Alkylaminoalkyl Derivatives of 8-Aminoquinoline[1]

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Derivatives of 8-aminoquinoline, notably Pamaquine (Plasmochin), display an apparently unique property in that they exert a curative action against relapsing malaria (*Plasmodium vivax*) infections when administered in conjunction with quinine.[2] Pamaquine, however, suffers from the disadvantage of being excessively toxic, and is reputed to be particularly so to non-Caucasian races. It therefore became of importance to synthesize a variety of derivatives of 8-aminoquinoline in the hope that antimalarial activity could be increased or that toxicity could be decreased. In the present paper, we present the synthesis of a number of drugs belonging in this category. The results of tests of the substances here described against various malarias will be described elsewhere.[2]

Despite the relatively large number of 8-aminoalkylaminoquinoline derivatives heretofore described in the literature, it is curious that few such substances embracing a secondary or primary terminal amino group have been prepared. Accordingly, primary attention has been directed to the synthesis of such derivatives. In addition, other derivatives of 8-aminoquinoline have been prepared.

In the current paper, the synthesis of the final derivatives of 8-aminoquinoline only is described in most cases. The preparation of the various alkylaminoalkyl halides required as intermediates is described in an accompanying paper.[3] Although the present communication deals largely with variations in the side chain of 6-methoxy-8-alkylaminoalkylaminoquinolines, opportunity has been taken to introduce nuclear variations of the quinoline ring system while holding the side chain constant or introducing only minor variations. Thus, the 5,6-dimethoxy-8-aminoquinoline nucleus, for which enhanced activity has been claimed,[4] has been chosen for the nucleus of several of the drugs prepared. On the other hand, drugs derived from other nuclei have been synthesized, as a rule using only two side chains— namely, the 2-diethylaminoethyl- and 6-diethylaminohexylamino residues. This choice was made with the feeling that the two side chains chosen, both readily available, would furnish a good over-all picture of the relative effectiveness of nuclear variations in the cases of relatively short and long alkyl groups.

Details of the syntheses of the nuclear variants of 8-aminoquinoline in so far as they represent new chemical individuals also will be described for the most part elsewhere. In many cases, the syntheses of the requisite 8-nitroquinolines were carried out in laboratories other than our own, and, because of the instability of the corresponding amino derivatives, the nitro compounds were reduced in our laboratories immediately prior to condensation with the side chain. The synthesis of 5,6-dimethoxy-8-aminoquinoline has been described previously.[5]

In the condensation of an 8-aminoquinoline with an alkylaminoalkyl halide, four typical procedures have been used. These are described in detail, together with their limitations, in the experimental part of this paper. The final drugs were purified as rigorously as possible by distillation and then converted to stable non-hygroscopic salts. Oxalates were found to be the most convenient salts for the majority of the drugs, and, since the dosage of drugs of this chemical group is usually small, the amount of oxalic acid present is not deleterious. However, it was found in many cases that oxalic acid did not unite in stoichiometric ratio with the organic base with the result that the elementary analyses deviated considerably from those postulated on the basis of a strict stoichiometrical relationship. Accordingly, in such cases the percentages of base and oxalic acid in the salts were determined. From these values the expected carbon and hydrogen figures were calculated. This method of analysis brought the observed carbon and hydrogen data into line with the calculated.

As a final check on the purity of the drugs, they were subjected to analysis for homogeneity by the counter current distribution technique of Craig.[6] Since rearrangements may occur during attachment of the side chain to the nucleus,[7] the counter current method provides a very useful means for detecting isomeric substances which would otherwise pass unnoticed. In this way the relative purity of each drug has been ascertained for the first time.

The drugs prepared, together with pertinent data on them, are listed in Table I. The sub-

(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 Columbia University.

(2) Antimalarial Drugs 1941–1945, published by the Survey of Antimalarial Drugs, in press.

(3) Elderfield, *et al.*, THIS JOURNAL, **68**, 1516 (1946).

(4) Schönhöfer, *Z. physiol. Chem.*, **274**, 1 (1942).

(5) Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946).

(6) Craig, *J. Biol. Chem.*, **155**, 519 (1944); Craig, Golumbic, Mighton and Titus, *ibid.*, **161**, 321 (1945).

(7) Elderfield, *et al.*, THIS JOURNAL, **68**, 1516 (1946).

stances are all derived from Type formula I. The designation SN refers to numbers assigned the drugs by the Survey of Antimalarial Drugs. The activities of the drugs will be reported in a forthcoming monograph.[2]

$$R_6 \diagup \overset{R_5 \quad R_4}{\diagdown} R_3$$
$$R_7 \diagdown \underset{R_8}{\diagup} \underset{N}{\diagup} R_2$$

I
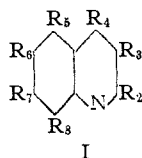
Of the drugs listed, only five require further comment. In experiment 14, the side chain was used in the form of the bromide hydrobromide directly as obtained by cleavage of the ether linkage in 1-methoxy-5-diethylaminopentane. In subsequent runs (experiments 15 and 16) purified side chain compound was used. The drug prepared in experiment 32 was shown to be reasonably homogeneous by the 8-plate technique of Craig. However, when the 24-plate technique was applied, the substance appeared to consist of two components in approximately equal amounts. We interpret this to indicate a possible separation of the two racemates.

In experiment 39, the drug obtained directly was badly contaminated. No explanation for this is at hand. However, by application of a modification of the 8-plate counter current technique, it was possible to remove the contaminants, leaving acceptably pure material. The curves showing the separation are given in Fig. 1.

