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.

Acknowledgment.—We wish to thank Dr. Liebe Cavalieri for assistance in several of the preparations described in this paper and for carrying out some of the elementary analyses.

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.

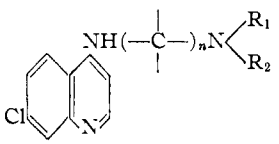
PHILADELPHIA, PENNSYLVANIA RECEIVED APRIL 5, 1946

[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.

(2) Present address: Vanderbilt University, Nashville, Tennessee.

(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.

TABLE I

MONOALKYL-SUBSTITUTED DIAMINES

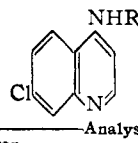
	Compound	Yield, %	B. p. °C.	Mm.	$n^{25}D$	d^{25}_4	Molecular refraction Calcd.	Found
1	cyclo-$C_6H_{11}NHCH_2CH_2NH_2$	83	101–102	14	1.4800	0.9153	43.98	44.15
2	iso-$C_3H_7NHCH_2CH_2NH_2$	50	135.5–137.5	767	1.4350	.8232	32.32	32.39
3	cyclo-$C_6H_{11}NHCH_2CHOHCH_2NH_2$	77	126–128[b]	2	1.4997	1.0135	50.12	49.97
4	iso-$C_3H_7NH(CH_2)_2NH_2$	54	161–162	770	1.4394	0.8271	36.94	36.99
5	iso-$C_3H_7NH(CH_2)_3CH(CH_3)NH_2$	58	55–56	3	1.4400	.8166	46.18	46.56
6	iso-$C_4H_9NH(CH_2)_3CH(CH_3)NH_2$	61	60–61	1	1.4411	.8198	50.80	50.99
7	t-$C_4H_9NH(CH_2)_3CH(CH_3)NH_2$	53	84–87	13	1.4398	.8178	50.80	50.99

	Formula	Analyses: Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Neutral equivalent Calcd.	Found[a]
1	$C_8H_{18}N_2$	67.55	67.65	12.75	12.88	19.70	20.00	71.1	70.5
2	$C_5H_{14}N_2$	58.77	58.83	13.81	13.86	27.42	27.37	51.1	49.9
3	$C_9H_{20}ON_2$	62.73	62.61	11.70	11.90	16.26	16.50	86.2	84.3
4	$C_6H_{16}N_2$	62.01	62.19	13.88	14.06	24.11	24.01	58.1	57.8
5	$C_8H_{20}N_2$	66.60	66.45	13.97	14.01	19.4	19.6	72.2	74.5
6	$C_9H_{22}N_2$	68.29	68.22	14.01	14.14	17.70	17.99	79.2	80.0
7	$C_9H_{22}N_2$	68.29	68.43	14.01	14.01	17.70	17.76	79.2	82.7

[a] Neutral equivalents were determined by titration with 0.1 N hydrochloric acid to an end-point (corresponding to titration of both amino groups) determined with a pH meter with a glass electrode and calomel half cell. [b] Crystallized on standing, m. p. 29–32°.

