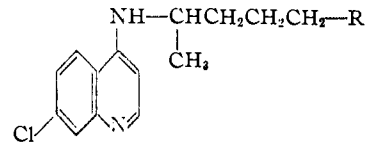
(9) Adams and Mahan, THIS JOURNAL, **64**, 2592 (1942).

(10) D. E. Pearson, W. H. Jones and Arthur C. Cope, THIS JOURNAL, **68**, 1225 (1946).

(11) Supplied by Merck and Company.

TABLE I

4-(4′-ALKYLAMINO-1′-METHYLBUTYLAMINO)-7-CHLOROQUINOLINES



No.	—R	Survey[a] number	M. p.,[b] °C.	Yield,[c] %	Formula
VI	—$NHCH_3$	SN 14,958	104–107.5	48.5	$C_{15}H_{20}ClN_3$
VII	—NHC_2H_5	SN 13,616	100–102	44	$C_{16}H_{22}ClN_3$
VIII	—$NHCH(CH_3)_2$	SN 14,079	100–102	50	$C_{17}H_{24}ClN_3$
IX	—$NH(CH_2)_3CH_3$	SN 14,078	60–63	17[h]	$C_{18}H_{26}ClN_3$
X	—$NHCH_2CH(CH_3)_2$	SN 15,067	67–71	40	$C_{18}H_{26}ClN_3$
XI	—$NHCH(CH_3)C_2H_5$	SN 15,062	65–69	33	$C_{18}H_{26}ClN_3$

Analyses, %							
Carbon		Hydrogen		Nitrogen		Neut. equiv.[g]	
Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
64.85	64.75[e]	7.26	7.55[e]	15.13	15.64[e]	139	142
65.85	65.56[f] 65.66	7.60	7.50[f] 7.43			146	148
66.76	66.82[f] 66.79	7.91	7.52[f] 7.67			153	155
67.59	67.19[f] 67.11	8.19	8.02[f] 7.85			160	162
67.59	67.97[d] 67.64	8.19	8.08[d] 8.05	13.14	13.39[d] 13.25	160	161
67.59	68.10[d] 67.83	8.19	8.19[d] 8.32	13.14	13.04[d] 13.02	160	160

[a] The Survey Number identifies the drug in the files of the Survey of Antimalarial Drugs. The activities of these will be tabulated in a forthcoming monograph. [b] M. p. values for solidified distillates. No b. p. values are given; vapor temperatures varied with apparatus and rate of heating but were usually within the range of 170–200° at approximately 0.05 mm. [c] Values are over-all yields of purified drugs from the carbinol, II. [d] Analysis by Dr. Carl Tiedcke, 366 Fifth Avenue, New York. [e] Analysis by Mr. B. H. Adelson, Northwestern University. [f] Analysis by Mr. William Saschek, Columbia University, College of Physicians and Surgeons. [g] Titration to quinoline endpoint with standard hydrochloric acid (*p*H meter). [h] III·HBr refluxed two hours with an excess of *n*-butylamine; later experience suggests that the yield could be improved by use of lower reaction temperature and longer reaction time.

TABLE II

SALTS OF QUINOLINE BASES

R	Survey number	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
—OH	SN 15,063	108–115	$C_{14}H_{17}ClN_2O\cdot HCl\cdot H_2O$	52.67	52.29[c] 52.14	6.32	6.39[c] 6.35	8.78	8.80[c] 8.86
—NH_2	SN 13,617	234–236 (dec.)	$C_{14}H_{18}ClN_3\cdot H_2SO_4\cdot 2H_2O$	42.26	42.72[c] 42.76	6.08	6.20[c] 6.08	10.56	11.20[c] 11.42
—NHC_2H_5	SN 13,616	220–221 (dec.)	$(C_{16}H_{22}ClN_3)_2(H_2C_2O_4)_3$[a]	53.46	53.01[b] 53.07 52.74[d]	5.90	6.04[b] 5.86 5.74[d]	9.84	9.94[d]

[a] Oxalic acid salt recrystallized from 70% methanol. [b] Analysis by Dr. L. Cavalieri. [c] Analysis by Dr. Carl Tiedcke. [d] Analysis by Mr. B. H. Adelson.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 51.23; H, 9.47. Found[12]: C, 51.28; H, 9.44.