In experiments 35 and 55, the presence of a third nitrogen in the side chain required some deviation from the standard procedures.

Experimental[8,9]

In all of the preparations involving 6-methoxy-8-aminoquinoline, commercial 6-methoxy-8-aminoquinoline (Winthrop Chemical Co., Inc.) was used after distillation *in vacuo* and recrystallization from methanol.

Coupling of 8-Aminoquinolines with Aminohalides. Procedure A.—This is substantially the method of Rohrmann and Shonle.[10] A mixture of 0.1 mole of an 8-aminoquinoline and 0.11 mole of amino halide was refluxed in 60 ml. of absolute alcohol for sixty hours. The reaction mixture was diluted to 300 ml., made strongly alkaline with sodium hydroxide and extracted with ether. After drying and removal of the solvent, the drug base was distilled directly at a pressure less than 0.5 mm. under nitrogen, the forerun of unreacted 8-aminoquinoline being collected separately.

Procedure B.—Based on information secured from Germany,[11] this method, which involves use of an extra mole of the 8-aminoquinoline as a buffer and of the side chain in the form of its salt, has given good results, particularly when applied to the coupling of a secondary halide. It is described in detail in the preceding paper.[7]

Procedure C.—Substitution of sodium acetate for an extra mole of nucleus as a buffer has been advantageous

(8) All melting points are corrected.

(9) Microanalyses by Mr. William Saschek and the Misses Lois May and Lathrope Baker.

(10) Rohrmann and Shonle, THIS JOURNAL, 66, 1640, 1643 (1944).

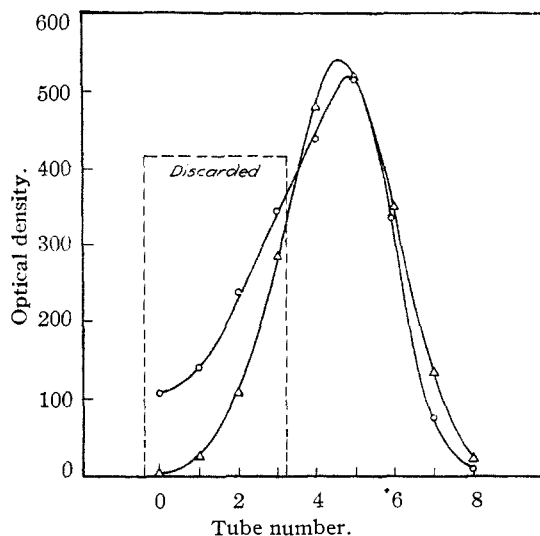(11) Private communication from Dr. K. C. Blanchard, OSRD Intelligence Representative.

Fig. 1.—System chloroform *vs.* 1 *M* (total) citrate buffer at *p*H 3; concentration of base, 21.3 mg. per ml. of each phase; concentration determined by absorption at 365 mμ; Δ, theoretical points; O, experimental points.

in cases where the nucleus has been inaccessible or where primary or secondary amino groups are present in the side chain. A mixture of 0.1 mole of the 8-aminoquinoline, 0.1 mole of aminoalkyl chloride hydrochloride (or aminoalkyl bromide hydrobromide), 0.2 mole of sodium acetate and 50 ml. of 50% alcohol was refluxed for seventy-two hours. It was then diluted to 250 ml. and worked up as in Procedure A.

Procedure D.—This has been a useful substitute in special cases where a difficultly obtainable nucleus is available. A mixture of 0.1 mole of 8-aminoquinoline and 0.2 mole of aminoalkyl halide in the form of its salt was heated with water as in Procedure B using sufficient disodium phosphate–citric acid buffer to provide a *p*H of 4.8. The reaction was worked up as in Procedure B.

Preparation of Salts of the Bases.—For the preparation of oxalates, the free drug base was dissolved in about fifty volumes of anhydrous ether. To this solution was added an amount of oxalic acid calculated to furnish a 1:1 ratio of base to acid dissolved in sufficient absolute alcohol that the final solution contained about 10% alcohol. In most cases the crystalline oxalate separated immediately. In others it was necessary to refrigerate the solution with occasional scratching. If the salt separated as an oil, the supernatant liquor was decanted and the salt generally crystallized on rubbing under fresh anhydrous ether. The oxalates were recrystallized from absolute alcohol or isopropanol. For the preparation of hydrochlorides or hydroiodides, the calculated amount of acid was added to the ethereal solution of the base.

Determination of Oxalic Acid and Base Content.—A sample of approximately 0.3 g. of an 8-aminoquinoline oxalate, weighed to the nearest mg., was dissolved in 20–30 ml. of water by gentle heating. If the drug is particularly insoluble, solution may be hastened by addition of a few drops of hydrochloric acid. The cooled solution was transferred quantitatively to a 250-ml. separatory funnel, made strongly basic with 10% sodium hydroxide solution and extracted with five 30-ml. portions of absolute ether. The combined ether extracts were washed with 20 ml. of water and the washings were added to the original aqueous solution.