TABLE II

7-CHLORO-4-AMINOALKYLAMINOQUINOLINES,



R group	Survey number[f]	Yield, %	M. p., °C.	Formula	Analyses: Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Chlorine, % Calcd.	Found	Neut. equiv. Calcd.	Found[a]
$-CH_2CH_2NH_2$	SN 14,724	21[b]	137–139	$C_{11}H_{12}N_3Cl$	59.59	59.7	5.45	5.6	18.97	18.7	15.99	15.9	110.9	110.8
$-CH_2CH_2NHCH(CH_3)_2$	SN 14,155	52[c]	129–130	$C_{14}H_{18}N_3Cl$	63.75	64.06	6.88	6.85	15.93	15.80	13.44	13.48	131.8	132.7
$-CH_2CH_2NHC_6H_{11}$(cyclo-)	SN 14,156	48[d]	151–151.5	$C_{17}H_{22}N_3Cl$	67.20	67.5	7.30	7.42	13.83	13.6	11.67	11.6	151.9	150.9
$-CH_2CHOHCH_2NHC_6H_{11}$(cyclo-)	SN 14,689	37[b]	145.5–146	$C_{18}H_{24}ON_3Cl$	64.76	65.0	7.25	7.5	12.60	12.5	10.63	10.5	167	165.5
$-CH_2CH_2CH_2NHCH(CH_3)_2$	SN 14,846	51[b]	107.5–108	$C_{15}H_{20}N_3Cl$	64.85	64.82	7.26	7.32	15.13	15.00	12.77	12.9	138.9	141.7
$-CH(CH_3)(CH_2)_3NHCH(CH_3)_2$	SN 14,079	48[c]	103–105.5[e]	$C_{17}H_{24}N_3Cl$	66.76	67.04	7.91	8.00	13.74	13.66	11.59	11.37	152.9	153.1
$-CH(CH_3)(CH_2)_3NHCH_2CH(CH_3)_2$	SN 15,067	28[c]	72–74[e]	$C_{18}H_{26}N_3Cl$	67.59	67.74	8.19	8.20	13.14	13.01	11.08	11.05	160	162.7
$-CH(CH_3)(CH_2)_3NHC(CH_3)_3$		49[d]	117–117.5	$C_{18}H_{26}N_3Cl$	67.59	67.69	8.19	8.18	13.14	13.18	11.08	11.07	160	162.8

[a] Determined as in footnote (a) Table I by titration to the relatively sharp second end-point. [b] Recrystallized from benzene. [c] Recrystallized from cyclohexane. [d] Recrystallized from methylcyclohexane. [e] Melting points were not depressed when mixed with samples prepared by another method by Carmack, Bullitt, Handrick, Kissinger and Von (ref. 4). [f] 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.

developed by Drake, *et al.*[7] A variation from the procedure usually employed by others consisted in the use of one rather than two molar equivalents of the diamine side chains. Excess 4,7-dichloroquinoline was removed from the hydrochlorides of the coupling products by extraction with ether, after which the bases were liberated with alcoholic alkali. The coupling products are described in Table II. The first five were purified by recrystallization, and the remaining three by a procedure including direct extraction with ether followed by re-extraction from a buffered solution at pH 4 to remove any remaining 4,7-dichloroquinoline, distillation at pressures below fifty microns, and crystallization.

Proof was obtained that coupling of the diamines with 4,7-dichloroquinoline occurred with the primary rather than the secondary amino group in three cases, and is assumed for the remaining compounds. 7-Chloro-4-(2-cyclohexylaminoethylamino)-quinoline gave no nitrogen in an analysis for primary amino groups by the Van Slyke method. Two of the drugs (SN 14,079 and SN 15,067) were proved by mixed m. p. to be

(7) Drake, Creech, Garman, Haywood, Peck, Van Hook and Walton, THIS JOURNAL, **68**, 1208 (1946).

identical with samples prepared by another method which could not lead to isomeric structures,[4] which Dr. Marvin Carmack kindly supplied.

Ethylenediamine and 1,3-diamino-2-propanol also were condensed with 4,7-dichloroquinoline. The products from condensation of ethylenediamine with both one and two moles of 4,7-dichloroquinoline were obtained, while only 1,3-bis-(7-chloro-4-quinolylamino)-2-propanol was isolated from the reaction with 1,3-diamino-2-propanol.

Antimalarial activity of the compounds described in this paper will be reported elsewhere. Most of them will be included in a monograph in preparation by the Survey of Antimalarial Drugs

Experimental[8]

Monoalkyl-substituted Diamines.—The following procedures were used in preparation of the diamines listed in Table I. Yields, physical constants and analytical data for each of the compounds are recorded in the table.