4-Amino-1-pentanol.—Distilled, but not recrystallized, 1-hydroxy-4-pentanone oxime (140 g.) was hydrogenated over 3–4 g. of Raney nickel catalyst at an initial pressure of 1800 lb. per sq. in. The temperature was raised cautiously during thirty minutes to 60° and eventually to 75°; uptake of hydrogen stopped after two mole equivalents had been absorbed. The product was purified by distillation, b. p. 117–119° (25 mm.); yield, 74–80%. A small amount of yellow by-product, b. p. 144–150° (1 mm.), was always formed. The freshly prepared material did not usually crystallize spontaneously, but unreacted 4-amino-1-pentanol recovered from the next step sometimes solidified to a colorless solid with setting point of 32°.

Because of the hygroscopic nature of the amino alcohol it was not analyzed, but was characterized as the dibenzoate, prepared by the Schotten-Baumann method and recrystallized from dilute alcohol, m. p. 99–100° (reported m. p. 87.5°[6]).

Anal. Calcd. for $C_{19}H_{21}NO_3$: C 73.29; H, 6.80. Found[12]: C, 73.31, 73.02; H, 6.27, 7.10.

4-(4′-Hydroxy-1′-methylbutylamino)-7-chloroquinoline (II).—A mixture of 1.6 moles of 4,7-dichloroquinoline[13] and 3.2 moles of 4-amino-1-pentanol was cautiously heated with stirring in a large round-bottomed flask equipped with a thermometer dipping into the liquid and protected by a soda-lime tube. By means of an oil-bath the temperature was brought gradually to 145 ± 2° and held there for four hours (constant stirring). Unless the temperature was carefully controlled the strongly exothermic reaction showed a tendency to become violent. The mixture was cooled to 100°, poured into water, and stirred to induce crystallization. It was washed with water, filtered, and the slightly moist solid recrystallized from 95% alcohol (Darco and Celite). The yield of first crop material was 70–75% of the theoretical, but additional quantities recovered from the first washings (by addition of potassium hydroxide) and from the alcohol filtrates brought the yield of product melting at 178–180° to 85–95% based upon dichloroquinoline. The material so obtained was satisfactory for use in the next step; several recrystallizations from 95% alcohol gave an analytically pure sample of colorless crystalline material, m. p. 179–181°.

Anal. Calcd. for $C_{14}H_{17}ClN_2O$: C, 63.51; H, 6.47; N, 10.58; neut. equiv., 265. Found[14]: C, 63.17; H, 6.41; N, 10.37; neut. equiv., 273.

The mono-hydrochloride mono-hydrate was prepared from the base by mixing 1.5 equivalents of concentrated hydrochloric acid with one molecular equivalent of base

(12) Analyses by Dr. L. Cavalieri.

(13) Supplied by the National Aniline Company.

(14) Analyses by Dr. Carl Tiedcke, 366 Fifth Avenue, New York, N. Y.

in an equal volume of water and recrystallizing the resulting solid from absolute alcohol–ether; needles, m. p. 108–115°; the salt is further described in Table II.

The excess of 4-amino-1-pentanol used in the preparation of II was recovered from the aqueous filtrates remaining after removal of II by saturation of the solution with potassium carbonate and extraction with ethyl alcohol. After purification and distillation, about 0.54 mole of amino alcohol was recovered out of each two moles used in the condensation reaction.