The ether solution was dried for at least two hours over 10–15 g. of anhydrous potassium carbonate. This may be done at room temperature, but if the solution is to be left overnight, it should be stored in a dark cool place. The solution was filtered into a 300-ml. round-bottom flask and

<div align="center">

TABLE I

DERIVATIVES OF 8-AMINOQUINOLINE

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No.	Survey Number	R_8	Other R's	Method	B. p. of base °C.	Mm.	Yield, %	Salt
1	3,114	$NH(CH_2)_2N(C_2H_5)_2$[a]	$R_6 = OCH_3$	A	170–172	0.15	50	Oxalate
2	3,114	....	....	A	170–175	.2	50	Oxalate
3	3,115	$NH(CH_2)_3N(C_2H_5)_2$[c]	$R_6 = OCH_3$	A	190–195	.2	63	di-HI
4	3,559	$NH(CH_2)_3NHCH(CH_3)_2$[e]	$R_6 = OCH_3$	C	175–180	.2	40	Mono-oxalate
5	8,233	$NHCH(CH_3)(CH_2)_3N(C_2H_5)$[g]	$R_5 = R_6 = OCH_3$	D	190–195	.5	27	di-HI·H_2O
6	8,233	....	....	D	179–185	.3	21	Oxalate
7	9,972	$NHCH(CH_3)(CH_2)_3NHCH(CH_3)_2$	$R_5 = R_8 = OCH_3$	D	190–195	.3	20	Oxalate
8	11,392	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	$R_5 = Cl; R_6 = OCH_3$	h	165–170	.2	45	di-HI
9	11,625	$NH(CH_2)_3N(C_2H_5)_2$	$R_5 = Cl; R_6 = OCH_3$	A	178–180	.3	25	di-HI·H_2O
10	11,889	$NH(CH_2)_3N(C_2H_5)_2$[i]	$R_5 = R_6 = OCH_3$	A	172–173	.2	57	di-HI
11	12,106	$NH(CH_2)_3N(C_2H_5)_2$	$R_2 = C_6H_5$	A	180–185	.15	69	di-HI
12	12,110	$NH(CH_2)_3N(C_2H_5)_2$	$R_2 = C_6H_5; R_6 = OCH_3$	A	205–210	.2	50	di-HI
13	12,903	$NH(CH_2)_3NHC_2H_5$	$R_6 = OCH_3$	C	175–180	.3	48	di-HCl
14	12,904	$NH(CH_2)_3N(C_2H_5)_2$[j,k]	$R_6 = OCH_3$	C	185–189	.15	48	di-HI
15	12,904	..............[k,l]	....	B	178–181	.3	19	Oxalate
16	12,904	..............[k,m]	....	B	177–180	.3	45	Oxalate
17	12,905	$NH(CH_2)_3O(CH_2)_3N(C_2H_5)_2$	$R_6 = OCH_3$	A	178–180	.2	10	None
18	13,125	$NH(CH_2)_3N(C_2H_5)_2$[n]	$R_6 = OH$	..	...		55	di-HBr·H_2O
19	13,155	$NH(CH_2)_3N(C_2H_5)_2$[o]	$R_5 = OC_6H_5; R_6 = OCH_3$	A	200–250	10^{-5}	..	Oxalate
20	13,232	$NH(CH_2)_6NHCH(CH_3)_2$	$R_6 = OCH_3$	A	188–189	.2	20	HCl·H_2O
21	13,232	....	....	C	180–185	.3	25	Oxalate
22	13,233	$NH(CH_2)_6NHCH_2CH_2CH_3$[p]	$R_6 = OCH_3$	A	185–189	.2	30	di-HI
23	13,233	....	....	A	...		..	Oxalate
24	13,272	$NHCH(CH_3)(CH_2)_3NH_2$	$R_4 = OCH_3$	B	175–177	.2	28	Half oxalate
25	13,272	....	....	B	175–179	.2	14	Oxalate
26	13,272	....	....	B	165–170	.002	18	Oxalate
27	13,273	$NHCH(CH_3)(CH_2)_3NHC_2H_5$	$R_6 = OCH_3$	B	185–190	.4	28	Oxalate
28	13,274	$NHCH(CH_3)(CH_2)_3NHCH(CH_3)_2$	$R_6 = OCH_3$	B	175–178	.2	35	Oxalate