N-Cyclohexylethylenediamine.—Cyclohexanone (25 g., 0.25 mole) and anhydrous ethylenediamine[9] (30 g., 0.5 mole) were mixed and allowed to stand for one hour, during which time considerable heat was evolved. The mixture was added to 0.5 g. of pre-reduced Adams platinum oxide catalyst in 25 ml. of absolute alcohol and hydrogenated at room temperature and an initial hydrogen pressure of two atmospheres. The reduction was complete in twelve hours. The product was purified by distillation through a 20-cm. Widmer column.

N-Isopropylethylenediamine.—Acetone (116 g., 2.0 moles) was poured slowly into anhydrous ethylenediamine (240 g., 4.0 moles) with occasional cooling in ice to moderate the reaction. After standing overnight the solution was added to 50 ml. of absolute alcohol containing 2.0 g. of pre-reduced Adams platinum oxide catalyst, heated to 60° and hydrogenated at that temperature and an initial pressure of two atmospheres. The reduction was complete in twelve hours. Distillation through a glass helix packed column with approximately twenty theoretical plates gave 101.6 g. of N-isopropylethylenediamine.

1-Cyclohexylamino-3-amino-2-propanol.—Cyclohexanone (49 g., 0.5 mole) was added slowly to redistilled 1,3-diamino-2-propanol (90 g., 1.0 mole) with cooling. The solution was added to 1 g. of pre-reduced platinum oxide catalyst in 50 ml. of absolute alcohol, heated to 60°, and hydrogenated at 60° and an initial pressure of two atmospheres. Reduction was 90% complete in five hours and the theoretical amount of hydrogen had been absorbed after sixteen hours. The catalyst was filtered and the product (66 g., described in Table I) purified by fractionation through a column containing a 25 × 1.5 cm. section packed with glass helices.

Hydrogenation of the reaction product from one mole of cyclohexanol and two moles of 1,3-diamino-2-propanol in 400 ml. of absolute alcohol in the presence of 6 g. of Raney nickel catalyst at 160° and an initial hydrogen pressure of two hundred atmospheres during twelve hours gave 80 g. (47%) of 1-cyclohexylamino-3-amino-2-propanol.

N-Isopropyltrimethylenediamine.—β-Isopropylaminopropionitrile was prepared by adding freshly distilled acrylonitrile (106.1 g., 2.0 moles) dropwise with stirring during two hours to isopropylamine (177.3 g., 3.0 moles) at a temperature below 30°. The reaction mixture was stirred overnight at room temperature and fractionated through a 20-cm. Widmer column. The yield of β-isopropylaminopropionitrile was 213 g. (95%), b. p. 86–87° (17 mm.); $n^{25}D$ 1.4290; d^{25}_4 0.8641; M_D calcd. 33.34, found 33.47; neut. equiv. calcd. 112.2, found (by electrometric titration) 111.2.

Anal. Calcd. for $C_6H_{12}N_2$: C, 64.24; H, 10.79. Found: C, 63.99; H, 11.01.

β-Isopropylaminopropionitrile (190.0 g., 1.69 moles) was hydrogenated in the presence of 20 g. of Raney nickel catalyst during two hours at 100° with an initial hydrogen pressure of one hundred and twenty atmospheres. Two fractionations through a 20-cm. Widmer column gave 105.3 g. of N-isopropyltrimethylenediamine. A higher boiling fraction (51 g., b. p. 104–106° (1 mm.)) was not investigated.

1-Alkylamino-4-aminopentanes.—The 5-alkylamino-2-pentanone oximes described below were reduced by the following general method, adapted from a procedure used for the reduction of oximes by Suter and Moffett.[10]

The oximes (0.1 mole) were dissolved in 250 ml. of *n*-butyl alcohol, which was refluxed gently while sodium (23 g., 1.0 mole) was added in small portions during a period of two hours. Refluxing was continued until all of the sodium had dissolved. The cooled mixture was poured into 500 ml. of water, cooled in ice, and acidified by slow addition with stirring of a slight excess of concentrated hydrochloric acid. The solution was warmed in a water-bath and concentrated *in vacuo* until salt began to precipitate. The cooled residue was made strongly alkaline with 40% sodium hydroxide solution, saturated with potassium carbonate, and extracted several times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. After removal of the ether the residue was fractionated *in vacuo*.