4-(4′-Bromo-1′-methylbutylamino)-7-chloroquinoline Hydrobromide (III·HBr).—To 70 ml. of 48% hydrobromic acid was cautiously added, with cooling and stirring, 15 ml. of concentrated sulfuric acid. Then 26.4 g. (0.1 mole) of the carbinol II was dissolved in the acid mixture and the resulting solution heated to boiling as rapidly as possible in an Erlenmeyer flask. The mixture was simmered gently until the formation of a turbidity denoted the separation of a second phase (usually about five minutes of heating was required). Heating was discontinued at once (longer heating appeared to destroy the product), the mixture was allowed to cool to 50°, and 100 ml. of water was added. The dense, viscous lower layer was taken up in chloroform, and the aqueous layer was extracted with several further portions of chloroform. The chloroform extracts were combined, dried over anhydrous magnesium sulfate, and, after removal of drying agent, the solution of salts of III in chloroform was transferred to the flask to be used for the final step and the solvent removed by distillation under reduced pressure with gentle warming in a water-bath.

The liquid salt obtained by the above procedure probably consisted of a mixture of the hydrobromide and sulfate salts of III. When 48% hydrobromic acid was used alone, the yield was less satisfactory, but a crystalline product could be isolated. Since the hydrobromide could not be prepared easily in pure state and since the crude liquid salt gave good results in the next step, the hydrobromide was not analyzed. Instead, the nicely crystalline, yellow, stable mono-picrate of III was prepared from the hydrobromide in aqueous solution. It melted, after several recrystallizations from alcohol–nitromethane, at 209–210°.

Anal. of III Picrate: Calcd. for $C_{14}H_{16}BrClN_2 \cdot C_6H_3N_3O_7$: C, 43.14; H, 3.44; N, 12.58. Found[14]: C, 43.66, 43.71; H, 3.38, 3.46; N, 12.95, 12.73.

The preparation of the liquid salt of III was carried out many times in the 0.1-mole scale; it was successfully carried out also in runs starting with 0.3 mole of II. The success of the next step was found to depend upon the time of heating of the carbinol II with the acid mixture. Prolonged action of the hot acid upon the mixture containing salts of III caused the immiscible layer partially to redissolve, and the product then subsequently extracted with chloroform yielded little or no drug when treated with amine.

Isolation of the Free Base, III, and Its Cyclization to 4-(2′-Methyl-1′-pyrrolidyl)-7-chloroquinoline (XII).—The viscous liquid salt of III obtained from 0.1 mole of II as described in the preceding section was shaken at 0° with a mixture of 15 g. of sodium carbonate, 100 ml. of water, and 50 ml. of ether. When the ether layer was separated, dried, and concentrated by evaporation, colorless, water-insoluble crystals of the free base, III, separated. The melting point was indefinite and attempted recrystallization from benzene transformed the product into a water-soluble, benzene-insoluble salt. The water-insoluble free base, III, gave the same picrate, m. p. 209–210° (dec.), as that obtained directly from the salts of III.

When the entire amount of free bromo base, III, obtained from 0.1 mole of II was heated for some time at 60–65° it was transformed completely into a water-soluble solid salt, presumably the hydrobromide of XII. From this substance the free pyrrolidine base, XII, was liberated with alkali and purified by distillation; 16.7 g. of a viscous, yellow liquid, b. p. 141–147° (0.02 mm.), was obtained, and this analyzed correctly for 4-(2′-methyl-1′-pyrrolidyl)-7-chloroquinoline. This compound was submitted for antimalarial tests as SN-14,959.

Anal. of XII: Calcd. for $C_{14}H_{15}ClN_2$: C, 68.16; H, 6.13; N, 11.36. Found: C, 67.57; H, 5.92; N, 11.70.[15]

The yellow crystalline mono-picrate of the liquid base, XII, melted at 229–230.5° (dec.) after recrystallization from alcohol–nitromethane.

Anal. of XII Picrate: Calcd. for $C_{14}H_{15}ClN_2 \cdot C_6H_3N_3O_7$: C, 50.48; H, 3.81; N, 14.72. Found[11]: C, 50.51, 50.28; H, 3.78, 3.81; N, 14.69, 14.65.

4-(4′-Ethylamino-1′-methylbutylamino)-7-chloroquinoline (VII) from III Hydrobromide.—The liquid mixture of salts of III was prepared from 0.3 mole of II by the procedure described above. The dry chloroform solution of product was transferred to a 1-liter round-bottomed flask and the solvent removed under reduced pressure. The viscous liquid was evenly distributed over the walls. The flask was then cooled in an ice-bath and 200 ml. of anhydrous ethylamine added. The stopper was wired on tightly and the mixture cooled and shaken until all of the salt of III dissolved. The solution was then allowed to stand for forty-two hours at room temperature. Excess ethylamine was removed by distillation, leaving the crude drug mixed with salts and by-product, XII.