29	13,354	$NH(CH_2)_6NHCH_3$	$R_6 = OCH_3$	A	185–188	.15	35	Mono-oxalate
30	13,355	$NH(CH_2)_3CH(C_2H_5)NHC_2H_5$	$R_6 = OCH_3$	B	167–169	.1	37	Mono-oxalate
31	13,356	$NH(CH_2)_3CH(NH_2)(n-C_4H_9)$	$R_6 = OCH_3$	B	165–170	.15	14	Mono-oxalate
32	13,371	$NHCH(CH_3)(CH_2)_2CH(CH_3)N(C_2H_5)_2$	$R_6 = OCH_3$	B	185–190	.4	21[q]	None
33	13,375	$NH(CH_2)_3N(C_2H_5)_2$[o]	$R_5 = p\text{-}OCH_3C_6H_4; R_6 = OCH_3$	A	220–230	10^{-6}	..	Oxalate
34	13,429	$NHCH(CH_3)(CH_2)_3NHCH_2CH_2CH_3$	$R_6 = OCH_3$	B	175–178	.2	35[q]	Oxalate
35	13,528	$NH(CH_2)_2N(CH_2)_2NH(CH_2)_2\rceil$	$R_6 = OCH_3$	C	220–225	.01	46	Oxalate
36	13,576	$NH(CH_2)_7N(C_2H_5)_2$[t]	$R_6 = OCH_3$	C	190–195	.15		Oxalate
37	13,618	$NH(CH_2)_3N(C_2H_5)_2$	$R_2 = CH_3$	C	145–155	.3	30	Oxalate
38	13,619	$NH(CH_2)_6N(C_2H_5)_2$	$R_2 = CH_3$	C	168–172	.2	35	Oxalate
39	13,619	....	....	C	168–172	.2	38	Oxalate
40	13,622	$NH(CH_2)_3N(C_2H_5)_2$	$R_4 = CH_3$	C	135–138	.2	30	Oxalate
41	13,623	$NH(CH_2)_6N(C_2H_5)_2$	$R_4 = CH_3$	C	175–185	.2	60	Oxalate
42	14,009	$NH(CH_2)_6N(C_2H_5)_2$	$R_5 = CH_3; R_6 = OCH_3$	C	190–195	.1	20	Oxalate
43	14,053	$NH(CH_2)_2N(C_2H_5)_2$[r]	$R_6 = Cl$	C	168–174	.25	28	Mono-oxalate
44	14,056	$NH(CH_2)_6N(C_2H_5)$[r]	$R_6 = Cl$	C	175–178	.002	16	Oxalate
45	14,088	$NH(CH_2)_6NHCH(CH_3)_2$	$R_5 = R_8 = OCH_3$	D	180–185	.3	29	Oxalate
46	14,089	$NH(CH_2)_6N(C_2H_5)_2$	$R_4 = CH_3$	C	170–175	.25	52	Oxalate
47	14,090	$NH(CH_2)_2N(C_2H_5)_2$	$R_4 = CH_3$	C	135–139	.2	26	Oxalate
48	14,187	$NHCH(CH_3)(CH_2)_3NHCH_2CH(CH_3)_2$	$R_6 = OCH_3$	B	180–184	.3	14	Oxalate
49	14,188	$NHCH(CH_3)(CH_2)_3NHC(CH_3)_3$	$R_6 = OCH_3$	B	180–185	.3	24	Oxalate
50	14,287	$NH(CH_2)_3NHCH_2CH_2CH_3$[s]	$R_6 = OCH_3$	C	183–185	.1	75	Mono-oxalate
51	14,841	$NH(CH_2)_2N(C_2H_5)_2$	$R_2 = R_6 = CH_3$	C	175–180	.2	48	Oxalate
52	14,885	$NH(CH_2)_2N(C_2H_5)_2$	$R_7 = CH_3$	C	141–143	.3	47	Oxalate
53	14,886	$NH(CH_2)_2N(C_2H_5)_2$	$R_5 = OCH_3$	C	184–186	1.1	50	Oxalate
54	14,981	$NH(CH_2)_6N(C_2H_5)_2$	$R_2 = R_4 = CH_3$	C	185–190	.4	50	Oxalate
55	15,000	$NH(CH_2)_6N\langle\ \rangle N—CH_2C_6H_5$[u]	$R_6 = OCH_3$					Dioxalate
56	15,030	$NH(CH_2)_6N(C_2H_5)_2$	$R_4 = CH_3$	C	188–191	.9	50	Oxalate
57	15,085	$NH(CH_2)_6N(C_2H_5)_2$	$R_5 = OCH_3$	C	195–200	1.3	15	Oxalate
58	..	$NH(CH_2)_6N(C_2H_5)_2$	$R_2 = R_5 = CH_3$	C	180–185	.3	53	Oxalate
59	..	$NHCH_2CHOH(CH_2)_2NHC_2H_5$	$R_6 = OCH_3$	B	185–190	.25	10	None
60	..	$NH(CH_2)_6N(C_2H_5)_2$	$R_4 = Cl$	C	194–196	.2	15	Oxalate