Catalytic hydrogenation of 5-isopropylamino-2-pentanone oxime under various conditions gave poorer yields of 1-isopropylamino-4-aminopentane than were obtained by the above procedure. Hydrogenation at 25 to 80° in the presence of Raney nickel in alcohol as a solvent with an initial hydrogen pressure of one hundred atmospheres gave a 19% yield. Hydrogenation at one to two atmospheres pressure and 65° in the presence of Adams platinum catalyst in alcohol gave 15% of the diamine, while at 25° in 90% alcohol containing three equivalents of hydrochloric acid the yield was 24%. Low boiling cleavage products were formed in each case.

5-Isopropylamino-2-pentanone Oxime.—Isopropylamine (45 g., 0.25 mole) was added to a solution of sodium carbonate (26.5 g., 0.25 mole) in 300 ml. of water and 50 ml. of alcohol. The solution was cooled to 20–30° and freshly distilled 5-chloro-2-pentanone (60 g., 0.5 mole) was added dropwise with stirring while the temperature was maintained at 20–30°. After standing overnight the solution was added rapidly with stirring to a solution of hydroxylamine prepared by adding 30 g. of sodium hydroxide in 100 ml. of water to 53 g. (0.75 mole) of hydroxylamine hydrochloride in 100 ml. of water. During the addition the temperature was kept at 20–25°. After standing overnight the mixture was extracted continuously with ether for twelve hours. The ether solution was dried over magnesium sulfate and concentrated under diminished pressure. The residue of the crude oxime crystallized as an orange solid, m. p. 65–75° (yield 59 g.). Two crystallizations from cyclohexane gave 36 g. (50%) of a slightly yellow product, m. p. 77–78°, which was used for reduction to the diamine. An analytical sample was prepared by several crystallizations from benzene; m. p. 80.5–81.5°.

Anal. Calcd. for $C_8H_{18}ON_2$: C, 60.71; H, 11.46; N, 17.70; neut. equiv., 158.2. Found: C, 60.84; H, 11.5; N, 17.6; neut. equiv. (by acidimetric titration of the amino group), 161.8.

The oxime was distilled in preparations which did not crystallize readily; b. p. 92–97° (0.5 mm.).

5-Isobutylamino-2-pentanone Oxime.—Isobutylamine was used in a procedure exactly similar to the one described above. The liquid product was purified by distilla-

(8) Melting and boiling points are uncorrected.

(9) Technical 70% ethylenediamine was dehydrated by treatment with successive portions of solid potassium hydroxide and warming on a steam-bath, followed by addition of sodium and distillation in the presence of metallic sodium.

(10) Suter and Moffett, THIS JOURNAL, **59**, 487 (1937).

tion (b. p. 91–101° (0.5 mm.)), after which it solidified. The yield from one molar quantities of reactants was 58 g. (34%), m. p. 43.5–45°. An analytical sample was prepared by one crystallization from cyclohexane; m. p. 45–46°.

Anal. Calcd. for $C_9H_{20}ON_2$: C, 62.75; H, 11.70; N, 16.27; neut. equiv., 172.3. Found: C, 62.98; H, 11.60; N, 15.85; neut. equiv. (by acidimetric titration), 172.2.