The reaction was also carried out at 125° in an autoclave, affording fair yields after several hours of heating, but side reactions accounted for more of the product at the higher temperature.

The crude product was purified in the following manner. After removal of excess ethylamine the residue was taken up in 200 ml. of ether (chloroform was substituted when difficulty was sometimes encountered as the result of the formation of three-liquid-phase systems), 300 ml. of water, and 100 g. of potassium carbonate. A mixture of liquid bases free of inorganic material was obtained upon removal of solvent from the dried ether (or chloroform) solution. The residual liquid was taken up in an equal volume of alcohol, and water was added to incipient turbidity. Then 6 *N* hydrochloric acid was added until a Beckman *p*H Meter indicated a *p*H reading of 8–8.2; 150 ml. of ether and 600 ml. of water were added and the solution thoroughly extracted with ether to remove the by-product, XII. (The ether extracts yielded the pyrrolidine compound, which proved to be identical with the compound previously obtained directly from the free base, III.) The aqueous solution, upon treatment with a solution of 30 g. of potassium hydroxide in 50 ml. of water, yielded the partially refined drug as an oil, which was removed by extraction with chloroform.

The solvent was removed from the clarified and dried chloroform solution of drug; the residual oil was dissolved in 150 ml. of absolute alcohol and added to a refluxing solution of 55.5 g. of oxalic acid dihydrate in 150 ml. of absolute alcohol. The crystalline oxalate was filtered, washed with absolute alcohol, and digested in 250 ml. of hot absolute alcohol, after which the solution was cooled and filtered. The free base was recovered from the oxalate salt by treatment with alkali in water and extraction with ether. The drug, freed of solvent, was distilled at 0.05 mm. as a highly viscous pale yellow oil at vapor temperatures of 173–175°. (The vapor temperature was dependent upon the apparatus and the rate of heating, therefore, did not represent a true boiling point.) The distillate slowly solidified to a pale yellow solid, m. p. 100–102°. The ethylamino drug and other members of the series were difficult to recrystallize without loss; since recrystallization did not appear to improve the analyses or melting points, the solid bases were submitted for testing without recrystallization. Further data on the compound VII are shown in Table I.

Drugs V-XI from III Hydrobromide.—The procedure described for the ethylamino drug, VII, was used for the preparation of the other drugs of the series, with some modifications in individual cases. The properties of the bases are shown in Table I and of several salts in Table II.

(15) Analysis by Mr. B. H. Adelson.

In each preparation the appropriate basic reagent was used in anhydrous form, and the condensation was carried out in a vessel appropriate for the pressure expected to be developed during the reaction. A small steel autoclave was used for the reactions with liquid ammonia and with the more volatile amines at elevated temperatures. Condensations with the butylamines at room temperature were carried out in an open round-bottomed flask equipped with reflux condenser.

4-(4'-Chloro-1'-methylbutylamino)-7-chloroquinoline (IV) and its Conversion to the Drug, VII.—The method described by Crum and Robinson[16] was used. The carbinol (II, 20 g.) in 40 ml. of chloroform was treated with 12 ml. of thionyl chloride in 10 ml. of chloroform and the temperature was allowed to rise to the boiling point. As soon as the solid had dissolved (ten minutes) the excess of reagent was removed by distillation. The residual oil, upon treatment with alcohol and aqueous alkali, solidified and was recrystallized from alcohol-water. The yield was 11.1 g., m. p. 129–130°, and 3.8 g., m. p. 120–125°. Two recrystallizations from 60% alcohol gave nearly colorless crystals, m. p. 131–131.2°.

Anal. Calcd. for $C_{14}H_{16}Cl_2N_2$: C, 59.37; H, 5.70; Cl, 25.04; N, 9.89. Found[14]: C, 59.18, 59.15; H, 5.97, 5.88; Cl, 25.40, 25.24; N, 10.64, 10.59.