[a] Rothman and Fricker[12] and Magidson, et al.,[13] describe the free base but no salts. [b] Homogeneity test done at Columbia University. [c] The free base[12,14,15] picrate,[16] monomeconate,[15,16] dimeconate[16] and dihydrochloride[16,17] and the methylene-bis-salicylate[14] have been described previously. [d] Homogeneity test by Dr. L. C. Craig, of the Rockefeller Institute for Medical Research. [e] The dioxalate (m. p. 136°),[16] the meconate[16] and the dihydrochloride[16] have been described previously. [f] Homogeneity test by Dr. John V. Taggart, of New York University College of Medicine. [g] The free base[13] has been previously described. [h] See experimental part of this paper for

(12) Rothmann and Fricker, German Patent 602,049; *Friedlander*, **21**, 292 (1934).

(13) Magidson, et al., *Arch. Pharm.*, **272**, 74 (1934).

(14) Magidson, et al., *J. Applied Chem.* (U. S. S. R.), **9**, 304 (1936).

(15) Magidson and Strukov, *Arch. Pharm.*, **271**, 569 (1933).

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

(17) Yanko, Mosher and Whitmore, THIS JOURNAL, **67**, 664 (1945)

TABLE I

DERIVATIVES OF 8-AMINOQUINOLINE

No.	Survey Number	M. p. of salt, °C.	Found % Acid	Found % Base	Calculated from Acid C	Calculated from Acid H	Calculated from Base C	Calculated from Base H	Formula Calcd. C	Formula Calcd. H	Formula Found C	Formula Found H	Homogeneity, %
1	3,114	132–134	24.2	71.8	59.8	7.0	58.0	6.7	..	..	58.0	7.0	98±1[b]
2	3,114	125–130	24.7	73.6	59.5	6.9	58.7	6.8	..	..	58.9	6.9	95±3[b]
3	3,115	207–208	..	..	..	..	..	..	37.6	5.0	37.8	5.2	>98[d]
4	3,559	195–196	..	..	..	..	..	..	59.6	6.9	59.3	7.0	97±2[f]
5	8,233	165–167	..	..	..	..	..	..	48.9	6.9	48.6	6.9	93±1[d]
6	8,233	126–128	20.8	76.7	60.6	7.6	59.6	7.5	..	..	60.8	7.7	97±3[b]
7	9,972	138–141	21.6	76.1	59.8	7.4	58.8	7.3	..	..	59.8	7.5	97±3[b]
8	11,392	185–188	..	..	..	..	..	..	37.8	4.9	38.8	4.2	
9	11,625	120–121	..	..	..	..	..	..	34.3	4.7	34.6	4.7	
10	11,889	176–178	..	..	..	..	..	..	37.7	5.1	37.9	5.1	92±2[d]
11	12,106	184–185	..	..	..	..	..	..	44.8	4.9	45.1	5.0	
12	12,110	197–198	..	..	..	..	..	..	44.6	5.0	44.9	5.2	
13	12,903	244–246	..	..	..	..	..	..	52.9	6.6	52.6	6.8	>98[b]
14	12,904	180–183	..	..	..	..	..	..	39.9	5.4	39.9	5.2	30-30-30[d]
15	12,904	87–90	25.4	71.8	60.9	7.5	59.5	7.3	..	..	60.4	7.4	97±3[b]
16	12,904	90–91	23.2	74.1	61.7	7.6	60.5	7.5	..	..	60.2	7.6	97±3[b]
17	12,905		..	..	..	..	..	..	69.6	9.0	69.9	9.0	
18	13,125	104–107	..	..	..	..	..	..	42.4	6.0	42.8	5.9	95±3[d]
19	13,155	185–187	19.3	78.7	64.0	6.7	62.9	6.5	..	..	63.7	6.4	93±3[b]
20	13,232	125–129	..	..	..	..	..	..	61.2	8.7	61.1	8.7	92±4[d]
21	13,232	150–155	21.4	76.8	62.5	8.0	61.8	7.9	..	..	62.3	8.0	94±3[b]
22	13,233	177–179	..	..	..	..	..	..	39.9	5.4	39.7	5.5	90±4[f]
23	13,233	164–167	22.1	74.8	62.2	7.7	60.8	7.5	..	..	61.6	7.6	94±3[b]
24	13,272	197–198	..	..	..	..	..	..	63.2	7.2	63.3	7.3	97[d]
25	13,272	162–167	17.2	81.3	62.1	7.1	61.5	7.1	..	..	61.8	7.3	99[b]
26	13,272	115–117											
27	13,273	175–178	23.6	74.4	60.4	7.2	59.7	7.1	..	..	59.9	7.2	99[b]
28	13,274	133–136	22.3	73.5	61.7	7.5	59.9	7.2	..	..	61.5	7.5	98±2[b]
29	13,354	138–140	..	..	..	..	..	..	60.5	7.2	60.7	7.2	
30	13,355	184–186	..	..	..	..	..	..	61.4	7.4	61.2	7.4	94±3[d]
31	13,356	102–104	..	..	..	..	..	..	61.4	7.4	61.2	7.1	96±3[d]
32	13,371		..	..	..	..	..	..	72.9	9.4	72.7	9.7	94[b]
33	13,375	122–126	18.1	78.3	62.5	6.7	62.0	6.7	..	..	62.0	6.5	92±3[b]
34	13,429	165–167	27.4	70.5	59.5	7.1	58.5	7.0	..	..	59.3	7.3	99[b]
35	13,528		22.3	72.3	60.0	7.4	58.2	7.0	..	..	59.1	7.2	96±2[b]
36	13,576		22.9	73.2	62.8	8.0	60.9	7.7	..	..	62.2	7.5	95±2[b]
37	13,618	150–151	25.7	73.0	62.5	7.3	61.6	7.2	..	..	62.4	7.3	94±3[b]
38	13,619	140–142	38.7	58.7	57.4	6.8	56.0	6.8	..	..	57.0	6.7	93±3[b]
39	13,619	147–149	41.4	57.3	56.0	6.8	55.3	6.7	..	..	55.6	6.4	95±2[b]
40	13,622	162–164	26.0	71.4	62.3	7.2	60.8	7.1	..	..	61.7	7.0	97±2[d]
41	13,623	135–137	36.0	63.0	58.8	7.2	58.1	7.1	..	..	58.9	7.2	98±2[d]
42	14,009	105–108	30.8	66.6	59.1	7.4	57.9	7.2	..	..	58.5	7.2	94±2[b]
43	14,053	158–160	..	..	..	..	..	..	55.5	6.0	55.4	6.3	99[f]
44	14,056	93–96	20.7	77.0	59.7	7.2	58.8	7.0	..	..	59.1	7.2	97±2[b]
45	14,088	135–137	20.3	77.5	60.8	7.7	60.0	7.5	..	..	60.8	7.6	96±2[b]
46	14,089	103–107	33.7	64.1	59.8	7.4	58.8	7.2	..	..	59.0	7.4	95±4[b]
47	14,090	152–154	26.2	72.0	62.1	7.2	61.3	7.1	..	..	61.7	7.4	94±3[d]
48	14,187	169–173	23.8	72.3	61.5	7.6	59.7	7.3	..	..	59.8	7.4	94±4[b]
49	14,188	140–145	25.0	73.7	60.9	7.5	60.5	7.5	..	..	60.6	7.4	96±4[b]
50	14,287	200–201	..	..	..	..	..	..	59.5	6.9	59.4	7.0	97[f]
51	14,841	156–157	24.8	73.1	63.1	7.6	62.3	7.4	..	..	63.0	7.5	95±3[b]
52	14,885	110–112	26.2	73.0	62.1	7.2	61.7	7.2	..	..	62.0	7.4	95±1[f]
53	14,886	155–156	24.7	74.2	59.5	6.9	59.0	6.9	..	..	59.3	6.9	93±3[b]
54	14,981	98–100	21.6	75.5	66.2	8.6	64.7	8.2	..	..	65.9	8.1	93±2[b]
55	15,000	205–207	..	..	..	..	..	..	60.7	6.5	60.6	6.2	94±2[b]
56	15,030	134–139	17.8	80.0	67.7	8.6	66.8	8.4	..	..	67.4	8.6	96±2[b]
57	15,085	93–95	21.3	78.7	63.1	7.9	63.1	7.9	..	..	62.8	7.7	96±2[b]
58		85–87	21.6	76.4	66.2	8.6	65.2	8.3	..	..	66.2	8.4	92±2[b]
59			..	..	..	..	..	..	66.4	8.0	66.5	8.3	
60		124–125	21.5	76.2	59.5	7.2	58.3	7.0	..	..	59.4	7.1	98