5-*t*-Butylamino-2-pentanone Oxime.—*t*-Butylamine[11] (20.0 g., 0.27 mole) was added to anhydrous potassium carbonate (37.3 g., 0.27 mole). The mixture was stirred vigorously and heated in a bath at 50–60° while 5-chloro-2-pentanone (32.6 g., 0.27 mole) was added dropwise during one hour. Benzene (75 ml.) was added and the bath was heated to 90–95° during four hours and held at that temperature for twenty hours. The benzene solution was filtered and washed with three 100-ml. portions of 3 *N* hydrochloric acid. The combined acid extracts were washed with benzene and then made alkaline by adding potassium carbonate. The solution so obtained was added dropwise to 0.27 mole of neutral hydroxylamine solution prepared as described above and stirred overnight at room temperature. Continuous extraction with ether for twenty-four hours followed by concentration of the ether extract gave 7.3 g. of the crude oxime as a white solid, m. p. 120–126°. Recrystallization from alcohol gave 5.2 g. (11%), m. p. 129–131°, which was used for reduction to the diamine. An analytical sample (recrystallized from alcohol) was prepared from a similar product obtained by heating equimolecular quantities of 5-chloro-2-pentanone and *t*-butylamine; m. p. 134–134.5°.

Anal. Calcd. for $C_9H_{20}ON_2$: C, 62.74; H, 11.70; N, 16.26; neut. equiv., 172.3. Found: C, 62.46; H, 11.82; N, 16.15; neut. equiv. (by acidimetric titration), 174.4.

7-Chloro-4-monoalkylaminoalkylaminoquinolines.—The compounds described in Table II were prepared by condensing 4,7-dichloroquinoline with the monoalkyl-substituted diamines listed in Table I by one of the two following procedures. Procedure A was used for the diamines containing a $-CH_2NH_2$ group, and B for the 1-alkylamino-4-aminopentanes.

A.—4,7-Dichloroquinoline (40.6 g., 0.205 mole) and the diamine (0.20 mole) were heated slowly with stirring in an oil-bath. The temperatures of the bath and the reaction mixture were observed until an exothermic reaction started, as indicated by a sudden rise in the reaction temperature, which usually occurred between 120 and 130°. The mixture was cooled slightly and held at a temperature a few degrees below this point for one to two hours. The reaction mixtures became very viscous and usually solidified. The temperature was raised slowly to 130–135° and held there for an additional two hours. After cooling, the solid, hygroscopic reaction mixtures were pulverized and extracted with ether (in a few instances with petroleum ether) overnight in a Soxhlet extractor to remove any excess 4,7-dichloroquinoline. Occasionally the solids coagulated during extraction, in which case they were ground again and re-extracted. The products were dissolved in hot alcohol and made alkaline, with a slight excess of sodium hydroxide. The hydrated bases which separated on cooling and dilution with water were dissolved in benzene, cyclohexane or methylcyclohexane and boiled to remove water of hydration. On cooling the anhydrous bases separated as white or pale yellow solids which were purified by recrystallization.

B.—The 1-alkylamino-4-aminopentane derivatives were added to approximately 25% of their weight of phenol and a 2 to 3% molar excess of 4,7-dichloroquinoline. The mixtures were stirred and heated at 150–160° for four hours. The rather dark, viscous reaction mixtures formed glasses on cooling, which were dissolved in hot alcohol and poured slowly into a large excess of cold 10% sodium hydroxide solution. The alkaline mixtures were heated on a water-bath and concentrated under diminished pressure to remove alcohol and any unchanged diamine. The products separated as oils from the residue, and were separated by several extractions with ether. In each case the ether solution was extracted with a slight excess of 3 *N* hydrochloric acid and the acid extract was buffered to *p*H 4 by addition of sodium acetate. The buffered solution was extracted with ether to remove unchanged 4,7-dichloroquinoline and then made strongly alkaline with sodium hydroxide. The product was removed by several extractions with ether. The ether extracts were dried over potassium carbonate, concentrated, and the residue was distilled in a small molecular still at pressures below fifty microns. The compounds distilled at bath temperatures of 180–200° as viscous yellow oils which solidified on standing and were purified by recrystallization.