The chloro compound (IV, 15 g., 0.05 mole), 8 g. (0.17 mole) of anhydrous ethylamine, and 10 ml. of ether were heated in a small autoclave for four hours at 140° and the mixture was then allowed to stand for fourteen hours at room temperature. From the reaction mixture 7.6 g. (49%) of VII was isolated; it was identical with the drug prepared from the bromide hydrobromide (III·HBr).

1-Ethylamino-4-pentanone Oxime.—Freshly distilled acetopropyl chloride (120.6 g., one mole) was added with stirring and cooling to 330 ml. of 33% aqueous ethylamine (2.23 moles); the temperature was maintained at 32–36° and the addition time was twenty minutes. The mixture was stirred for an additional hour, after which the two-phase orange-colored mixture was added dropwise with stirring to a solution of 111 g. (1.61 moles) of hydroxylamine hydrochloride and 132 g. of sodium hydroxide in 350 ml. of water. The mixture was agitated for approximately two hours at 33° and then neutralized with 60 ml. of concentrated hydrochloric acid. The oxime was extracted with several portions of benzene (further continuous extraction of the aqueous solution yielded only a small additional quantity of oxime), and was distilled after removal of the benzene; yield, 107 g. (75%), b. p. 110–112° (0.5 mm.). The distillate solidified to a colorless solid, m. p. 74–78°, which tended to darken upon standing.

The initial reaction of acetopropyl chloride and ethylamine may form 1-ethyl-2-methyl-Δ^2-pyrroline as an intermediate. In one run starting with 30 g. of acetopropyl chloride and 92 g. of a 33% aqueous solution of ethylamine, the pyrroline was isolated by extraction with ether and fractional distillation of the organic material. 1-Ethyl-2-methyl-Δ^2-pyrroline was obtained as a fraction of 11.2 g. (40%), b. p. 82° (105 mm.) (reported b. p. 73.5–74.5° (55 mm.)[9]). It darkened upon standing at room temperature, but was preserved without apparent decomposition in the refrigerator. When treated with hydroxylamine hydrochloride and aqueous alkali as described in the preceding paragraph the pyrroline yielded 1-ethylamino-4-pentanone oxime in 31% yield. It is therefore advantageous not to isolate the pyrroline in the preparation of the oxime from acetopropyl chloride.

1-(N-Acetyl)-ethylamino-4-pentanone Oxime.—1-Ethylamino-4-pentanone oxime (78 g.) was acetylated with 55 ml. of acetic anhydride at temperatures not exceeding 100°. The excess of acetic anhydride was decomposed with 10 ml. of water, and the resulting mixture fractionally distilled. The acetylated product was obtained as 58.4 g. (58%) of an orange liquid, b. p. 125–140° (0.06 mm.). In another run, 10 g. of oxime yield 6.4 g. of acetylated product, b. p. 138–140° (0.02 mm.).

1-(N-Acetyl)-ethylamino-4-aminopentane.—1-(N-Acetyl)-ethylamino-4-pentanone oxime (58.4 g.) was hydrogenated over 3–4 g. of Raney nickel catalyst in 30 ml. of methanol previously saturated with dry ammonia at 15°. An initial pressure of 1800 lb. per sq. in. and temperature of 90° were used. Absorption of two moles of hydrogen was complete in about one and one-quarter hours. The reduction product was obtained by fractional distillation; yield, 35.4 g. (61%) of pale green liquid, b. p. 104–120° (0.7–0.8 mm.). An undistillable residue of 10.2 g. remained.