synthesis. [i] The free base has been described previously.[18,19] [j] Prepared from crude 5-diethylaminopentyl bromide hydrobromide. [k] The free base[15] and dimeconate[15] have been described previously. [l] Prepared from pure 5-diethylaminopentyl bromide hydrobromide. [m] Prepared from pure 5-diethylaminopentyl chloride hydro-

chloride. [n] Prepared according to Magidson and Bobyshev,[20] who report the dihydrobromide melting at 135–137°. [o] Drug base prepared by Dr. Walter M. Lauer at the University of Minnesota. Oxalate prepared at Columbia University. [p] The hydroiodide underwent slow decomposition. [q] Over-all yield on two reactions: bromination of alcohol with thionyl bromide and coupling of the bromide with the nucleus. [r] The 6-chloro-8-aminoquinoline

(18) Schönhöfer and Andersag, German Patent 536,447; Friedlander, 18, 2718 (1931); Schönhöfer, Z. physiol. Chem., 274, 1 (1942).

(19) Swiss Patents 160,092; 160,093; 160,094; 160,095; Chem. Zentr., 104, II, 1719 (1933).

(20) Magidson and Bobyshev, J. Gen. Chem., (U. S. S. R.) 8, 899 (1938).

used was prepared by Drs. C. S. Sherman and L. Goldman at Cooper Union, New York City. [s] The free base[21] the dioxalate[20] (m. p. 173°) and dihydrochloride have been reported previously. [t] The free base[22,23] and the dihydrochloride[23] have been reported previously. [u] Side chain prepared by Dr. Byron Riegel of Northwestern University.

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the drying agent was washed at least three times with anhydrous ether, or until it was colorless. After concentrating the ether solution to about 30 ml., it was transferred quantitatively to a tared 50-ml. stoppered Florence flask and concentrated, finally under water pump vacuum, until the weight was constant to the nearest mg. The percentage of free base was calculated to the nearest tenth of a per cent. and was reproducible to the nearest per cent.

The pH of the aqueous solution was adjusted to 6 with hydrochloric acid, and the oxalic acid was precipitated as calcium oxalate in the usual manner. The precipitate was collected on a sintered Gooch funnel and washed twice with water. The calcium oxalate was dissolved in 3 N sulfuric acid by filtering the acid through the funnel leaving any non-basic impurities on the funnel. Oxalate ion was determined in the filtrate by titration with standard 0.1 N potassium permanganate solution. The percentage of oxalic acid was calculated to the nearest tenth of a per cent. and was reproducible to the nearest per cent.

6-Methoxy-8-{6'-[1-(4-benzylpiperazyl)]-hexylamino}-quinoline, SN-15,000.—Because of the presence of an additional nitrogen atom in the side chain, a modification of Procedure A was used for this preparation. A mixture of 50.4 g. of 6-[1-(4-benzylpiperazyl)]-hexylbromide hydrobromide,[24] 52.2 g. of 6-methoxy-8-aminoquinoline and 400 ml. of absolute alcohol was refluxed for five days. After pouring the mixture into excess dilute sodium hydroxide solution, the oil which separated was extracted with ether. Distillation of the oil gave 30 g. of unreacted 6-methoxy-8-aminoquinoline (b. p. 115–120° (0.002 mm.)), 10 g. of material boiling at 120–160° (0.002 mm.), which was probably a derivative of the side chain, and 20 g. (46%) of nondistillable oil. In an attempt to remove the benzyl group, the oil was shaken under hydrogen with 1 g. of palladium oxide[25] in 200 ml. of glacial acetic acid. Although the calculated amount of hydrogen was absorbed in one hour, the benzyl group remained intact. After removal of the acetic acid, the residue was made strongly alkaline with potassium hydroxide and the base was extracted with ether. The material was now distillable and yielded 15 g. of light brown oil which boiled at 225–240° (0.01 mm.). Conversion of the oil to the oxalate gave a crystalline salt, the properties of which are given in Table I.