4,4-(Ethylenediimino)-*bis*-(7-chloroquinoline) (SN 14,725) and **4-(2-Aminoethylamino)-7-chloroquinoline** (SN 14,724).—Anhydrous ethylenediamine (12.0 g., 0.2 mole) and 4,7-dichloroquinoline (40.6 g., 0.205 mole) were added to 40 g. of phenol and heated to 110–120° for four hours in an oil-bath. In the early stages of the exothermic reaction the mixture was cooled slightly whenever the temperature of the reaction mixture exceeded the bath temperature by 5°. The product was cooled, pulverized and extracted with ether for six hours. The solid mixture of hydrochlorides was added to a solution of 50 g. of potassium hydroxide in 300 ml. of water and 400 ml. of alcohol and shaken mechanically overnight. Filtration of the mixture separated 20 g. of crude 4,4-(ethylenediimino)-bis-(7-chloroquinoline), a very insoluble high-melting solid which was purified by recrystallization from 800 ml. of diethyleneglycol and washing with hot alcohol. The yield of the pure compound (assigned code number SN 14,725 by the Survey of Antimalarial Drugs) was 14 g. (37%); m. p. 334.5–337° (dec.).

Anal. Calcd. for $C_{20}H_{16}N_4Cl_2$: C, 62.67; H, 4.21; N, 14.62; Cl, 18.50. Found: C, 62.6; H, 4.6; N, 14.4; Cl, 18.4.

The alkaline filtrate was concentrated *in vacuo* to remove alcohol. Crude 4-(2-aminoethylamino)-7-chloroquinoline (18 g.) separated from the residual water solution on cooling. Two crystallizations from benzene yielded 9 g. of the pure compound (Table II).

1,3-*bis*-(7-Chloro-4-quinolylamino)-2-propanol (SN 14,865).—1,3-Diamino-2-propanol (17.1 g., 0.19 mole) and 4,7-dichloroquinoline (39.6 g., 0.2 mole) were added to 20 g. of phenol. The mixture was heated in a bath at 120–135° with stirring. After one hour the temperature of the reaction mixture rose suddenly to 175°. The product was cooled, ground and extracted with ether in a Soxhlet extractor overnight. The solid was again ground, re-extracted for several hours, and then dissolved in 500 ml. of alcohol. The solution was made alkaline by addition of 200 ml. of 15% potassium hydroxide solution. The alcohol was removed by concentration *in vacuo*. The crude solid which was separated by filtration (25 g.) was purified by three crystallizations from alcohol, which gave 15 g. (36%) of pure 1,3-bis-(7-chloro-4-quinolylamino)-2-propanol (assigned code number SN 14,865). This compound had a double melting point; m. p. 143–145°, resolidifying and remelting at 261–263° (dec.).

Anal. Calcd. for $C_{21}H_{18}ON_4Cl_2$: C, 61.02; H, 4.39; N, 13.56; Cl, 17.15; neut. equiv., 206.7. Found: C, 60.77; H, 4.37; N, 13.7; Cl, 17.1; neut. equiv. (by acidimetric titration), 208.1.

The 1:1 condensation product which presumably was present in the reaction mixture was not isolated.

We are indebted to Mr. S. M. Nagy and Mrs. C. K. Fitz for all analyses.

Summary

Monoalkyl-substituted diamines have been prepared by reductive alkylation of ethylenediamine and 1,3-diamino-2-propanol with acetone or cyclohexanone, and by sodium and butyl alcohol reduc-

(11) We are indebted to Dr. George H. Coleman for supplying this intermediate.

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]

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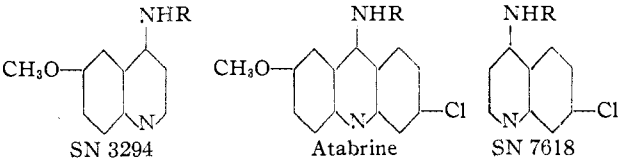
Because of the reported antimalarial activity[2] of 4-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline (SN 3294) and 4-(3-diethylamino-1-methylpropylamino)-6-methoxyquinoline (SN 5063) it seemed to be desirable to reinvestigate these compounds. Their synthesis by the method described by Magidson 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

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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 G. 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).