4-(4'-Ethylamino-1'-methylbutylamino)-7-chloroquinoline (VII) from 4,7-Dichloroquinoline and 1-(N-Acetyl)-ethylamino-4-aminopentane.—A mixture of 20 g. (0.1 mole) of 4,7-dichloroquinoline and 34 g. (0.2 mole) of 1-(N-acetyl)-ethylamino-4-aminopentane was heated in an oil-bath at 140–145° for four hours with occasional agitation. The mixture stood at room temperature for sixteen hours, then was liquefied by warming and poured into 100 ml. of water containing 20 ml. of concentrated hydrochloric acid. Basic compounds were liberated by addition of 50 ml. of 37% potassium hydroxide and the mixture was extracted with a little ether to remove unreacted 4,7-dichloroquinoline. Chloroform extraction then removed the acetylated drug. An attempt was made to hydrolyze the N-acetyl group from the side chain of the drug with hot 6 *N* hydrochloric acid, but since most of the material was unchanged after five and one-half hours of refluxing it was necessary to recover the acetylated drug and use a somewhat more severe hydrolytic treatment.

The recovered N-acetylated drug, after being redistilled, was refluxed for six hours with 100 ml. of concentrated hydrochloric acid. An additional 25 ml. of hydrochloric acid was added and the solution refluxed for an additional six hours. The solution was basified and the crude drug extracted in the usual manner and distilled at 0.05 mm. A somewhat low-boiling fraction of 4 g. was collected, then 5.4 g. of drug at vapor temperatures of 164–165° (0.02 mm.). The latter fraction crystallized when seeded with the free base obtained by the alternative procedure described above, and appeared to be identical with the sample previously prepared.

Hydrogenation of 1-Ethylamino-4-pentanone Oxime.—1-Ethylamino-4-pentanone oxime (49.8 g., 0.34 mole) was hydrogenated in absolute alcohol over Raney nickel at an initial hydrogen pressure of 1800 lb. per sq. in. and reaction temperature of 65–70°. The reaction mixture also contained 60 ml. of absolute alcohol previously saturated with dry ammonia at 15° for the purpose of suppressing the formation of secondary amines. The hydrogenation was highly exothermic, and it was therefore necessary to approach the temperature of hydrogenation cautiously in order to avoid uncontrolled rise of temperature with resultant resinification of the organic material. The water was removed from the product by distillation with benzene. Fractional distillation yielded 8.2 g., b. p. 118–124°, which was probably 1-ethyl-2-methylpyrrolidine (reported b. p. 119–120°,[17] 118.5–119.5°[9]), and 6.7 g. of colorless liquid, b. p. 174–181°, which must have been 1-ethylamino-4-aminopentane. The lower boiling fraction behaved like a tertiary amine in the Hinsberg and Schotten–Baumann reactions. The higher boiling fraction reacted like a primary amine in the Hinsberg reaction with benzenesulfonyl chloride and was benzoylated under Schotten–Baumann conditions, but in neither case could the products be induced to solidify.

No attempt was made to condense 1-ethylamino-4-aminopentane directly with 4,7-dichloroquinoline.

Identification of 4-Methylamino-7-chloroquinoline as a By-product in the Preparation of Drug VI.—In one run, 0.05 mole of the carbinol, II, was converted into III hydrobromide in the usual way. The crude liquid salt was treated with a considerable excess of anhydrous methylamine in an autoclave at 125° for three hours. When the product was worked up in the usual way a crystalline solid separated, which, after recrystallization from aqueous

(16) Crum and Robinson, *J. Chem. Soc.*, 561 (1943).

(17) Signaigo and Adkins, THIS JOURNAL, **58**, 359 (1936).

methanol, gave 2.4 g. of tan crystals, m. p. 245–251° (dec.). After purification by sublimation under reduced pressure and further recrystallization, the compound melted at 249–251° and did not show a depression of melting point when mixed with synthetic 4-methylamino-7-chloroquinoline. It showed a neutral equivalent of 196 against standard hydrochloric acid.

A sample of authentic 4-methylamino-7-chloroquinoline was prepared in 67% yield by the condensation of methylamine with 4,7-dichloroquinoline. After purification by recrystallization from methanol it melted at 251.5–252.5°.

Anal. Calcd. for $C_{10}H_9ClN_2$: C, 62.34; H, 4.71; N, 14.54; neutral equivalent, 193. Found[14]: C, 62.41, 62.30; H, 4.71, 4.62; N, 14.70, 14.54.