6-Methoxy-8-[6'-(1-piperazyl)-hexylamino]-quinoline, SN-13,528.—In this case also it was necessary to use an extra equivalent of buffer in the condensation reaction. Reaction of 82 g. of 6-(1'-piperazyl)-hexyl bromide dihydrobromide[3] and 104 g. of 6-methoxy-8-aminoquinoline by Procedure A gave a crude drug which appeared to be contaminated with by-products arising from the side chain which interfered with distillation. The crude material was boiled for one and one-half hours with 30% potassium hydroxide solution after which the oily base distilled readily, yielding 32 g. (46%) of material boiling at 215–230° (0.001 mm.). After a second distillation, the drug (24.5 g.) was converted to the oxalate and examined for homogeneity and showed the presence of 28% impurity. Purification was accomplished by utilizing the information gained by the homogeneity test which indicated that the impurities were definitely less basic than the bulk of the material. A solution of 30 g. of the oxalate in 6 liters of citric acid–citrate buffer at pH 3.85 was extracted with two 1500-ml. portions of chloroform. The buffered solution was then

(21) Baldwin and Robinson, J. Chem. Soc., 1264 (1934).
(22) Magidson, Madaeva and Rubtsov, J. Gen. Chem., (U. S. S. R.), 5, 1506 (1935); Arch. Pharm., 273, 320 (1935).
(23) Altman, Rec. trav. chim., 57, 941 (1938).
(24) Courtesy of Dr. Byron Riegel of Northwestern University.
(25) Shriner and Adams, THIS JOURNAL, 46, 1683 (1924).

made strongly alkaline and extracted with ether, yielding 11.1 g. of base boiling at 210–215° (0.001 mm.). From this the oxalate was prepared.

Purification of 6-Methoxy-8-(7'-diethylaminoheptyl-amino)-quinoline, SN-13,576.—The drug, prepared by Procedure C, when examined for homogeneity by the Craig technique[6] using cyclohexane and a citrate buffer system, showed the presence of at least three components, none of which comprised more than 70% of the total. It was assumed that the major component was the desired substance. The mixture contained about 20% of a more basic component and a few per cent. of a less basic component. Neither redistillation of the base nor recrystallization of the salt improved the purity of the sample. Accordingly, the drug oxalate (40 g.) was purified by a modification of the technique used in the distribution analysis.

A preliminary run was made using 400 mg. of material in the 8-plate technique of Craig. In this the concentration of the drug was 21.3 mg. base per ml. of each phase. Chloroform was used rather than cyclohexane, which was used in the distribution analysis, and the salt concentration of the buffer (1 M in total citrate) was decreased from that (2 M in total citrate) used in the distribution analysis, in order to facilitate handling larger amounts of material. Concentrations were measured spectrophotometrically with a Beckman quartz spectrophotometer, and were based on the absorption maximum at 365 mμ. Since calculation showed that the inhomogeneity in tubes 0, 1, 2 and 3 represented 19% of the total amount of base present, tubes 4 through 8 should contain material of acceptable homogeneity. Deviations of the experimental from the theoretical curve (Fig. 1) in tubes 4, 6 and 7 are probably due to slight variations of the distribution coefficient with concentration and to experimental error.

Since the pilot run indicated that satisfactory purification could be effected, the remainder of the 40 g. of drug oxalate was subjected to exactly the same treatment. Inasmuch as it was unnecessary to separate the material in tubes 4 through 8 (separatory funnels were used), eight plates were applied in four funnels. The lower layers from funnel 3 were combined and retained. This chloroform solution, therefore, contained all the material in tubes 4 through 8 in the pilot run.

TABLE II

SUBSTITUTED 8-AMINOQUINOLINES

	M. p., °C.		Analyses, % Calcd.		Found	
Other R's	Observed	Reported	C	H	C	H
R₆ = Cl[a]	151 –153	150–152[a]	..	..	..	..
R₅ = OCH₃						
R₂ = CH₃[b]	51 – 53	56[c]	..	..	..	..
R₄ = CH₃[b]	80 – 81	84[d]	..	..	..	..
R₅ = CH₃[e]	137 –138.5	....	..	..	..	..
R₆ = OCH₃						
R₆ = CH₃[f]	62 – 63	60– 62[g]	..	..	..	..
R₂ = R₆ = CH₃[h]	103 –105	....	76.7	7.0	76.6	6.9
R₇ = CH₃[i]	41 – 43	....	75.9	6.4	75.6	6.2
R₅ = OCH₃[f]	89.5– 91	....	68.9	5.8	68.9	5.9
R₂ = R₄ = CH₃[j]	93.7– 94.2	89– 92[k]	..	..	..	..
R₅ = CH₃[f]	46 – 47	....	75.9	6.4	76.2	6.3
R₄ = Cl[l]	99 –100	....	60.5	3.9	60.6	3.8

[a] Prepared according to Robinson and Tomlinson, J. Chem. Soc. 1524 (1934). [b] Nitro compound from Dr. H. E. French, University of Missouri. [c] Doebner and Miller, Ber., 17, 1698 (1884). [d] Johnson and Hamilton, THIS JOURNAL, 63, 2864 (1941). [e] Prepared by Carmack, Kissinger and Von, private communication. [f] Nitro compound from Dr. C. S. Pease, Oregon State College. [g] Richter and Smith, THIS JOURNAL, 66, 396 (1944). [h] Nitro compound from Dr. C. C. Price, University of Illinois. [i] Nitro compound from Drs. C. S. Pease, Oregon State College, and R. E. Lutz, University of Virginia. [j] Prepared by Dr. E. B. Hartshorn, private communication. [k] Roberts and Turner, J. Chem. Soc. 1832 (1927). [l] Nitro compound in part by Dr. C. S. Sherman, Cooper Union.

The chloroform solution thus obtained was extracted with an equal volume of 1 M citric acid. The extract was made strongly alkaline and extracted with ether. The material extracted by the ether, after drying, was distilled, the part boiling at 190–195° (0.15 mm.) being collected. The recovery was 19 g. (60%). After conversion to the oxalate, the drug was re-examined by the 8-plate technique and showed the presence of 3% of the more basic inhomogeneity and 2% of the less basic inhomogeneity, which is within acceptable limits.

Reduction of 8-Nitroquinoline Derivatives. (a) With Stannous Chloride.—This method has been described in detail in a preceding paper.[5] If the aminoquinoline was a liquid, it was extracted with ether or chloroform. The material obtained on removal of the solvent was used directly.

(b) **With Iron and Acetic Acid.**—In the case of the reduction of 7-methyl-8-nitroquinoline by method (a), some nuclear chlorination occurred despite all precautions. Pure 7-methyl-8-aminoquinoline was obtained by use of iron and acetic acid.[26] A mixture of 10 g. of 7-methyl-8-

(26) Private communication from Dr. Walter Lauer of the University of Minnesota.

nitroquinoline, 100 ml. of water, 5 ml. of glacial acetic acid, 1 ml. of dibutyl ether and 10 g. of iron filings was heated under reflux with stirring on the steam-bath for seventeen hours. The mixture was filtered, the filtrate was made basic and filtered again. The precipitate was washed once with acetone, and the combined aqueous filtrate and acetone washings were extracted three times with ether. The solid residue from the acetone wash was extracted three times with boiling acetone and filtered after each extraction. The material from the combined acetone and ether extracts, after drying, was distilled, the fraction boiling at 172–175° (22 mm.) being collected. The distillate was recrystallized from alcohol.

The properties of the various 8-aminoquinolines are given in Table II. In all cases R_8 is NH_2.

Summary

1. The synthesis of fifty-one analogs of Pamaquine (Plasmochin) has been described.

2. The synthesis of five new derivatives of 8-aminoquinoline has been described.

[Contribution from the Laboratories of the University of Maryland]

Synthetic Antimalarials. 8-(5-Isopropylaminoamylamino)-6-methoxyquinoline (SN-13,276)[1] and Some Related Compounds[2]

By Nathan L. Drake, John Van Hook, John A. Garman, Robert Hayes, R. Johnson, G. W. Kelley, Sidney Melamed and Richard M. Peck

Clinical studies have indicated that SN-13,276 is a promising antimalarial.[2] The present paper describes the preparation of the drug and some of its close relatives.

In general the method of preparation follows that of Plasmochin. 8-Amino-6-methoxyquinoline is alkylated by means of 1-chloro-5-isopropylaminopentane hydrochloride, the drug is isolated as its monohydrochloride, converted to free base, and precipitated from alcohol as the monophosphate.

Demethylation of SN-13,276 by means of hydriodic acid[3] at 100° yields the corresponding quinolinol which was submitted for testing as its dihydriodide. Care must be taken not to overheat the reaction mixture during the removal of the methyl group; at temperatures above 100°, an excessive amount of the side-chain suffers cleavage from the nucleus.

The side-chain of SN-13,276 has been attached to 8-amino-5,6-dimethoxyquinoline, and to 8-amino-5-chloro-6-methoxyquinoline. The corresponding drugs separate nicely as monohydriodides.

The other relatives discussed are 8-(5-t-butylaminoamylamino)-6-methoxyquinoline and 8-

(1) See Antimalarial Drugs, 1941–1945, F. Y. Wiselogle, Editor, in press. The survey number (SN) identifies the drug in the Survey Office and in the monograph.

(2) This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Maryland.

(3) See Drake, et al., This Journal, **68**, 1536 (1946), for a similar demethoxylation of SN-11,191.

(5-t-amylaminoamylamino)-6-methoxyquinoline.[4]

The preparation of the side-chain of these drugs is easily accomplished from dihydropyran. When dihydropyran is treated with aqueous acid, a vigorous reaction takes place and the dihydropyran dissolves. If this solution is brought to about pH 8.0 by means of isopropylamine and subjected to hydrogenation in the presence of Adams catalyst and a molar equivalent of isopropylamine, 5-isopropylamino-1-pentanol is produced and can be isolated as the hydrochloride. Thionyl chloride converts the hydrochloride practically quantitatively into 1-chloro-5-isopropylaminopentane hydrochloride, the compound necessary for the preparation of SN-13,276. Other amines can be substituted quite satisfactorily for isopropylamine in this synthesis.

The alkylation of 8-amino-6-methoxyquinoline by 1-chloro-5-isopropylaminopentane hydrochloride takes place smoothly. The quinoline (2 moles), the chloride-hydrochloride (1 mole), and a small amount of water are stirred at 80° for twenty hours (internal t.) and then at 103–104° for four hours. The melt is poured into a small amount of water and brought to about pH 5.0 by means of alkali and sodium acetate. Extraction of the hot solution with benzene or toluene removes excess nucleus. When the extracted

(4) Survey numbers will not be assigned to any more drugs, at least at present. Some of the compounds in the present paper will be given with the U. M. numbers by which they will be identified to the pharmacologists who test them.