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Summary

4-(4′-Amino-1′-methylbutylamino)-7-chloroquinoline and six drugs of the series of 4-(4′-monoalkylamino-1′-methylbutylamino)-7-chloroquinolines were synthesized, with alkyl groups as follows: methyl, ethyl, isopropyl, *n*-butyl, isobutyl, and *s*-butyl.

An improved procedure for the preparation of 4-amino-1-pentanol was developed. 1-Ethylamino-4-aminopentane and 1-(N-acetyl)-ethylamino-4-aminopentane were prepared.

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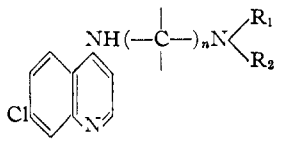
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Synthesis of Monoalkyl-substituted Diamines and their Condensation Products with 4,7-Dichloroquinoline[1]

BY D. E. PEARSON,[2] W. H. JONES AND ARTHUR C. COPE

The antimalarial activity of a number of 7-chloro-4-dialkylaminoalkylaminoquinolines (I) prepared and tested as part of the antimalarial program sponsored by the Committee on Medical Research suggested that similar compounds with side chains terminating in a secondary amino group (II) should be investigated.



I, R_1 and R_2 are alkyl
II, R_1 is H, R_2 is alkyl

Compounds prepared by condensation of 4,7-dichloroquinoline with ethylenediamine, 1,3-diamino-2-propanol and some of their monoalkyl derivatives are described in this paper. Also included are several similar compounds with the following types of side chains, which were investigated more extensively in other laboratories: $-NH(CH_2)_3NHR$[3]; $-NHCH(CH_3)(CH_2)_3NHR$.[4]

Monoisopropyl and cyclohexyl derivatives of ethylenediamine were prepared by reductive alkylation of the diamine with acetone and cyclohexanone. This synthesis appears to be a simpler method for preparing these compounds than alkylation procedures employing alkyl halides which have been used for preparing primary alkyl homologs.[5] 1-Cyclohexylamino-3-amino-2-propanol was prepared in a similar manner from cyclohexanone and 1,3-diamino-2-propanol. Hydrogenation with Adams platinum catalyst at room temperature or 60° in each case gave better yields than reductions in the presence of Raney nickel at higher temperatures and pressures. N-Isopropyltrimethylenediamine was prepared by adding isopropylamine to acrylonitrile and hydrogenating the addition product.[6] Three 1-alkyl amino-4-aminopentanes, $RNH(CH_2)_3CH(CH_3)NH_2$, in which R was isopropyl, isobutyl and tertiary-butyl were prepared by reaction of 5-chloro-2-pentanone with the respective primary amines, followed by reaction with hydroxylamine to give the 5-alkylamino-2-pentanone oximes. The procedure used was based on one employed for the ethylamino homolog by Carmack, Bullitt, Handrick, Kissinger and Von.[4] Catalytic hydrogenation of 5-isopropylamino-2-pentanone oxime produced extensive cleavage and gave low yields of 1-isopropylamino-4-aminopentane under all conditions which were investigated, but a sodium and butyl alcohol reduction procedure was applied successfully to each of the oximes.

The diamines which were prepared and are described in Table I were condensed with 4,7-dichloroquinoline by heating the reactants alone or in the presence of phenol with careful temperature control, according to procedures similar to those

(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 the Massachusetts Institute of Technology.

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(3) Tarbell, Shakespeare, Claus and Bunnett, THIS JOURNAL, **68**, 1217 (1946).

(4) Carmack, Bullitt, Handrick, Kissinger and Von, *ibid.*, **68**, 1220 (1946).

(5) Aspinall, *ibid.*, **63**, 852 (1941), has prepared monomethyl, ethyl and benzylethylenediamine by alkylating N-benzenesulfonyl-N′-acetylethylenediamine in alkaline solution and hydrolyzing the products. Linsker and Evans, *ibid.*, **67**, 1581 (1945), have prepared higher molecular weight primary monoalkylethylenediamines by direct alkylation with alkyl chlorides or bromides.

(6) See ref. 3 for application of this synthesis to other amines and references to the earlier literature.